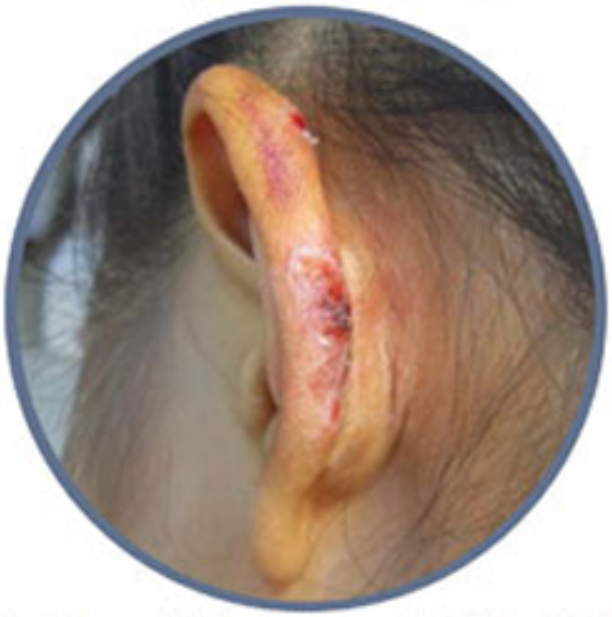
Bangkok Hospital Group

THE BANGKOK MEDICAL JOURNAL

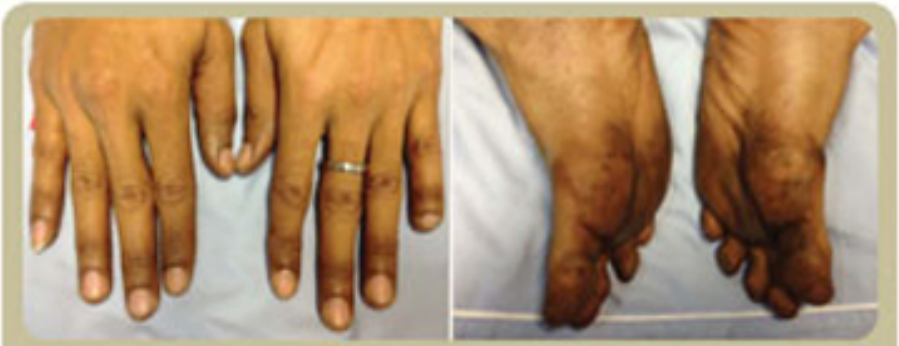
February 2013, Volume 5

Highlights

What is your diagnosis?



Case 1: A 9-year-old Thai girl presented with pink plaques on the left ear for 6 months.



Case 2: A 32-year-old man developed hyperpigmentation on the dorsum of hands and feet.

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Editorial

The 5th edition of the Bangkok Medical Journal brings you an informative collection of articles from our internists, oncologists and radiology specialists, and submissions from international guest authors, Frans Van de Werf FJ, Andrew Smith, and Beate Hanson.

The first ever PET/CT scanner in Thailand was introduced by the Wattanasoth Hospital; we give an overview of its functions and benefits. We also present a study from a pulmonologist who has uncovered a higher incidence in lung cancer cases among women who are passive smokers. In addition, the role of tomosynthesis is explored as an important tool in the early detection of breast cancer, particularly in Thai women.

Road accidents remain a major cause of injury and disability - it is the second leading cause of death in Bangkok after heart disease. We present a road map, drawing on successful road safety schemes overseas, to help change behavior and to reduce the number of fatalities in Thailand. We also present a study on the prevention of head injuries for motorcycle riders and passengers who travel without wearing a helmet.

A special highlight is the Hypertension Registry at the Bangkok Hospital Medical Center, we strive to improve the quality of care given to our patients and to increase awareness around hypertension and its management. Initial findings give valuable information on how to improve the services provided to patients.

We encourage and support the use of studies in furthering medical knowledge and the sharing of tips and experience among peers. In this edition, we showcase practical suggestions and methods on how to perform an effective and robust study.

In November last year, FIFA hosted the 2012 Futsal World Cup in Thailand. Brazil defended its title, winning the tournament for a record 5th time. The Bangkok Academy of Sports Exercise Medicine, established by the Bangkok Hospital, is an accredited FIFA medical center of excellence, one of several around the world. Three futsal players were successfully treated at BASEM during the tournament; we present case studies of diagnostic methods in sports injuries, particularly Futsal.

We offer two interesting cases: chronic plaque on the ear, and palmar-plantar erythrodysesthesia for continuing medical education, highlighted on the cover page of this volume.

We hope you enjoy this latest edition of the Bangkok Medical Journal. Happy reading!

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Hypertension Registry at the Bangkok Hospital Medical Center: The First 7 Months' Experience

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Keywords:
hypertension registry, hight blood pressure, Bangkok Hospital, Thailand

OBJECTIVE: The Hypertension Registry at the Bangkok Hospital Medical Center was established in June 2012. It aimed to raise awareness of the availability of appropriate hypertension health services, to optimize the quality of care, and to systematically build a database of clinical outcomes. The purpose of this article is to highlight the main data collected from patients with hypertension who took part in the Hypertension Registry Programme. These findings will help improve services and will lead to better clinical outcomes in the future.

MATERIALS AND METHOD: A retrospective review was conducted of all the participants in the Hypertension Registry from June 2012 to December 2012. Descriptive data is presented as absolute numbers and percentages.

RESULTS: A total of 647 patients with hypertension were registered, half of all registrants were overweight, 51.9% had dyslipidemia and 34.8% had diabetes. The most frequent investigations done to assess cardiovascular risk were electrocardiograms (EKG) 34.4%; chest x-rays 27.9%; Ankle Brachial Index (ABI) 19.5%; and urine microalbumin (MAU) 18.1%. In 3.9% of cases no antihypertensive medication was required and 53.5% of patients were prescribed a single item of medication. Angiotensin-receptor blockers (ARB) were the most frequently prescribed antihypertensive medication. Up to 90% of cases were well controlled and achieved a systolic blood pressure (SBP) < 140 mmHg. and diastolic blood pressure (DBP) < 90 mmHg.

CONCLUSION: The Hypertension Registry at the Bangkok Hospital Medical Center provides multiple advantages in collecting relevant information to further optimize the quality of hypertensive services offered and to improve the quality of life of patients with hypertension.

The Hypertension Clinic is a part of the Internal Medicine Outpatient department (OPD) at the Bangkok Hospital Medical Center. Hypertension patients account for 15% of all Internal Medicine OPD visits. It is now widely accepted that hypertension management is also a concern to other cardiovascular risk factors. Besides the process of measuring blood pressure and prescribing medications, better management can help prevent more cardiovascular vascular complications.[1-4]

The primary goals of the Hypertension Registry are:

1) to create data as a tool for quality control (QC) to help improve the quality of future services and planning
2) to create awareness of other associated medical conditions that are risk factors beyond blood pressure levels in both patients and service providers to increase public awareness

3) to make use of electronic medical records (EMR) to benefit both patients and service providers
4) to improve service efficiency and continuous education of clinical staff and physicians by periodically creating feedback data reports

During the first seven months of the Hypertension Registry, 647 patients with hypertension enrolled in the programme. The objective of the study is to highlight the main data of patients who registered in the programme compared to a group enrolled in one physician's hypertension registry.

Materials and Methods

The Hypertension Registry was established in June 2012. Patients' demographic and clinical information of is retrieved from two data sources: the electronic medical records (EMR) and collating information by hand. The process to create a registry entry is as follows:

The staff

1) Coordinator Nurses (who also play a role as educators) open each case entry by inputting the initial information (a new case entry is partly picked up from ICD-10 diagnosis in the department and some cases are opened by physicians themselves or through physician assistants who inform the nurse coordinators). An icon is created in the EMR for each case and flagged as a hypertension registry member case. A review and data input for antihypertensive medications prescribed is inputted, plus information is audited to check the entries are correct. A summary is generated periodically (every 3-6 months) with assistance from Information Technology staff to create reports for the Hypertension Clinic and as a feedback information mechanism for the physicians involved.
2) Physician Assistants coordinate physicians and coordinators.
3) Physicians who attend the patient and act as team consultants.
4) Information Technology (IT) staff help the team from an early stage in the process and create appropriate software for the electronic medical records, create additional input questionnaires for specific data, and create programmes for the data summary system.

The Process

1) The demographic information of each registrant is linked to the EMR once the patient is entered into the hypertension registry and a HT icon is created on each individual EMR to flag the patient as a member of the registry. The patient's past history and any associated illnesses are reviewed from the EMR and the patient record files and also available including interviewing the patient during an education session conducted by a nurse coordinator.
2) Laboratory investigations identify any organ damage i.e. EKG, echocardiography, chest x-ray, urine for microalbumin (MAU) and Ankle Brachial Index (ABI) by using a vascular screening machine *"VaSera"* (this machine measures both ABI x CAVI) which also measures a Cardio-Ankle Vascular Index (CAVI).[5-8] The results of each investigation are retrieved from the EMR and input into the registry by directly linking the information to the date the investigations were performed. At present, only the linked information can be accessed in bulk but the results from various measurements still need to be input manually.
3) Medication use was reviewed from the EMR and the medical records file. Antihypertensive medication was classified into 9 groups; 1) Diuretics, 2) Dihydropyridine calcium channel blockers (DHP CCB), 3) Non dihydropyridine (non DHP CCB), 4) Angiotensin-converting enzyme inhibitors (ACEI), 5) Angiotensin II receptor blockers (ARB), 6) Direct renin inhibitors (DRI), 7) Alpha blockers, 8) Beta blockers, and 9) Others. The combination antihypertensive tablet was counted as 2 or 3 isolated medications that are the components of the pill prescribed at the same time. The medication is entered by trade name and is automatically allocated to the group they belong to in accordance with the preset lists of the antihypertensive medication database.
4) At each visit the registrant's height (cm), and body weight (kg) is reviewed and this data is added to the individual's database by the physician assistants. Blood pressure values (both systolic and diastolic) are collected after visits to the physician. The data inputs are corrected and audited by nurse coordinators and the team every 2-4 weeks.
5) The summary is preset for future periodic reports. It was set to be searchable by period of time from one to several months to years and searchable by service providers, and by name, by group or by individual physician.

A whole staff team meeting, including IT staff, reviews the process and reports back every 2-3 months.

Results

Since June 2012, when the Hypertension Registry was created, the number of registrants has gradually increased through a better understanding of the team members (Figure 1). A total of 647 cases were registered during the first 7 months.

Sex

About 57% of cases were female. The outnumbering of men by women was also true for the total of hypertension cases at the Bangkok Hospital Medical Center as well as the cases of one physician (Figure 2).

Age

Most registrants (74.5%) were aged between 51 and 80 years old compared to patients who registered in one physician's registry (Figure 3).

Body Mass Index

Of those, half of all patients had a BMI of more than 24.99 and were categorized as overweight (Figure 4).

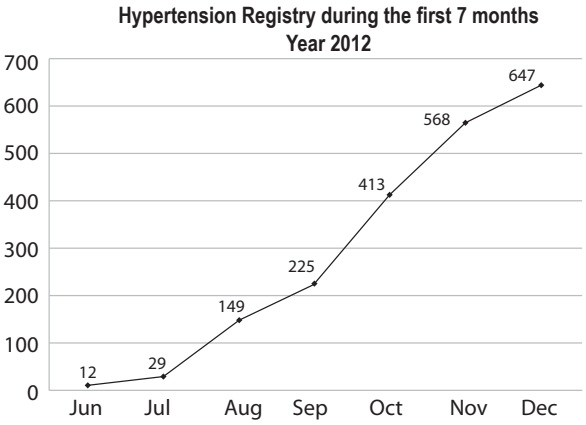

***Figure 1**: Demonstrates the progression of the number of enrolled cases in the Hypertension Registry during the first 7 months*

History of risk factors

According to an initial interview of 84 cases, 51.9% had dyslipidaemia and 34.8% had diabetes mellitus (DM). Heart disease was found in 4.4%, kidney disease in 3.7%, stroke in 3.2%, and 0.7% of cases interviewed had peripheral vascular disorder as in Figure 5.

Laboratory investigations: EKG was the most frequently ordered investigation (34.4%) followed by chest x-ray, ABI, and MAU in 27.9%, 19.5% and 18.1% respectively while ABI was the second most frequent investigation required in one physician's registry group (Figure 6).

Antihypertensive medication: 3.9% of all registry cases did not need any antihypertensive agents to control blood pressure. Most cases (53.5%) took only one item of antihypertensive medication. Of the remaining 32%, 8.5%, and 2.2 % used 2, 3, and 4 antihypertensive medications respectively (Figure 7). ARB was the most common group prescribed for the treatment of hypertension (35.6%). The second most common drug was DHP CCB (32.7%) and if combined with non DHP CCB (2.9%) then the percentage of the use of CCB would be equal to the ARB group. Beta blockers were used in 14.5% of cases and were more common than Diuretics (9.9%), ACEI (3.0%), alpha blockers (1.0%) and DRI (0.3%). Among 647 cases from the Hypertension Registry, there were no patients who used any antihypertensive medication marked as 'others' (Figure 8).

Achievement of blood pressure goal: approximately 90% of registrants had well controlled blood pressure by achieving SBP < 140 and DBP < 90 mmHg (Figure 9).

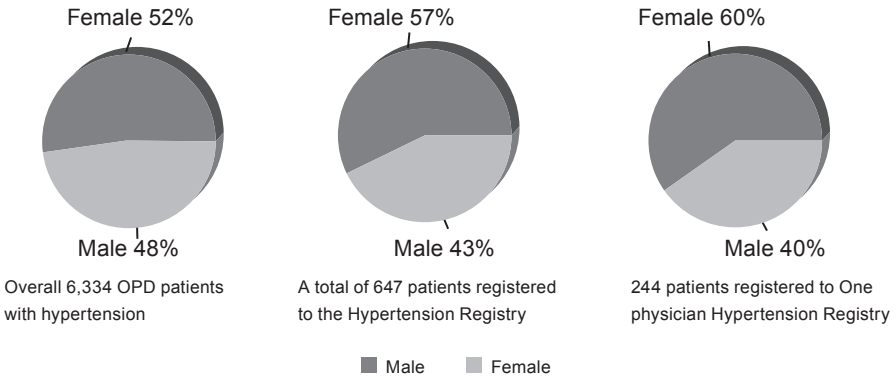

***Figure 2**: Sex distribution of 6,334 hypertension patients from the whole medical center (the left is compared with 647 cases from The Hypertension Registry (middle) and 244 cases from one physician hypertension registry (right) during the same period.*

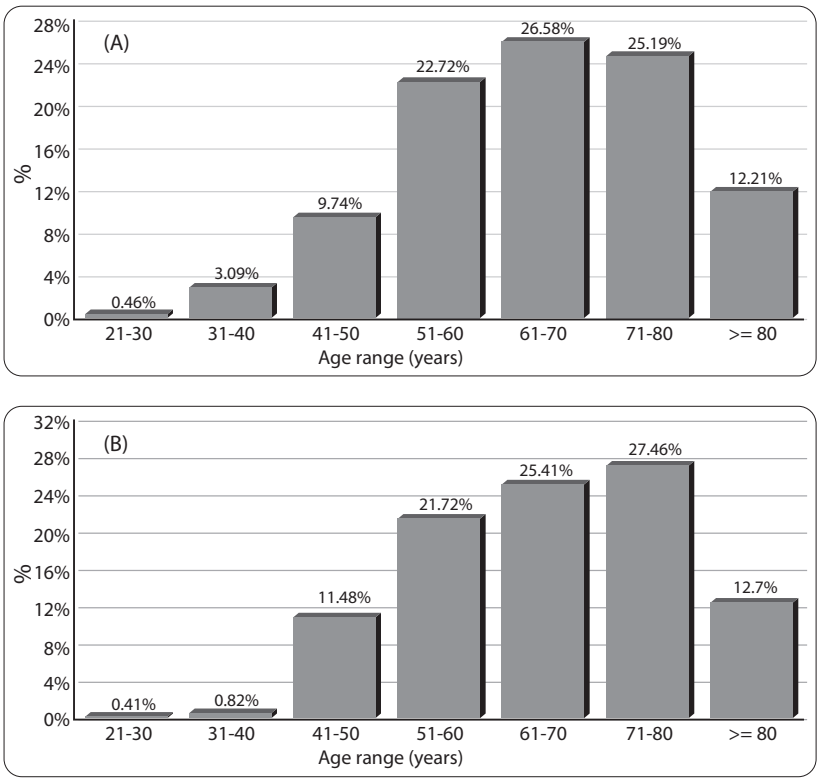

Figure 3*: Age distribution amongst 647 patients who participated in the Hypertension Registry (A) compared to 244 patients from one physician's registry (B).*

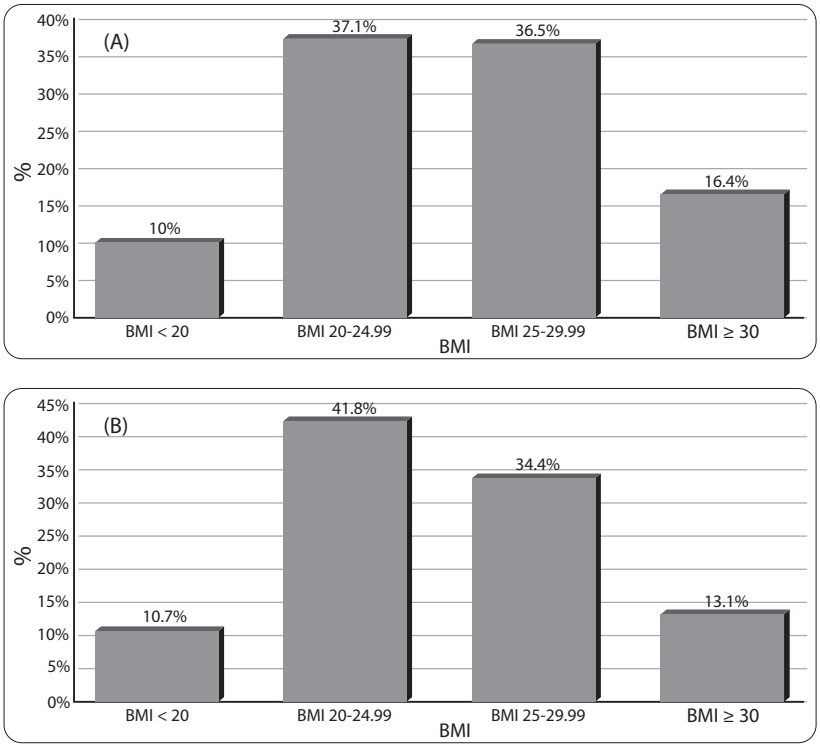

Figure 4*: The Body Mass Index (BMI) distribution of 647 registrants who participated in the Hypertension Registry (A) compared to 244 cases from one physician's registry (B).*

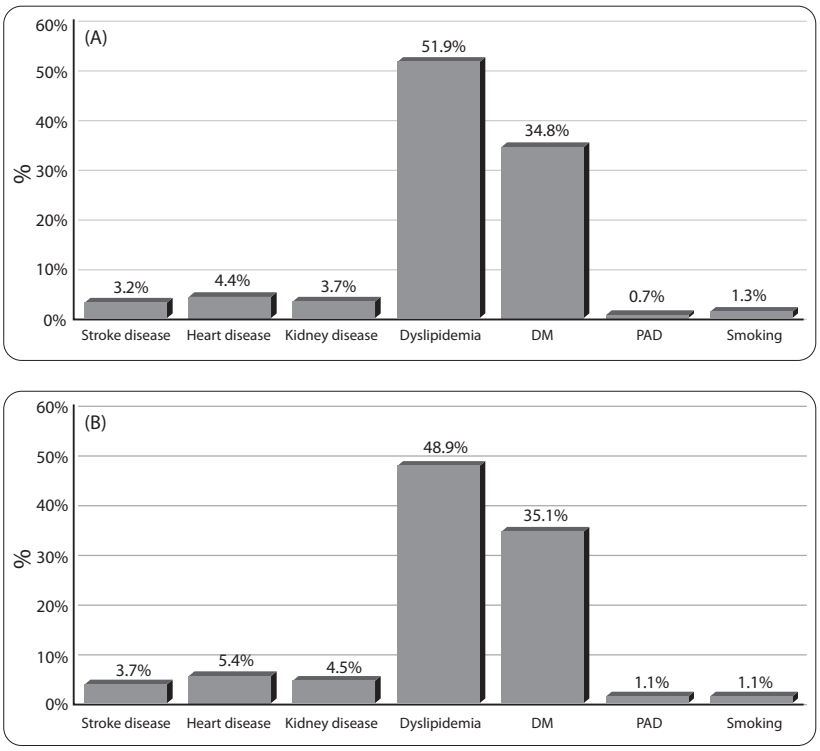

***Figure 5**: Associated risk conditions from the history of 84 patients from the Hypertension Registry interviewed (A) compared to 44 patients from one physician's registry (B).*

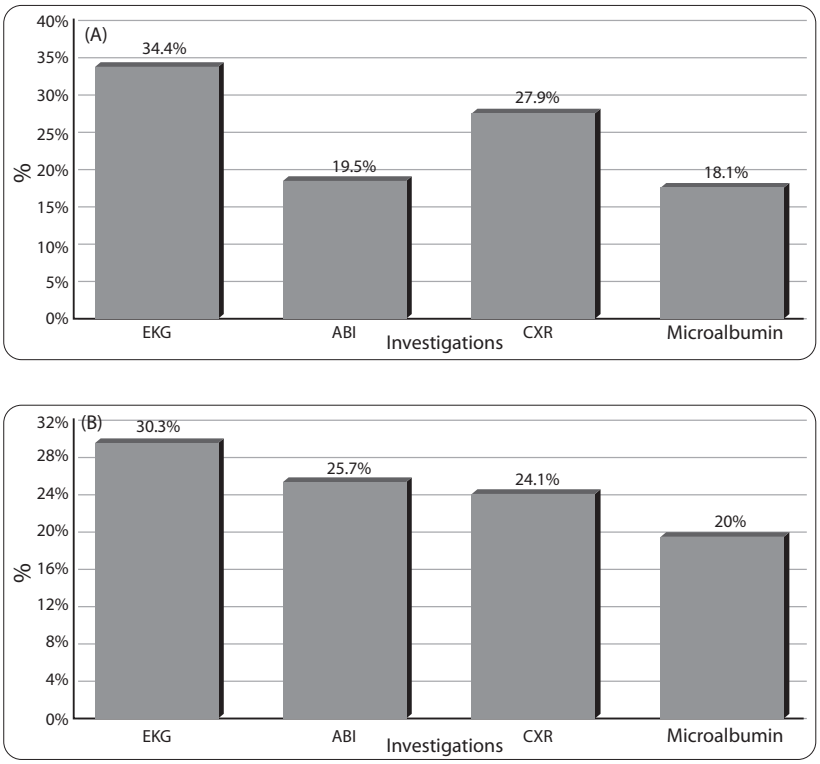

***Figure 6**: Percentage of investigations done in 647 cases from the Hypertension Registry (A) compared to 244 cases from one physician's registry (B).*

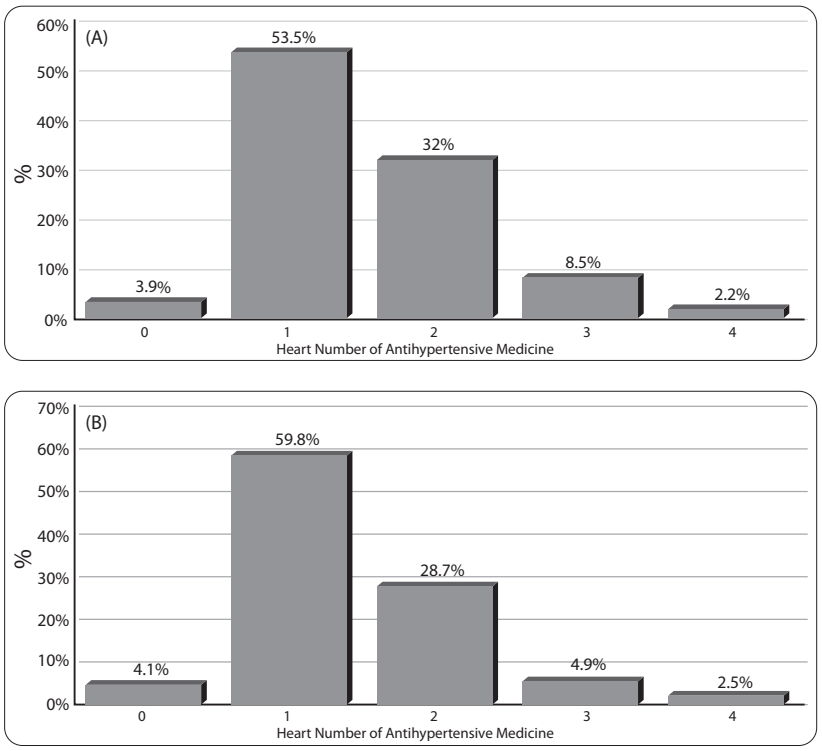

***Figure 7**: Distribution of registrants using 0 to 4 items of antihypertensive medications amongst 647 cases from the Hypertension Registry (A) and 244 cases from one physician's registry (B).*

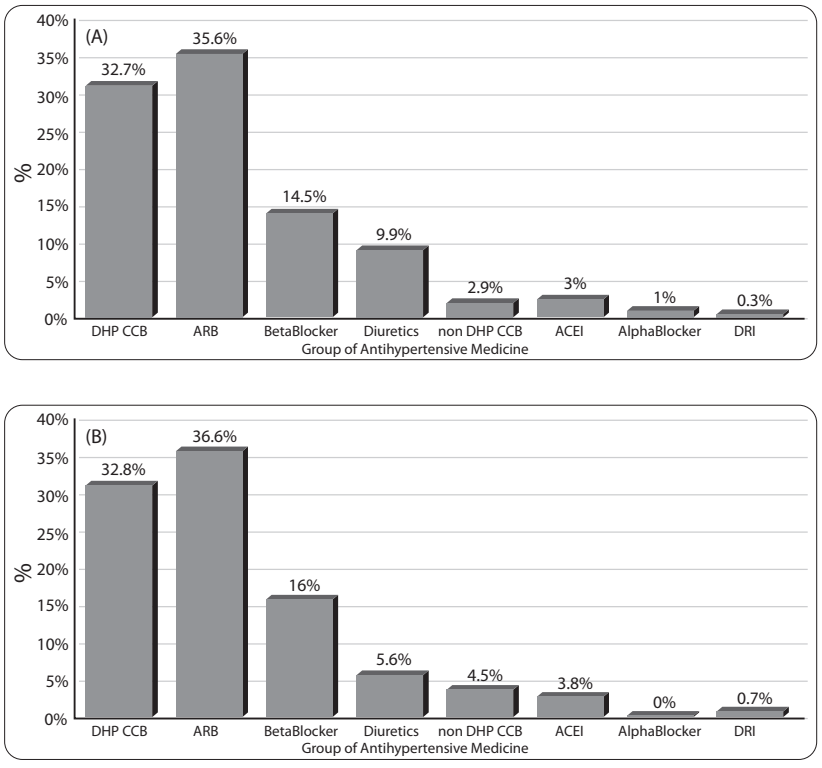

***Figure 8**: Group of antihypertensive medications amongst 647 cases from the Hypertension Registry (A) compared to 244 cases from one physician's registry (B).*

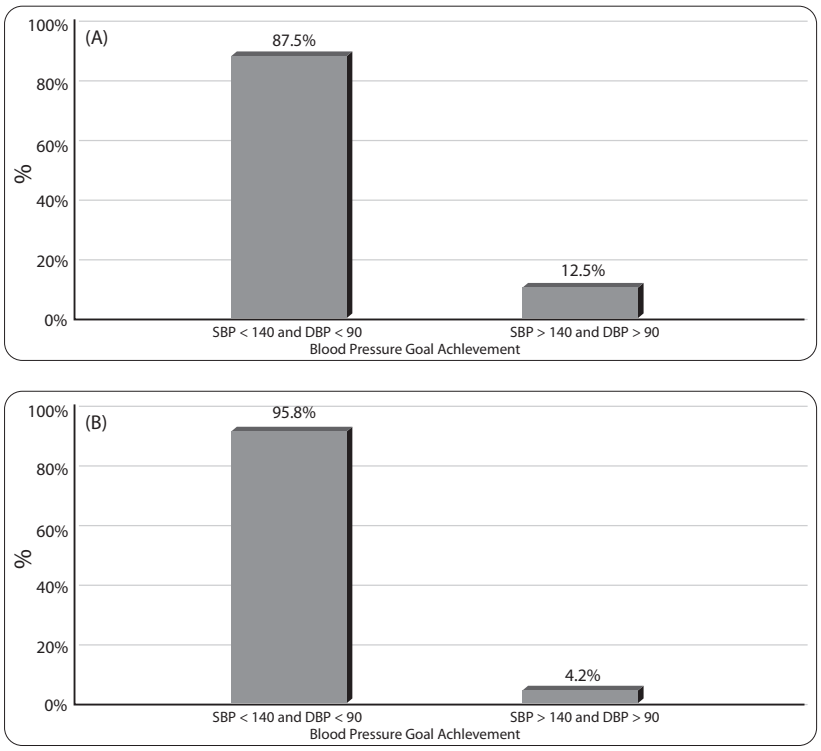

***Figure 9**: Percentage of cases achieving goal of treatment, SBP < 140 and DBP < 90 in 337 cases from the Hypertension Registry (A) and 120 cases from one physician's registry (B).*

Discussion

During the initial 7 months of the Hypertension Registry, we can see many broad ideas that can be used to improve hypertension clinical services. About half of all cases were overweight (BMI > 24.99 kg/m^2), and an EKG was taken assess any left ventricular hypertrophy evidence (only about a third of participants), urine micro-albumin was tested in less than a fifth of the cases despite much evidence to suggest that this simple test can warn us of the cardiovascular risk in hypertensive patients etc. All this information is critical for hospital staff to be able to plan for better services. Furthermore, the registry data can also be a good tool for patient education. It was surprising to discover that more than half of all patients only need one antihypertensive medication and about 90% of cases achieved the BP goal. These initial registry cases, however, will slowly and continuously accumulate, so it may be too soon to extrapolate, as this sample may not represent the reality. Time is needed for the registry system to develop and for staff to improve their skills and increase their experience. Also, larger numbers are required in the registry to help build a better picture of the current situation. This Hypertension Registry is a dynamic tool, able to accommodate frequent updates and to be adapted in the future if required. We hope to learn more from our information with a larger number of participants in the hypertension registry numbers, accompanied by a growth in global medical knowledge and guidelines.

Conclusion

The Hypertension Registry provides multiple benefits and valuable information. It is progressing well, and may yield firmer conclusions when the registry grows in numbers.

Acknowledgements

The authors and the Hypertensive Registry team would like to thank the CEO, the Bangkok Hospital Directors, the Medicine Patient Care Group Manager, and the President of the Medical Staff Organization of The Bangkok Hospital Medical Center for all their support towards this project's development.

References

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
2. Mancia G, De Backer G, Dominiczak A , et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007;25:1751-62.
3. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92.
4. Thai Hypertension Society Writing Group. Thai Guidelines on the treatment of hypertension update 2012. (Accessed January 2013, at http://www.thaihypertension.org/files/216_1.Hypertension_Guideline_2012.pdf.)
5. Yingchoncharoen T, Limpijankit T, Jongjirasiri S, et al. Arterial stiffness contributes to coronary artery disease risk prediction beyond the traditional risk score (RAMA-EGAT score). *Heart Asia* 2012;4:177-82 doi: 10.1136/heartasia-2011-010079.
6. Yambe T, Yoshizawa M, Saijo Y, et al. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed Pharmacother* 2004;58:S95-8.
7. Arterial Stiffness Index "CAVI"; CAVI (Cardio-Ankle Vascular Index). (Accessed January 2013, at http://www.fukuda.co.jp/english/products/special_features/vasera/cavi.html)
8. Gojaseni P, Phaopha A, Chailimpamontree W, et al. Prevalence and risk factors of microalbuminuria in Thai nondiabetic hypertensive patients. *Vasc Health Risk* Manag 2010;6:157-65.

A Prospective Randomized Trial for Reduction of Serum Low Density Lipoprotein (LDL) with Plant Stanol Ester Mixed in Coffee in a Hypercholesterolemic Thai Population.

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Keywords:
plant stanol ester, coffee, LDL, hypercholesterolemia, Thai

OBJECTIVE: To determine whether replacing ordinary coffee with coffee mixed with the plant stanol ester decreases the serum low density lipoprotein (LDL) level in moderately hypercholesterolemic Thais.

MATERIALS AND METHODS: A randomized, double-blind, placebo-controlled trial of a common daily coffee was conducted on May 1, 2012 with continued treatment and follow-up through June 1, 2012. A total of 54 Thais whose serum LDL levels ranged from 130 to 239 mg/dL at randomization, were enrolled and randomized into two groups. The participants consumed a cup of plant stanol mixed coffee or a cup of placebo coffee once a day. The percentage of serum LDL reduction was measured at the end of the study.

RESULTS: Thirty-three subjects were randomized into each group. Forty-seven subjects completed the study, 30 in the group receiving coffee with added plant stanols as ester and 17 in the placebo coffee group. Statistical analysis was done by unpaired t-test using PASW (Predictive Analytics SoftWare) Statistics 18 (SPSS Inc., IL, USA). The results showed a significant difference in mean reduction of LDL levels ($p < 0.001$, 95% CI = 6.92 – 18.57). The means were 12.77% in the first group and 0.03% in the second group (SD = 9.33 and 9.88, respectively).

CONCLUSION: Among this population of hypercholesterolemic Thais, the daily replacement of an ordinary cup of coffee with a plant stanol mixed coffee reduced serum LDL levels by 12.77% demonstrating the efficacy of the cholesterol-lowering ingredient in the new food matrix.

Plant stanol is a compound of phytosterol (equivalent to cholesterol in mammals). It is found in natural foods particularly whole grains. Plant stanol ester (Benecol®) is an end result of esterifying stanol and fatty acid from vegetable oil. The obtained ester has high fat solubility sufficient to be incorporated into many processed foods. Laboratory evidence has shown that the plant stanol ester binds with diet cholesterol in the bowel lumen and limits cholesterol absorbtion. The plant stanol ester itself is also practically nonabsorbable. In 1995 an article published in the New England Journal of Medicine[1] showed that plant stanol ester significantly reduces serum low LDL and total cholesterol (TC). Since then more than 60 articles have been published with similar results. A study done in Greece[2] found that plant stanol ester spread reduced (by 1 month) TC 14%, LDL-Cholesterol (LDL-C) 16%, high-sensitivity C-reactive Protein (hsCRP) 17% and estimated cardiovascular disease (CVD) risk 30%. A study done in USA[3] showed that giving plant stanol containing spread to patients who had already been taking statin drugs

for 8 weeks, further reduced LDL-C by 14% compared with the placebo group. The effect of plant stanol is dose dependent. In one study[4] when patients were given 3 grams per day (gm/d) of plant stanol, the serum LDL-C decreased by 7.4%. When dose was increased to 6 gm/d, the serum LDL-C dropped a further 4.5%. When the dose was increased to 9 gm/d the serum LDL-C decreased by an additional 5.4% making a total reduction of 17.4% with a 9 gm/d dose. In one study,[5] increasing the dose to 8.8 gm/d reduced total serum and LDL-C concentrations by 12.0% and 17.1% from controls without changing liver enzymes, markers of hemolysis, serum vitamins A, D, and ɣ-tocopherol concentrations. The ratios of α-tocopherol to cholesterol were also unchanged although the serum β-carotene concentrations dropped. This study implied that a high dose of plant stanol did not significantly interfere with the absorption of fat soluble vitamins. The addition of 1 gm of plant stanol to a 150 ml cup of low fat (0.7%) yogurt three times a day also reduced LDL-C by 13.7%.[6] One study done in metabolic syndrome patients found that plant stanol reduced not only LDL-C by 12.8% but also triglycerides by 27.5%.[7]

Plant stanol ester is used nowadays in the manufacture of several processed foods such as bread spreads, low fat dairy products, yogurt, soy-based or cereal-based products, pasta, and soft drinks etc. The idea of replacing coffee cream made of trans fat or carbohydrate is appealing for those who have hypercholesterolemia and still habitually drink coffee with cream. So far there is no randomized controlled study to assess the LDL lowering effect of plant stanol ester in coffee. On the other hand, data concerning the efficacy of plant stanol ester among Thais is still very limited. This study will bridge both knowledge gaps.

Materials and Methods

The study was a randomized, double-blind and placebo-controlled trial of a parallel design with an intervention and a control group. The time frame of the trial was from May 1 to June 1, 2012. The plant stanol ester and a placebo coffee sample were prepared and analyzed. The plant stanol coffee sample contained a total plant stanol value of 11.22 gm/100 gm (expected value 11.76 gm/100 gm) or 1.91 gm/17 gm in each bag (expected value 2 gm/17 gm in each bag). The placebo coffee sample contained total plant stanol 0.02 gm/100 gm (expected value 0 gm/100gm). A 1/1 randomization was performed using a computer generated randomization list.

The intervention group consumed one cup a day of coffee enriched with 2 gm of plant stanol ester Benecol® per cup, for 30 days. The control group consumed the same coffee products with no added plant stanols. The products were received blind, and labelled with computer generated different codes. The codes were only revealed after the analysis was concluded. Table 1 showed the subjects' baseline characteristics. Routine laboratory measurements were made to ensure each subject was in good health

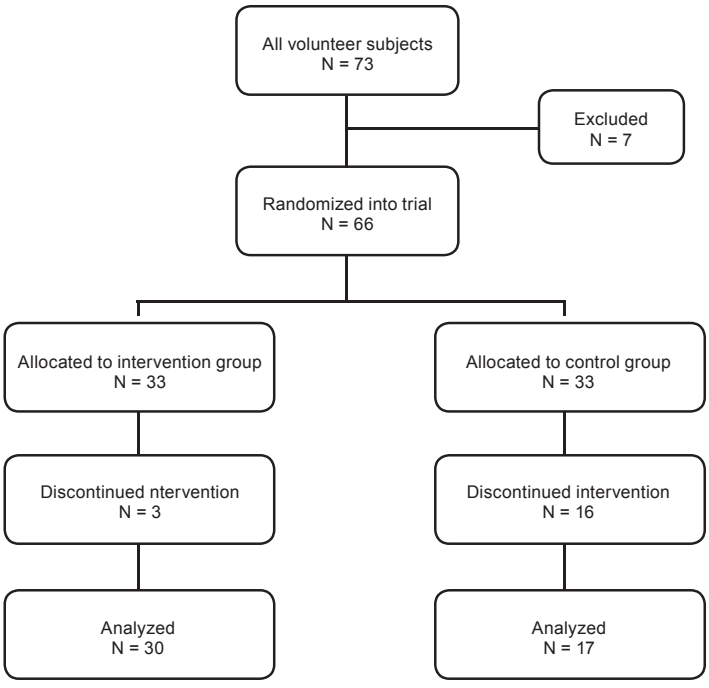

***Figure 1**: Subject eligibility and adherence*

Table 1: Basic characteristics and initial measurements of analyzed subjects

	Intervention Group	Control Group	Total
n	30	17	47
Age (years)	45 (9)	44 (8)	45 (9)
Males (n (%))	8 (17%)	5 (11%)	13 (28%)
Body weight (kg)	64.7 (7.2)	63.1 (9.1)	64.1 (8.2)
Height (cm)	161.4 (4.5)	162.1 (4.5)	161.6 (4.6)
BMI (kg/cm^2)	24.8 (2.7)	24 (3.3)	24.5 (3)
Abdominal circumference (cm)	77.9 (9.7)	76.2 (9.6)	77.3 (9.9)
Pulse	77 (8)	74 (6)	76 (7)
Blood pressure	131/81 (14, 10)	126/78 (8,5)	129/79 (12, 9)
Triglycerides (mg/dL)	145 (91)	95 (35)	127 (79)
Total choleseterol (mg/dL)	250 (33)	237 (31)	245 (33)
HDL (mg/dL)	56.1 (13.4)	61.4 (10.7)	58.0 (12.9)
LDL (mg/dL)	178 (33)	165 (25)	173 (31)

Values are given as means (SD) BMI = Body Mass Index, LDL = Low Density Lipoprotein HDL = High Density Lipoprotein

before commencing the study. Subjects were asked to list any medications, vitamins or nutritional supplements they were currently taking via a structured questionnaire handed out at the start and end of the process. Blood samples after a 12 hour fast were taken, at the beginning and at the end of the intervention.

Subjects were then compared for changes in serum LDL-C levels. The primary endpoint was the relative reduction of directly measured LDL compared to each subjects' pre-intervention values. Statistical analysis was done with an unpaired t-test using PASW Statistics 18 (SPSS Inc., IL, USA).

Results

A total of 73 Thais whose serum LDL levels ranged from 130 to 239 mg/dL were enrolled and assessed for eligibility. Seven of them did not meet the inclusion criteria and were excluded, leaving 66 of them for randomization. Thirty-three subjects were allocated to the intervention group and 33 were allocated to the control group. Forty-seven subjects completed the study: 30 in the first group and 17 in the second group. (Figure 1)

The results showed a significant difference in mean reduction of LDL levels ($p < 0.001$, 95% CI = 6.92 - 18.57). The means were 12.77% in the first group and 0.03% in the second group (SD = 9.33 and 9.88, respectively).

Discussion

The drop-out rate in the control group was higher than the intervention group. The taste of the placebo coffee is probably one of the causes. The 12.77% mean LDL reduction difference implies that plant stanol ester in a form of coffee mix reduced LDL-C in a similar percentage to other forms such as yogurt, or bread spread. The findings are encouraging for patients with hypercholesterolemia, and habitual coffee with cream drinkers. Replacing ordinary coffee cream or trans-fat coffee cream with a plant stanol ester will help both the reduction of LDL and maintain a creamy coffee taste. Since there have been so few publications about plant stanol ester in Asian populations, this study is a contribution to show that plant stanol ester reduces LDL in Thai population in a similar way to Caucasian populations.

Conclusion

Among this group of Thai population with hypercholesterolemia, the daily replacement of an ordinary cup of coffee with a plant stanol-mixed coffee reduced serum LDL levels by 12.77%.

Conflict of interest statement

The authors claim no conflict of interest associated with the manuscript.

Acknowledgements

This work was supported by a research grant from The Phyathai Hospital Group, Bangkok, Thailand.

Statement of authorship

Dr. Sant Chaiyodsilp had the primary responsibility for the research design, supervised the execution of the study, and wrote the manuscript except for the statistical analysis section. Miss. Yuwaret Khunaphakdipong prepared the experimental and control coffee samples. Miss. Rungsiya Srisawas and Mrs. Thanavee Pureekul carried out the studies and were responsible for the organization of data collection. Dr. Paul Chaiyodsilp performed the statistical analyses and outcome assessments. All authors read and approved the final manuscript.

References

1. Miettinen TA, Puska P, Gylling H, et al. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1995;333:1308-12.
2. Athyros VG, Kakafika AI, Papageorgiou AA, et al. Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. *Nutr Metab Cardiovasc Dis* 2011;21:213-21.
3. Blair SN, Capuzzi DM, Gottlieb SO, et al. Incremental Reduction of Serum Total Cholesterol and Low-Density Lipoprotein Cholesterol With the Addition of Plant Stanol Ester-Containing Spread to Statin Therapy. *Am J Cardiol* 2000;86:46-52.
4. Mensink RP, de Jong A, Lütjohann D, et al. Plant stanols dose-dependently decrease LDL-cholesterol concentrations, but not cholesterol-standardized fat-soluble anti oxidant concentrations, at intakes up to 9 g/d. *Am J Clin Nutr* 2010;92:24-33.
5. Gylling H, Hallikainen M, Nissinen MJ, et al. The effect of a very high daily plant stanol ester intake on serum lipids, carotenoids, and fat-soluble vitamins. *Clin Nutr* 2010 ;29:112-8.
6. Mensink RP, Ebbing S, Lindhout M, et al. Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. *Atherosclerosis* 2002;160: 205-13.
7. Plat J, Brufau G, Dallinga-Thie GM , et al. A Plant Stanol Yogurt Drink Alone or Combined with a Low-Dose Statin Lowers Serum Triacylglycerol and Non-HDL Cholesterol in Metabolic Syndrome Patients. *J Nutr* 2009;139:1143-9.

Higher Incidence of Lung Cancer in Female Passive Smokers

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Keywords:
female passive smoking, lung cancer, adenocarcinoma and squamous cell carcinoma, environmental tobacco smoke

OBJECTIVE: To evaluate whether passive smoking in females is significantly correlated with a higher incidence of lung cancer.

MATERIALS AND METHODS: In 2011, a survey was conducted of a sample of lung cancer patients who received treatment at the Bangkok Lung Center to ascertain their exposure to passive smoking.

RESULTS: The responses to the survey yielded a significant correlation between the incidence of lung cancer and exposure to passive smoking.

CONCLUSION: Recommendations based on the results of the study include improving health education campaigns and increasing public awareness of the health risks associated with passive smoking, as well as a re-evaluation of current lung cancer screening practices currently accepted by the medical establishment in Thailand.

In recent decades, healthcare professionals and oncology specialists have become increasingly focused on the role of second hand smoke as a cause or contributing factor to the incidence of lung cancer in non-smokers. Studies which indicate a correlation between passive smoking and an increased risk for developing lung cancer can be used as evidence to encourage further public education and anti-smoking campaigns. Additionally, relatives and friends of smokers will have access to scientifically tested information, enabling them to make informed choices about their exposure to passive smoking. The purpose of the study is to evaluate whether there is a correlation between passive smoking and lung cancer.

Materials and Methods

In 2011, 226 lung cancer patients from Bangkok Lung Center were evaluated based on their occupation, exposure to passive smoking, family history of cancer and other co-morbidities. The studied sample consisted of men and women with late stage lung cancer who were admitted to Bangkok Hospital between January 1 - December 31, 2011. These patients had previously undergone chemotherapy and radiation therapy. The diagnosis was proven by lung pathology, and the patients were evaluated retrospectively. Data was collated using IBM SPSS statistics analysis. Researchers measured the collated data for indications of a significant amount of lung cancer occurrences within the group of females who had been exposed to passive smoking. The rate of 5% was chosen to indicate a significant occurrence.

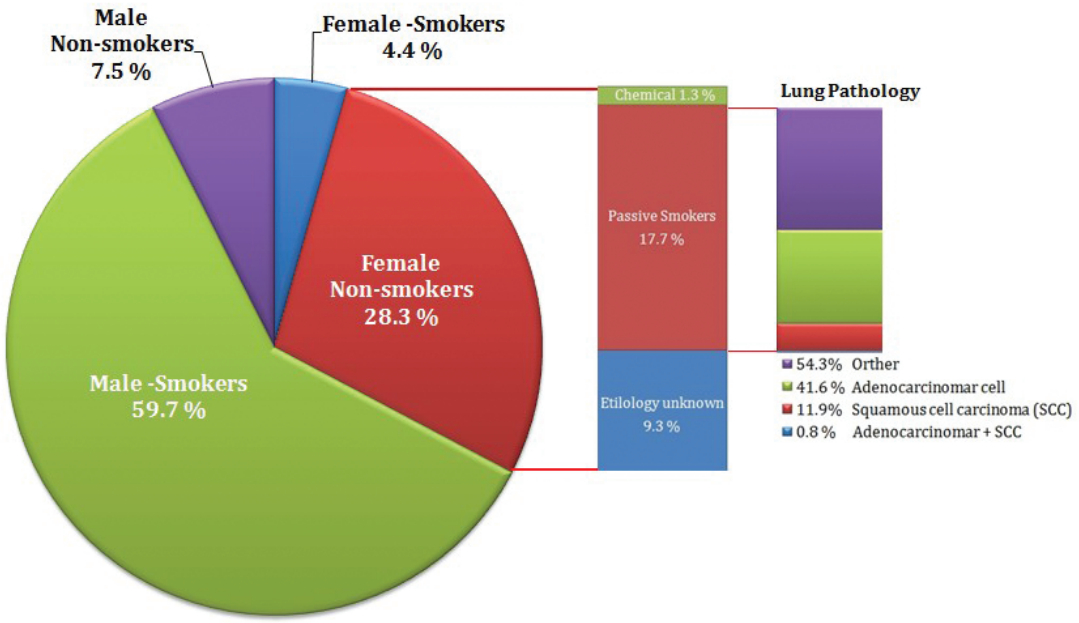

***Figure 1**: Statistics of male and female participants in the study*

Table 1: Characteristics and Initial measurements of analysis subjects

Data	Male	Female
n	152	74
Age (mean) years	32-82 (55.97)	32-82 (52.98)
Smoker	135 (59.7%)	10 (4.40%)
Non-smoker	17 (7.5%)	64 (28.3%)
Etiology unknown	13 (5.7%)	21 (9.3%)
Passive-smokers	3 (1.3%)	40 (17.7%)
Etiology unknown	1 (0.4%)	3 (1.3%)

Results

The study yielded the following results: of 152 male patients, 135 were smokers (59.7%) and 17 (7.5%) were non-smokers. The age ranged from 32-82 years. The mean age for male patients was 55.97 and the mean age for female patients was 52.98. The mean age for all patients was 54.99. All of the participating patients in the study were Thais. Among the 17 non-smoking males, 3 were passive smokers and 1 worked in a chemical factory. There were 74 females, 10 (4.4%) were smokers and 64 (28.3%) were non-smokers. Among 64 non-smoking females, 40 were passive smokers ($p < 0.001$) and 3 worked in a chemical factory (Figure 1, Table 1).

The occurrence of lung cancer in female passive smokers was found to be significantly high at 17.7%. Moreover, lung pathology revealed adenocarcinoma as the most common type of cancer in this group (41.6%). Cases of squamous cell carcinoma (SCC) amounted to 11.9% and 0.88% had both adenocarcinoma and SCC.

Discussion

Lung cancer is diagnosed more frequently than any other type of cancer in both men and women, and while smoking remains the predominant cause, recent studies reveal that lung cancer rates among people who have never smoked are higher in women than in men.[1] In industrialized countries, lung cancer rates have a direct relationship to smoking behaviors. In Asia, particularly in China, the pattern varies such that lung cancer rates in men reflect high smoking rates but high rates among non-smoking women appear to be related to other factors.[2] The following were identified as potential risk factors: cooking oil vapour, exposure to environmental tobacco smoke (ETS), occupational hazards such as exposure to toxins and chemicals i.e. asbestos and ambient air pollutants.

Northern Thai women have one of the highest incidences of lung cancer in Asia. The incidence rate, however, differs significantly from region to region despite similar low smoking prevalence, lifestyle factors and diet. Several studies were conducted, including: a study of local sources of drinking water, a mutagenicity test of urine samples, and fungi and bacteria were measured in indoor living areas. The fungus Microsporum canis was identified as a possible cause of the high incidence of chronic respiratory diseases among women in Sarapee. The women had an elevated concentration of the fungus serum antigen, which was commonly found in Sarapee indoor air.[3]

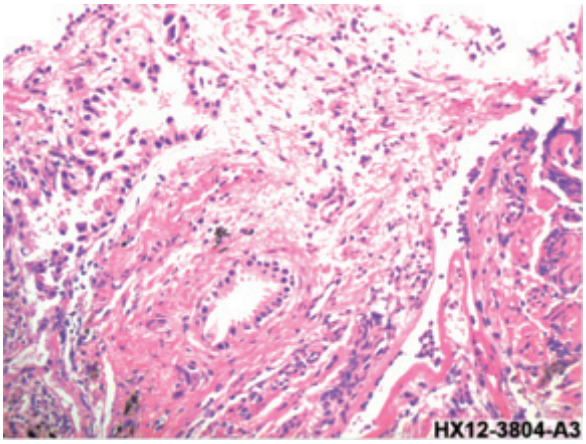

***Figure 1**: Microscopy: Infiltrating groups of malignant cuboidal to columnar epithelial cells with glandular formation are seen in chronically inflamed anthracotic bronchial and lung tissue biopsies. Moderate nuclear pleomorphism of the malignant cells is noted.*

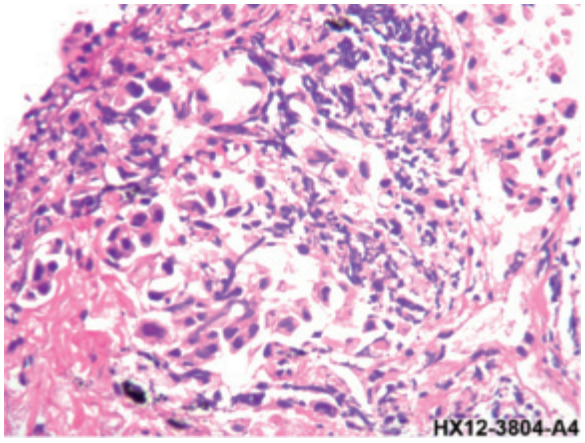

***Figure 2**: Immunohistochemistry is positive for CK7, CEA, TTF-1, lung adenocarcinoma is confirmed on both histopathology and immunohistochemistry.*

In 2011, a study in Morocco[4] yielded slightly similar results. The studied sample consisted of women with lung cancer who were admitted between January 2004 and December 2008. The diagnosis was proved by anatomo-pathologic analysis of biopsy specimen. The study found 101 women among 1,680 cases of lung cancer. Percentage of never-smokers was 75%, 14% were passive smokers and 11% are smokers. The proportion of non-small cell lung cancer (NSCLC) at stage IV was higher (82%); 16% of cases were at stage III and 2% were at stage II. The proportion of adenocarcinoma (ADK) among never and passive smokers is higher than squamous cell carcinoma (SCC) (69.4% vs. 30.6%), while among women who are smokers, the most frequent histological type is SCC (63.6%). ADK appears to be the most frequent cell type among never and passive smokers. ADK is significantly associated with lower rates of survival.

Lung adenocarcinoma is the most common primary carcinoma arising in women. For reasons not examined within the scope of this particular study, but potentially due to changes in smoking habits, adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung carcinoma in present days (Figures 2 and 3).

The study confirms the significant correlation between passive smoking and lung cancer. In 2007, 11 million of the 51 million people in Thailand aged over 15 years old were identified as smokers.[5] This delineates a 1:5 ratio of smokers to non-smokers. Families with smoking family members have the greatest risk of exposure to second-hand smoke. Wives who have smoking husbands have a higher risk of developing lung cancer than women who have non-smoking husbands.[6] Other risks include occupational hazards such as exposure to toxins and chemicals, i.e. asbestos and ambient air pollutants. Since the health risks from asbestos exposure increases with heavier exposure and longer exposure time, patients who have worked around carcinogen-exposed workplaces are at higher risk. However, researchers have also found asbestos-related diseases in individuals who only experienced brief exposures. Generally, those who develop asbestos-related diseases show no signs of illness for a long time after their first exposure.[7]

A study published in 2008 conducted a cross-sectional exposure survey among nonsmoking women and children in Eastern Europe, Latin America, Asia and the Middle East. The research used passive air monitors to measure household air nicotine concentrations and a hair nicotine test to measure personal exposure to passive smoking.[8] After surveying a total of 1,284 households in 31 countries including Laos, Cambodia, Thailand and China, findings suggested that the number of smokers in a household is directly related to the level of hair nicotine concentration. When there were a larger number of smokers, the level of nicotine concentration in the hair was higher, thus creating an elevated risk for developing tobacco smoke exposure-related diseases. A similar study was done in urban and rural China, measuring nicotine levels specifically in public places. Airborne nicotine was detected in 91% of the locations sampled and provided evidence for the need to protect the public from exposure to passive smoking.[9]

In India, there have only been a few studies on the pulmonary effects of passive smoking. One study examined 9,090 adolescent school pupils and discovered that exposure to environmental tobacco smoke (ETS) was correlated with an increased risk of asthma. Another study showed that ETS exposure was a trigger for an acute exacerbation of asthma. Passive smoking subtly affects

airflow mechanics. Another study found a correlation between passive smoking and lung cancer. In this study, 50 healthy non-smoking women exposed to passive tobacco smoke were matched to 50 women of the same age who had not been exposed to tobacco smoke. In a study carried out in collaboration with the International Agency for Research on Cancer, exposure to ETS during childhood was strongly linked to an higher rate of lung cancer (OR = 3.9, 95% CI 1.9-8.2). In conclusion, passive smoking can lead to several adverse pulmonary conditions, just as seen in other countries; this is also reported in India.[10]

The results of this study identify a significant risk factor for developing lung cancer: exposure to passive smoking. These results also support the conclusions of other studies conducted internationally. The evidence is clear: continued exposure to passive smoking significantly increases the risk of cancer. The continuance and strengthening of public health campaigns to discourage smoking is necessary to combat this growing public health risk. The population needs to be further educated about the dangerous risks associated with passive smoking.

Furthermore, a re-evaluation of lung cancer screening guidelines is recommended. The current National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) have been updated in 2012 to include recommendations for lung cancer screening from a new Lung Cancer Screening Panel.[11] While their recommendations are up to date, especially in the use of technologically-advanced equipment for the detection of cancer in the earliest, most curable stage, screening should be expanded to include additional risk groups (such as passive smoke). In light of the increase in the occurrence of lung cancer in females exposed to passive smoke, more comprehensive screening guidelines would assist medical professionals in increasing the detection of developing cancers. Additionally, based on our finding the guidelines' recommended age to begin routine screening should be performed in earlier age group (< 50 years old) particularly for those with passive smokers.

The NCCN Guidelines provide:

- Individuals without symptoms of lung cancer be assessed for risk based on the following factors: age, smoking history, radon exposure, occupational exposure, cancer history, family history of lung cancer, lung disease history, and secondhand smoke exposure.
- Screening with helical LDCT is recommended for patients at high risk, defined as:
  - Age 55 to 74, with 30 or more pack-year history of smoking tobacco (category 1); if a former smoker, must have quit within 15 years (category 1)
  - Age 50 or older and 20 or more pack-year history of smoking and one additional risk factor (other than secondhand smoke) (category 2B)
- Routine lung cancer screening is not recommended for the moderate-risk group, defined as age 50 or older and 20 or more pack-year history of smoking or secondhand exposure and no additional risk factors, or for low-risk individuals, who are under 50 and/or have a less than 20 pack-year history of smoking.[11]

The data in this study indicates that the mean age for all patients was 54.99. Considering that these are advanced stage cancer patients, the development of the disease is presumed to have begun approximately 10 years before this evaluation. Adhering closely to the current guidelines could potentially increase the number of undiagnosed cases.

Conclusion

This study shows high incidence of lung cancer in female passive smokers. The main lung cancer is adenocarcinoma. To reduce this incidence, we support health education campaigns and also emphasize health screening for female passive smokers under 50 years old.

References

1. Samet JM, Avila-Tang E, Boffetta P, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res* 2009;15:5626-45.
2. Lam WK, White NW, Chan-Yeung MM. Lung cancer epidemiology and risk factors in Asia and Africa. *Int J Tuberc Lung Dis* 2004;8:1045-57.
3. Lam WK. Lung cancer in Asian women-the environment and genes. *Respirology* 2005;10:408-17.
4. Errihani H, Ouaouch S, Abahssain H, et al. Smoking, passive smoking, and lung cancer cell types among women in Morocco: Analysis of epidemiologic profiling of 101 cases. 2011 ASCO Annual Meeting . *J Clin Oncol* 29:2011 (suppl; abstr 7069).
5. National Statistics Office. Thailand lauded for efforts to snuff out smoking. 2002. (Accessed on November 9, 2012 at http://www.globalsmokefreepartnership.org/index.php?section=artigo&id=133)

6. Ko YC, Lee CH, Chen MJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int J Epidemiol* 1997;26:24-31.
7. National Cancer Institute. Asbestos Exposure and Cancer Risk. 2009. (Accessed on November 9, 2012 at http://www.cancer.gov/cancertopics/factsheet/Risk/asbestos)
8. Wipfli H, Avila-Tang E, Navas-Acien A, et al. Secondhand smoke exposure among women and children: Evidence from 31 countries. *Am J Public Health* 2008;98:672-9.
9. Stillman F, Navas-Acien A, Ma J, et al. Second-hand tobacco smoke in public places in urban and rural China. *Tob Control* 2007;16:229-34.
10. Gupta D, Aggarwal A, Jindal S. Pulmonary effects of passive smoking: the Indian experience. *Tob Induc Dis* 2002;1:129-36.
11. NCCN Institutes New Guidelines on Lung Cancer Screening: Panel advocates screening high-risk individuals. JNCCN 2012. (Accessed January 14, 2013, at http://www.jnccn.org/site/highlights2012/lungscreen.xhtml)

Original Article

Respiratory Disturbance and IgE Caused by Traffic-related Air Pollution

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Keywords:
particulate matter less than 2.5 microns, microbial, respiratory symptoms, pulmonary function test, sweepers, IgE, air pollution

OBJECTIVE. This was a cross-sectional study to identify the association of microbial and particulate matter less than 2.5 microns (PM2.5) with respiratory symptoms and pulmonary function impairment among street sweepers.

MATERIALS AND METHODS. A number of 97 street sweepers at Rajthevee District in Bangkok participated in this research. The samples of particulate matter less than 2.5 microns were collected by attaching a Model 200 Personal Environmental Monitor (PEM™) to the street sweepers' collar near the breathing zone during their work shift. Microbial air samples were collected by Microflow 90 by following the street sweepers twice a day at 06.00-07.00 am and 10.00-11.00 am. The respiratory symptoms were assessed by questionnaire and the St George's Respiratory Questionnaire. Pulmonary functions were tested using a spirometer.

RESULTS. There was an association between particulate matter less than 2.5 microns with stuffy nose ($p < 0.01$) and cough ($p < 0.05$), fungi at 06.00-07.00 am was associated with wheezing ($p < 0.05$). However, there was no significant association between bacteria and respiratory symptoms and no significant association between particulate matter less than 2.5 microns or microbial agents with pulmonary function impairment among street sweepers. The mean of serum IgE among 15 sweepers who had wheezing was 277.07 IU/ml (range 12 - 1,088 IU/ml). There was correlation between poor pulmonary function and increased IgE levels.

CONCLUSION. The street sweepers who work in traffic areas exposed to PM2.5 and fungi were linked to respiratory symptoms and risk to asthma.

Thailand is a developing country that is moving away from agriculture to industrialization. Due to the rapid development with expansion of economics, society, education and communication, Bangkok has become one of the cities with air pollution, especially particulate matter less than 10 microns (PM 10) and particulate matter less than 2.5 microns (PM2.5), which is caused by automobile exhaust especially diesel,[1] smoke from burning wood and factories.[2-7] Air pollution problems affect people's health, especially causing respiratory diseases.

The results of previous epidemiological studies by both Thai and foreign researchers showed that there was a relationship between exposure to PM2.5 and health effects in both the short-term and long-term, causing diseases such as asthma, chronic lung inflammation, deterioration of lung function, respiratory tract infection and lung cancer. PM2.5 can be deposited in the respiratory tract more easily than larger particles.[8-12] Not only the

size of particulate matter affects mortality and morbidity but also the concentration and components.[13] However, these will vary according to activity and the environment.[14] In addition, many studies indicated that some microbial agents such as bacteria and fungi affect the respiratory system. Kurup V et al.[15] in 2000 showed that fungi in the air were associated with allergy and asthma. There were 4 - 11% of fungi contaminants in PM2.5.[16] Besides, the correlation of microbials in the air and particulate matter showed that PM2.5 and PM10 in the summer and autumn would be higher than other seasons.[17] Most of the fungi were found in PM 2.1- 3.3.[18]

Boonchoo W.[19] in 2005 studied the effects of PM10 on the pulmonary function of street sweepers. In this study, researchers specifically studied the microbes that sweepers could be exposed to during work shifts, becauses there was a lot of fine particulate matter, bacteria and fungi spread during sweeping. Moreover, they were working near the roadside which was a risk of PM2.5; and the emissions from vehicles. Therefore, we aimed to study the concentration of PM2.5, bacteria and fungi that may affect the respiratory symptoms and pulmonary function of the sweepers.

Materials and Methods

Samples selection

One hundred and ninety people were sweepers at Rajthevee district. They worked three shifts per day. The first shift operated by 100 sweepers was in the morning from 05.00 am to 01.00 pm; the second shift operated by 80 sweepers was in the afternoon from 01.00 pm to 09.00 pm; and the last shift operated by 10 sweepers was at night from 09.00 pm to 05.00 am. Rajthevee district had several places which were sources of particulate matter less than 2.5 microns and microbes such as hospital, skytrain, a street market, construction and heavily trafficked roads. The study group was selected from the sweepers working in the morning shift at Rajthevee District in Bangkok. The method was to follow up the activities of the sweepers who had worked more than 3 months at Rajthevee district in Bangkok (Figure 1), the sweepers who were not currently sick or admitted in hospital, the sweepers who worked by sweeping the road and who volunteered in this study. So, a number of 97 sweepers at Rajthevee District in Bangkok participated in this research.

This study was accepted by the Review Committee of the CHEST 2012 Annual Meeting in Atlanta on July 09, 2012.

Sampling and analysis

Collection of PM2.5

The samples of PM2.5 were collected during February-June 2011 using Polytetrafluoroethylene (PTFE) filters (Model 225-1709, SKC Inc. USA), the filters were equilibrated on desiccators in the controlled room for 24 hours before and after sample collection.

Figure 1: *Shows 50 districts of Bangkok, Thailand. Rajthevee district is highlighted in red.*

The temperature for this room was 20-23°C (± 2°C) and the relative humidity was 30-40% (± 5% RH). The Model 200 Personal Environmental Monitor (PEM™) was attached to the sweepers' collar near the breathing zone with a personal sampling pump (Gilair 5/Gilian, USA). The personal sampling pumps were calibrated using DryCal DC-lite at flow rate 4 L±20 ml/min. The time average for sampling was about 6 hours during the work shift. Each filter was weighed by using a microbalance (METTLER Model UMT-5) before and after sampling collection.

The concentration of PM2.5 in micrograms/m^3 was calculated as follows:

C = Ms/ Vs

C = concentration of PM2.5, µg/m^3

Ms = mass of PM2.5, µg

Vs = the volume of air sampled, m^3

Collection of microbial agents

Microbial air samples were collected during February-June 2011 using Microflow 90 (Aquaria, Italy) following the sweepers twice a day at 06.00-07.00 am and 10.00-11.00 am. Microflow 90 was calibrated by the calibrator at a flow rate of 30 L/min, volume 100 L. Four percent of Sabouraud dextrose agar was used for collecting fungi and plate count agar was used for collecting bacteria. After collecting samples, plates with agar were incubated at a suitable temperature for bacteria and counted within 48 hours and fungi was counted within 5 days.

The concentration of microbial was calculated as follow:

$$\text{Microbial in air (cfu/m}^3\text{)} = \frac{\text{All colonies on plate x 1000}}{\text{Flow rate (L/min) x time of sampling (min)}}$$

Measuring pulmonary function

The sweepers' pulmonary function at the end of their work shift was measured using a spirometer (DATOSPIR 120 Model D, Spain). The sweepers were informed and a demonstration was made by the researcher before the test. The Thoracic Society of Thailand's guideline of pulmonary function test was used.

In addition, the general characteristic and respiratory symptoms questionnaires were used in this study. A chest specialist and occupational medic audited the questionnaire before being used.

Testing Serum IgE

The sweepers with wheezing were selected for testing serum IgE.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16). Chi-square test or Fisher's exact test was used for analyzing any association between PM2.5, bacteria and fungi with respiratory symptoms. Pearson correlation was used for analyzing the association between PM2.5, bacteria and fungi with pulmonary function test.

Results

Concentration of PM2.5 and microbial

The samples of PM2.5 and microbial were collected from 97 sampling sites at Rajthevee district. The average concentration of PM2.5 was 373.72 μg/m^3 (SD = 165.35). A total of 194 air samples were collected for investigating bacterial counts and 194 air samples were collected for investigating fungal counts. It was found that the mean of bacterial counts at 06.00-07.00 am was 885.83 cfu/m^3 (SD = 264.69), and at 10.00-11.00 am was 741.90 cfu/m3 (SD = 245.92). The mean fungal counts at 06.00-07.00 am was 620.37 cfu/m^3 (SD = 215.01), and at 10.00-11.00 am was 462.79 cfu/m3 (SD = 202.73).

Respiratory symptoms

The respiratory symptoms of sweepers in this study were classified into five symptoms. The results were shown in Table 1.

Table 1: The respiratory symptoms of the sweepers

Symptoms*	Numbers (n = 97)	Percentages (%)
1. Cough	62	63.9
2. Phlegm	37	38.1
3. Dyspnea	34	35.1
4. Wheezing	18	18.6
5. Stuffy nose	60	61.9

* One sweeper may have more than one symptom

The 95 sweepers were tested for pulmonary function at the end of work. Only two sweepers could not be tested because one person was post-operative for a stomach surgery and another one had had a motorcycle accident. The values from the spirogram were FVC (Forced Vital Capacity), FEV_1 (Forced Expiratory Volume in one second), FEV_1/FVC ratio and $FEF_{25-75\%}$ (Forced Expiratory Flow at 25 - 75% of FVC). The classification of the severity pulmonary function impairments were graded into 4 levels as shown in Table 2. The interpretation of pulmonary function impairment was classified into two patterns: restrictive disorder as found in 33 workers (97.06%) and obstructive disorder as found in 1 worker (2.94%).

The association between PM2.5 and microbes with respiratory symptoms

The association of PM2.5 and microbes with respiratory symptoms was analyzed using Chi-square test or Fisher's exact test. The PM2.5 was associated with stuffy nose ($p < 0.01$), and associated with cough ($p < 0.05$). The data is shown in Table 3. The fungi at 06.00-07.00 am were associated with wheezing ($p < 0.05$). The data is shown in Table 4. There was no significant association between bacteria and respiratory symptoms.

The association between PM2.5 and microbes with pulmonary function.

There was no significant association found between PM2.5, bacteria and fungi with a pulmonary function test in sweepers. The data is shown in Table 5.

Table 2: Classification of the severity of pulmonary function impairment (n= 95)

Classification	FVC	FEV_1	FEV_1/ FVC	$FEF_{25-75\%}$
Normal	62 (65.26%)	88 (92.63%)	95 (100%)	95 (100%)
Mild	26 (27.37%)	5 (5.26%)	-	-
Moderate	7 (7.37%)	2 (2.11%)	-	-
Severe	-	-	-	-

Table 3: The association between concentrations of PM2.5 and respiratory symptoms (n = 97)

Symptoms	Number of worker	Concentration of PM2.5 (μg/m^3)		*p* value
		< 200	> 200	
Cough				
Yes	62 (63.9%)	3 (4.8%)	59 (95.2%)	0.033*
No	35 (36.1%)	7 (20.0%)	28 (80.0%)	(C = 0.23)
Phlegm				
Yes	37 (38.1%)	3 (8.1%)	34 (91.9%)	0.737
No	60 (61.9%)	7 (11.7%)	53 (88.3%)	
Dyspnea				
Yes	34 (35.1%)	1 (2.9%)	33 (97.1%)	0.158
No	63 (64.9%)	9 (14.3%)	54 (85.9%)	
Wheezing				
Yes	18 (18.6%)	1 (5.6%)	17 (94.4%)	0.683
No	78 (80.4%)	9 (10.3%)	70 (89.7%)	
Stuffy nose				
Yes	60 (61.8%)	2 (3.3%)	58 (96.7%)	0.006**
No	37 (38.2%)	8 (21.6%)	29 (78.4%)	(C = 0.28)

C = Contingency coefficient *Correlation is significant at *p* value < 0.05 **Correlation is significant at *p* value <0.01

Table 4: The association between concentrations of fungi and respiratory symptoms (n = 97)

Symptoms	Number of worker	Concentration of fungi 06.00-07.00 am (cfu/m^3)		*p* value
		< 1,000	> 1,000	
Cough				
Yes	62 (63.9%)	59 (95.2%)	3 (4.8%)	>0.99
No	35 (36.1%)	34 (97.1%)	1 (2.9%)	
Phlegm				
Yes	37 (38.1%)	35 (94.6%)	2 (5.4%)	0.63
No	60 (61.9%)	58 (96.7%)	2 (3.3%)	
Dyspnea				
Yes	34 (35.1%)	31 (91.2%)	3 (8.8%)	0.12
No	63 (64.9%)	62 (98.4%)	1 (1.6%)	
Wheezing				
Yes	18 (18.6%)	15 (83.3%)	3 (16.7%)	0.02*
No	79 (80.4%)	78 (98.7%)	1 (1.3%)	(C = 0.29)
Stuffy nose				
Yes	60 (61.9%)	56 (93.3%)	4 (6.7%)	0.29
No	37 (38.1%)	37 (100%)	0 (0.0%)	

C = Contingency coefficient *Correlation is significant at *p* value < 0.05

Table 5: Correlation between concentrations of PM2.5, bacteria and fungi with pulmonary function of sweepers by Pearson correlation.

Value of spirogram	Variable				
	PM 2.5	Bacteria 1st	Bacteria 2nd	Fungi 1st	Fungi 2nd
FVC					
Pearson Correlation(r)	-0.082	0.016	-0.018	0.057	0.073
p value	0.43	0.88	0.86	0.58	0.48
FEV_1					
Pearson Correlation(r)	-0.032	0.010	-0.030	0.075	0.062
p value	0.76	0.93	0.77	0.47	0.55
FEV_1/FVC					
Pearson Correlation(r)	0.125	0.004	0.009	0.053	-0.045
p value	0.23	0.97	0.93	0.61	0.66
$FEF_{25-75\%}$					
Pearson Correlation(r)	-0.065	0.036	0.017	0.146	0.081
p value	0.53	0.72	0.87	0.16	0.43

1st as sampling collection at first time (06.00-07.00 am) 2nd as sampling collection at second time (10.00-11.00 am)

Serum IgE

Among 15 sweepers who had wheezing, the mean of IgE levels was 277.07 IU/ml (range 12-1,088 IU/ml). Nine sweepers were more than the standard of 100 IU/ml. There was a correlation between poor pulmonary function and increased IgE levels.

Discussion

The concentration of PM2.5 was different in each street area of the sweepers. This might be caused by different traffic conditions, environment, construction, trading on the street and the place to rest during working (for example, sweepers rested during work near an intersection, under expressway, store, bus stop, or in a building). Wang G et al.[20] in 2002 assessed concentrations of PM2.5 at 6 sampling site in Nanjing. The average concentration of particulate matter 2.5 was 481.4 $\mu g/m^3$, the most concentrations of particulate matter 2.5 were found at heavy traffic areas. Bacteria and fungi were mostly found in the area of heavy traffic and crowded areas with lots of street venders. The dusty road was similar to the one studied by Luksamijarulkul P and Kongtip P.[21] in 2010 who analyzed the microbial count and particulate matter of 10 microns on roadside areas under skytrain stations in Bangkok. The highest concentration was at the Victory Monument area that had many people and heavy traffic.

The association of PM2.5 and microbes with respiratory symptoms was not found. Perhaps the sweepers used a veil or mask during work and worked during certain periods of time by sweeping the streets twice per work shift, and not sweeping continuously all day. This may have explained the few respiratory symptoms in sweepers. Morgenstern V et al.[22] in 2007 studied respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children in the city of Munich, Germany. Significant associations were found between the pollutant PM2.5 and sneezing, runny/stuffed nose during the first year of life (OR 1.16, 95% CI = 1.01 to 1.34) that was similar to the effects observed for the second year of life. Patel MM et al.[23] in 2010 studied concentration of black carbon and PM2.5 with respiratory symptoms in high school students in New York City and found that increments of black carbon were associated with increased wheeze, shortness of breath, and chest tightness. However, concentration of PM2.5 was not consistently associated with increment of symptoms. Mopuang M.[24] in 2005 studied concentration of PM10 and microbial count with respiratory symptoms among street vendors in Bangkok Fashion City found that the prevalence of air quality related to illnesses in studied street venders was 58%. It was shown that 28% had eye irritation symptoms, 16.67% had shortness of breath and/or sore throat, and 10.67% had running nose symptoms. The relationship between studied factors including bacterial counts and PM10 and air quality related to illnesses was analyzed, and showed no significant association ($p > 0.05$).

Many studies show that exposure to fine particulate matter would affect lung function.[25-30] However, our study proposed to test the association between the concentration of PM2.5 and microbial agents with pulmonary function in sweepers by the Pearson correlation test and it showed statistical significance. But the duration of work was associated with pulmonary function in sweepers. This might be due to the sweepers having worked twice a

day in work shifts (not continuously) and that they were protected by using a mask during sweeping. It might be that pulmonary function would be affected in the future if the sweepers are exposed to fine particulate matter and microbial agents for a longer time with high concentration. The study of Gotschi T et al.[31] in 2008 assessed FEV_1, FVC and the ratio of (FEV_1/FVC) for 9 years in following up adults from 21 European centers. Fine particles (PM2.5) were measured in 2000/2001 using central monitors. The result found no significant associations between city-specific annual mean PM2.5 and average lung function levels. The study of Pawaree K.[32] in 2004 found no association between inhalable dust and pulmonary function of sugar mill workers. In this study, there was correlation between poor pulmonary function and increased IgE levels (Table 6). Sherrill DL et al.[33] in 1999 studied total serum IgE and its association with asthma symptoms and allergic sensitization among children in USA. The result showed that both persistent wheezing and early sensitization were associated with high serum IgE levels at all ages. Shadick NA et al.[34] in 1996 studied the relationship of serum IgE level and the rate of decline of pulmonary function in Boston. The result also showed that an increment of levels of serum IgE was associated with lower levels of pulmonary function.

Table 6: Correlation between serum IgE levels with pulmonary function of sweepers by Pearson correlation.

Variable	Value of spirogram			
	FVC	FEV_1	FEV_1/FVC	$FEF_{25-75\%}$
IgE (n=15)				
Correlation(r)	-0.255	-0.314	-0.163	-0.282
p value	0.36	0.25	0.56	0.31

Conclusion

Although the results from this study revealed a relationship between concentrations of PM2.5, bacteria and fungi with some respiratory symptoms, it did not show a relationship with pulmonary function impairment among sweepers. We may need to perform a longitudinal study. We recommend to select and use personal protective equipment that could effectively protect the workers as well as finding a method to reduce the particulate matter in ambient air.

Acknowledgements

This study was partially funded by the Center of Excellence on Environmental Health, Toxicology and Management of Chemical (ETM) under the Science & Technology Postgraduate Education and Research Development Office (PERDO) of the Ministry of Education. The authors would like to thank the Public Cleansing and Public Park Section of Rajthevee District, Bangkok, and staff of the Environmental Quality and Laboratory Division of Pollution Control Department.

References

1. Cheng Y, Lee SC, Ho KF, et al. Chemically- speciated on-road PM2.5 motor vehicle emission factors in Hong Kong. *Sci Total Environ* 2010;408:1621-7.
2. Chuersuwan N, Nimrat S, Lekphet S, et al. Levels and major sources of PM2.5 and PM10 in Bangkok Metropolitan Region. *Environ Int* 2008;34:671-7.
3. Stephen G, Issarayangyun T, Liu Q. Exploring variability in pedestrian exposure to fine particulates (PM2.5) along a busy road. *Atmos Environ* 2008;42:1665-76.
4. Weinstein JP, Hedges SR, Kimbrough S. Characterization and aerosol mass balance of PM2.5 and PM10 collected in Conakry, Guinea during the 2004 Harmattan period. *Chemosphere* 2010;78:980-8.
5. Tan Z, Tay R. Sources contributing to PM2.5 in a commercial truck cabin in winter. *Transport Res Transport Environ* 2008;13:54-8.
6. Kim Oanh NT, Upadhyay N, Zhuang YH, et al. Particulate air pollution in six Asian cities: Spatial and temporal distributions, and associated sources. *Atmos Environ* 2006;40:3367-80.
7. Li X, Yue W, Iida A, et al. A study of the origin of individual PM2.5 particles in Shanghai air with synchrotron X-ray fluorescence microprobe. *Nucl Instr and Meth in Phys Res* 2007;260:336-42.
8. Pope CA, Burnett RT, Thun MJ, et al. Lung cancer, Cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132-41.
9. Pope CA, Dockery DW. Health Effects of Fine Particulate Air Pollution: Lines that Connect 2006 CRITICAL REVIEW J. *Air & Waste Manage Assoc* 2006;56:709-42.
10. Wang G, Huang L, Gao S, et al. Measurements of PM10 and PM2.5 in urban area of Nanjing, China and the assessment of pulmonary deposition of particle mass. *Chemosphere* 2002;48:689-95.
11. Vichit-Vadakan N, Ostro BD, Chestnut LG, et al. Air Pollution and Respiratory Symptoms: Results from Three

Panel Studies in Bangkok, Thailand. *Environ Health Perspect* 2001;109(suppl 3):381-7.
12. Simoni M, Scognamiglio A, Carrozzi L, et al. Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. *J Expo Sci Environ Epidemiol* 2004;14:144-52.
13. Politis M, Pilinis C, Lekkas TD. Ultrafine particulates (UFP) and health effects. Dangerous. Like no other PM? REVIEW AND ANALYSIS. *Global NEST Journal* 2008;10:439-52.
14. Maite V, Claudia L, Oscar I, et al. Personal exposure to particulate matter less than 2.5 lm in Mexico City: a pilot study. *J Expo Anal Environ Epidemiol* 2004;14:323-9.
15. Kurup V, Shen H, Banerjee B. Respiratory fungal allergy. *Microbes Infect* 2000;2:1101-10.
16. Wumiloju TO, Miller JD, Mayer MP, et al. Methods to determine the biological composition of particulate matter collected from outdoor air. *Atmos Environ* 2003;37:4335-44.
17. Adhikari A, Reponen T, Grinshpun SA, et al. Correlation of ambient inhalable bioaerosols with particulate matter and ozone: A two-year study. *Environ Pollut* 2006;140:16-28.
18. Raisi L, Lazaridis M, Katsivela E. Relationship between airborne microbial and particulate matter concentrations in the ambient air at a Mediterranean site. *Global NEST Journal* 2010;12:84-91.
19. Wasuthep B. A comparative study of lung function of street sweepers in inner and outer regions of Bangkok metropolis. A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science Mahidol University 2005.
20. Wang G, Huang L, Gao S, et al. Measurements of PM10 and PM2.5 in urban area of Nanjing, China and the assessment of pulmonary deposition of particle mass. *Chemosphere* 2002;48:689-95.
21. Luksamijarulkul P, Kongtip P. Microbial count and particulate matter levels in roadside air samples under skytrain stations, Bangkok, Thailand. *Southeast Asian J Trop Med* 2010;41:678-84.
22. Morgenstern V, Zutavern A, Cyrys J, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occup Environ Med* 2007;64:8-16.
23. Patel MM, Chillrud SN, Correa JC, et al. Traffic-Related Particulate Matter and Acute Respiratory Symptoms among New York City Area Adolescents. *Environ Health Perspect* 2010;118:1338-43.
24. Mopuang M. Microbial air quality and particulate matter and related illnesses among street venders in Bangkok fashion city. A thesis submitted in partial fulfillment of the requirements for the degree of master of science Mahidol University, 2005.
25. Neubergera M, Schimek GM, Horak F, et al. Acute effects of particulate matter on respiratory diseases, symptoms and functions: epidemiological results of the Austrian Project on Health Effects of Particulate Matter (AUPHEP). *Atmos Environ* 2004; 38:3971-81.
26. Jedrychowski W, Perera PF, Whyatt R, et al. Wheezing and lung function measured in subjects exposed to various levels of fine particles and polycyclic aromatic hydrocarbons, *CEJ Med* 2007;2:66-78.
27. Kasamatsua J, Shimab M, Yamazakic S, et al. Effects of winter air pollution on pulmonary function of school children in Shenyang, China. *Int J Hyg Environ Health* 2006;209:435-44.
28. Gauderman JW, Gilliland FG, Vora H, et al. Association between Air Pollution and Lung Function Growth in Southern California Children. *Am J Respir Crit Care Med* 2002;166:76-84.
29. Trenga CA, Sullivan JH, Schildcrout JS, et al. Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest* 2006; 129:1614-22.
30. Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, et al. Air Pollution, Airway Inflammation, and Lung Function in a Cohort Study of Mexico City Schoolchildren. *Environ Health Perspect* 2008;116:832-8.
31. Gotschi T, Sunyer J, Chinn S, et al. Air pollution and lung function in the european community respiratory health survey. *Int J Epidemiol* 2008; 37:1349-58.
32. Pawaree K. A comparative study of dust exposure to pulmonary function impairment of sugar mill worker. A thesis submitted in partial fulfillment of the requirements for the degree of master of Science Mahidol University, 2004.
33. Sherrill DL, Stein R, Halonen M, et al. Total serum IgE and its association with asthma symptoms and allergic sensitization among children. *J Allergy Clin Immunol* 1999;104:28-36.
34. Shadick NA, Sparrow D, O'Connor GT, et al. Relationship of serum IgE concentration to level and rate of decline of pulmonary function: the Normative Aging Study. *Thorax* 1996 ;51:787-92.

Efficacy of the Comprehensive Headache Clinic at the Bangkok Hospital: The First 6 Months' Report

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Keywords:
headache clinic, primary headache, secondary headache, migraine, HIT-6, Bangkok hospital

OBJECTIVE: To study the efficacy of the Comprehensive Headache Clinic.

MATERIALS AND METHODS: There were 302 patients who presented at the Headache clinic between July 2011 and January 2012. The efficacy of treatment was evaluated with questionnaires including Headache Impact Test™ (HIT-6™), Pain Score, and Headache frequency per week.

RESULTS: Of the 302 cases, 113 (37.42%) completed a four-week followup. The efficacy of treatment was analysed by using Paired T-test. The impact of headache symptoms, the severity, and the frequency of headache per week had decreased significantly from a statistical point of view. HIT-6™ Score day 0 = 62±5.66, day 28 = 52±7.15 ($p < 0.01$, t = 2.13), Pain Score day 0 = 7±1.92, day 28 = 3±2.46 ($p < 0.01$, t = 1.96), Headache frequency per week day 0 = 3±2.68, day 28 = 1±1.87 ($p < 0.01$, t = 2.58).

CONCLUSION: Findings from the Comprehensive Headache Clinic significantly demonstrate efficacy in reducing severity, frequency, and the impact of headache symptoms on patients' daily lives.

Headache is the primary symptom that brings the patient to see the neurologist. A survey by the World Health Organization (WHO) in 2007 found that the incidence of headache affected up to 47% of the population worldwide.[1] These headaches not only cause annoyance but also influence the quality of life.

A survey by David B. Matchar and colleagues[2] found that certain types of headache, such as migraine, could cause inability to work in more than 85% of patients. If calculated in terms of direct, economic loss the sum was estimated to be as much as USD 13 billion annually, and WHO had stated that headache was a health problem affecting 1 in 20 working people in the world.[3]

The International Headache Society (IHS) has divided headache into three groups, namely, 1) Primary headaches, 2) Secondary headaches and 3) Cranial neuralgias, central and primary facial pain, and other headaches.[4]

Primary headaches are caused by abnormalities of the brain and nervous system itself. No abnormality can be detected by radiological and laboratory tests. Examples of primary headaches include migraine headaches, tension type headache, and trigeminal autonomic cephalalgias (TACs) such as cluster headache, etc.

Secondary headaches are headaches caused by internal or external conditions such as brain tumor, cerebral hemorrhage, cerebral venous thrombosis, head injury, sinusitis, eye disorders, abnormalities of the teeth or temporomandibular joints, infectious diseases, etc. It is necessary for this group to have additional investigations such as Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), and blood tests.

Cranial neuralgias, central and primary facial pain, and other headaches are from other causes. For example, headaches caused by abnormalities of the 5th or 9th cranial nerves or an inflammation of occipital nerves, etc.

Approximately 20% of the patients who visited the Neuroscience Center at Bangkok Hospital presented headaches as a primary symptom. Therefore, the Comprehensive Headache Clinic has been established and initiated a multidisciplinary team made up of headache specialists, nurses, rehabilitation doctors, physical therapists, clinical psychologists, and medical acupuncturists who can provide comprehensive assessment, treatment and headache education in accordance with international standards.

The aims of the Comprehensive Headache Clinic are to reduce the frequency and severity of the symptoms, offer effective treatments according to international standards, decrease the overuse of pain medications, enhance quality of life, and educate patients and their families so that they are able to take care of themselves and manage their headaches appropriately.[5]

Treatment guidelines in the Comprehensive Headache Clinic

Pharmacologic treatment

Acute Treatment

1. Acute pain medications are administrated intravenously or orally as indicated, according to the standard treatment guidelines from the American Academy of Neurology and European Federation of Neurology Society.[6-10]
2. Occipital nerve block, Trigger point injection, and/or Peripheral nerve block are performed as indicated.[11,12]

Prophylactic Treatment

1. Prophylaxis medications are administrated as indicated, according to standard treatment guidelines from the American Academy of Neurology and European Federation of Neurology Society.[6-10]
2. Occipital nerve block or Botulinum toxin injection are performed as indicated.[12,13]

Non-pharmacologic treatments[14,15]

1. Acupuncture
2. Rehabilitation
3. Biofeedback
4. Cognitive behavioral therapy, Relaxation training, Depression and anxiety screening.

Materials and Methods

Headache Impact Test™ (HIT-6™), the pain score, and the headache frequency per week were used to evaluate the progression of clinical and therapeutic responses in each patient.

Headache Impact Test™ (HIT-6™) Version 1.1[15]

The test was developed to help patients to communicate their feelings about headache especially in terms of the severity of symptoms and the impact on their daily life. There are 6 questions for patients to answer according to how they feel and the scores will be calculated. The symptoms of headache are divided into 3 levels: Mild score of 50-55 (the headache had a minimum impact on daily life and did not require medical attention), Moderate score of 56-59 (the headache had a moderate impact on daily life and required medical attention), Severe score of ≥ 60 (the headache had severe impact on daily life and required urgent treatment).[16] HIT-6™ record form and interpretations are shown in Table 1.

Pain Score

The pain assessment was graded on a numerical rating scale (NRS) with a score of 0-10. There were 4 levels starting from 0 = no pain, 1-3 = mild pain, 4-6 = moderate pain, and 7-10 = severe pain.[17]

Headache frequency per week

The number of headache attacks per week was asked.

Statistical analysis

Patient characteristics were described as absolute numbers, percentage, mean, and standard deviation (SD).

Inferential statistics was used with Paired sample T-test to determine the headache scores before treatment (Day 0) versus after treatment (Day 28).

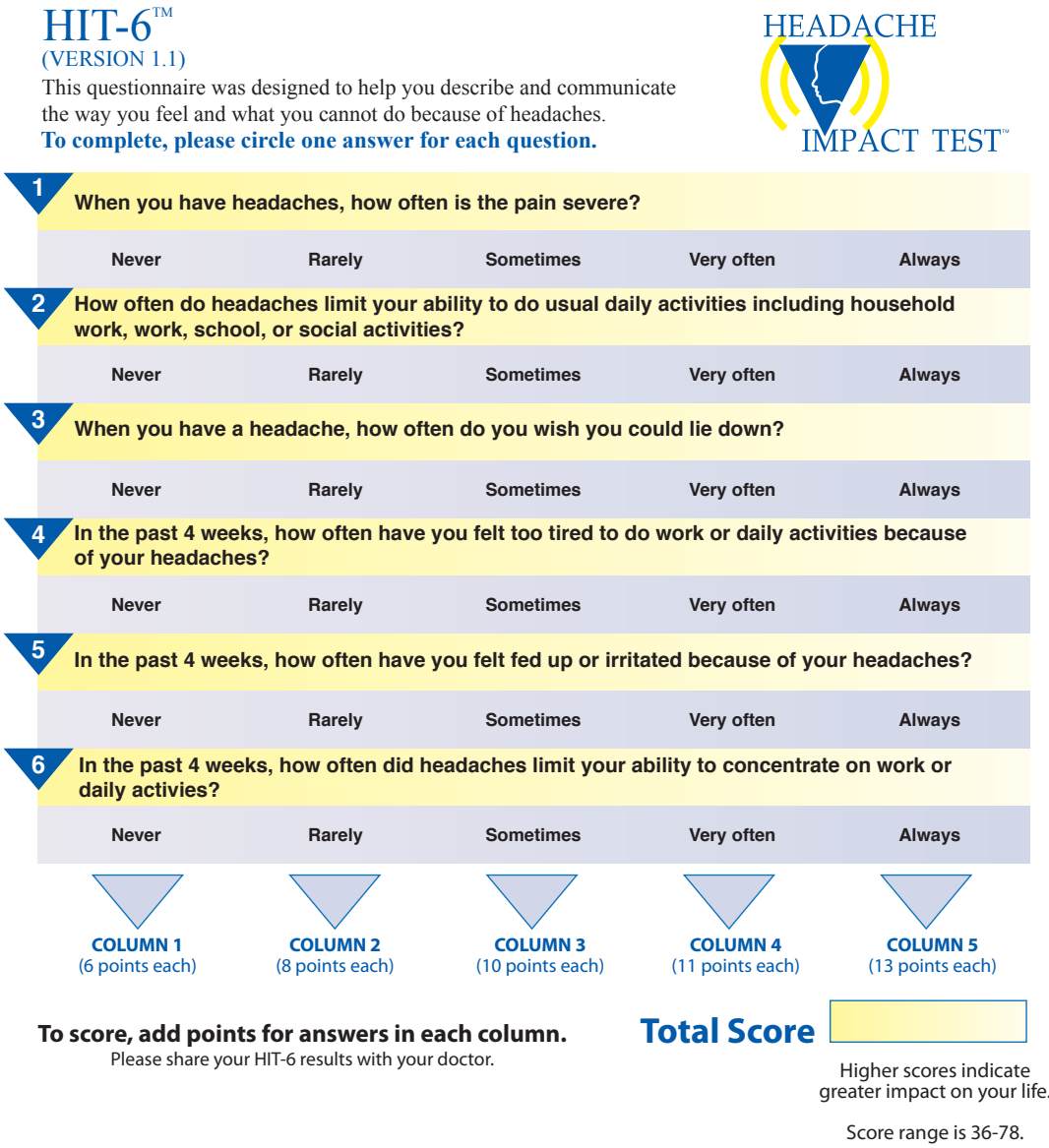

***Figure 1**: The Headache Impact Test™(HIT-6™) form.*

Table 1: The Headache Impact Test™(HIT-6™) interpretation.

Score	Level	Mean
50-55	Mild	Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.
56-59	Moderate	Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.
≥ 60	Severe	Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers.

Table 2: Patient characteristics and Headache subtypes

Details	Thai (n = 237)	Foreign (n = 65)	Total (n = 302)
Sex			
Male	59 (19.54%)	28 (9.27%)	87 (28.81%)
Female	178 (58.94%)	37 (12.25%)	215 (71.19%)
Age (years)			
15-35	132 (43.71%)	26 (8.61%)	158 (52.32%)
36-55	84 (27.81%)	25 (8.28%)	109 (36.09%)
56-75	18 (5.96%)	12 (3.98%)	30 (9.94%)
76-95	3 (0.99%)	2 (0.66%)	5 (1.65%)
Average age (Mean ± SD)	**37.15 ± 13.12**	**40.53 ± 14.21**	**37.82 ± 13.36**
Headache classifications			
Primary Headache	185 (61.26%)	46 (15.23%)	231 (76.49%)
Secondary Headache	29 (9.59%)	16 (5.30%)	45 (14.89%)
Cranial Neuralgia, Central and Primary Facial Pain and Other Headaches	23 (7.62%)	3 (1.00%)	26 (8.62%)

Results

Since the opening of the Comprehensive Headache Clinic at Bangkok Hospital on July 2011 there were 302 patients with headaches that were treated in the clinic during the first 6 months (until January 2012).

Population

Of the 302 patients, 237 (78.5%) were Thai, 65 (21.52%) were overseas visitors, 87 (28.81%) being male and 215 (71.19%) being female. Age range between 15 and 35 years in 52.32% and over 35 years old in 47.68%.

Headaches were classified, according to the International Headache Society (IHS), into:

Primary headache in 229 cases (75.83%): migraine headache 168 cases (73.36%), tension type headache 42 cases (18.34%), other primary headaches 16 cases (6.99%), and cluster headache 3 cases (1.31%).

Secondary headache in 47 cases (15.56%): cervicogenic headache 30 cases (63.83%), medication overuse headache 11 cases (23.40%), and post-traumatic headache 3 cases (6.38%) and other secondary headaches 3 cases (6.38%).

Cranial Neuralgia, central and primary facial pain and other headache accounted for 26 cases (8.61%): occipital neuralgia 8 cases (30.77%), other primary facial pain 7 cases (26.92%), other cranial neuralgia 6 cases (23.08%), and trigeminal neuralgia 5 cases (19.23%). Patient characteristics and headache subtypes were shown in Table 2.

From 302 patients, there were 113 cases (37.42%) who completed a four-week followup period. Those that did not come for followup include 111 cases (36.75%) with mild headache that did not require any further treatment; 63 cases (20.86%) did not keep their appointment and when we called to check how they were, they said that their headaches had improved a lot; 15 cases (4.97%) continued their treatment abroad.

Those with completed a four-week followup were asked to answer three evaluation forms. Comparisons between the first day of treatment (Day 0) and the last day after 4 weeks of treatment, using the Paired T-test, showed a statistically significant decrease in the impact of headache, the severity of headache, and the frequency of headache per week. HIT-6™ Score day 0 = 62±5.66, day 28 = 52±7.15 ($p < 0.01$, t = 2.13), Pain Score day 0 = 7±1.92, day 28 = 3±2.46 ($p < 0.01$, t = 1.96), Headache frequency per week day 0 = 3±2.68, day 28 = 1±1.87 ($p < 0.01$, t = 2.58) (Table 3 and Figure 2).

Discussion

From our Comprehensive Headache Clinic, on the first day (Day 0) patients had an average headache score (HIT-6™) of 62 (severe headache impact), average pain score of 7 (severe pain score) and the average headache frequency score was 3 times per week (high frequency). After the 4 weeks treatment of headache, we found that the severity of headache had improved to mild degree and the average headache score (HIT-6™) decreased to 52 (mild headache impact), the average pain score was reduced to 3 (mild pain score), and the average of

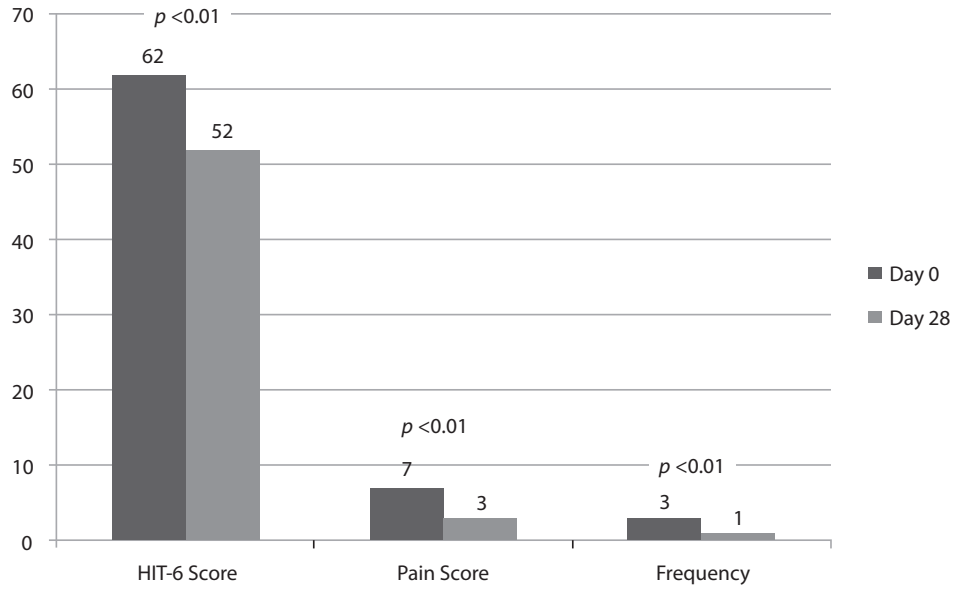

Figure 2: *Graph shows the comparison of the headache score on Day 0 vs. Day 28*

Table 3: Comparison of headache scores on Day 0 vs. Day 28

Parameter	Mean	SD	t	*p*-value
HIT-6™ Score				
Day 0	62	5.66	2.13	< 0.01
Day 28	52	7.15		
Pain Score				
Day 0	7	1.92	1.96	< 0.01
Day 28	3	2.46		
Frequency				
Day 0	3	2.68	2.58	< 0.01
Day 28	1	1.87		

headache frequency was reduced to once per week (low frequency). As a result, these patients had a significant increase in their quality of life due to reduced suffering from headaches.

Using HIT-6™ score, pain score, and headache frequency per week for treatment evaluation helps patients to communicate more effectively with their physicians. As a result, treatment can be given more effectively and patients can better notice the progression of treatment.

Sauro KM, et al.[18] showed in their trial of the Calgary Headache Assessment and Management Program (CHAMP) that the multidisciplinary team were able to significantly reduce the HIT-6™ score from 63.6 to 58.2 ($p < 0.001$) in three months' duration.

We propose that by forming a similar Comprehensive Headache Clinic with a multidisciplinary team helps us to improve assessment and treatment of patients with a holistic approach which will accentuate the effectiveness of treatment.

Conclusion

A multidisciplinary team in the Comprehensive Headache Clinic can improve the patient's quality of life by significantly reducing the severity of headache, the frequency, and the impact of headache symptoms. Headache scores will help the patient and physician to reach a common understanding.

References

1. Silberstein SD, LiPton RB, Dodick DW, et al. Wolff 's Headache and Other Head Pain. United States of America: Oxford University Press, Inc. 2008.
2. Matchar DB, Harpole L, Samsa GP, et al. The Headache Management Trial: A Randomized Study of Coordinated Care. *Headache* 2008;48:1294-310.
3. Stewart WF, Lipton RB, Kolodner KB, et al. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999; 19:107-14.
4. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia* 2004; 24:1-160.
5. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-62.
6. Holland S, Silberstein SD, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1346-53.
7. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 2012;52:930-45.
8. Evers S, Afra J, Frese A, et al. European Federation of Neurological Societies. EFNS guideline on the drugtreatment of migraine-revised report of an EFNS taskforce. *Eur J Neurol* 2009;16:968-81.
9. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache –Report of an EFNS task force. *Eur J Neurol* 2010;17:1318-25.
10. Francis GJ, Becker WJ, Tamara M. Pringsheim. Acute and preventive pharmacologic treatment of cluster headache. *Neurology* 2010;75:463-73.
11. Ashkenazi A, Blumenfeld A, Napchan U, et al. Interventional Procedures Special Interest Section of the American. Peripheral Nerve Blocks and Trigger Point Injections in Headache Management-A Systematic Review and Suggestions for Future Research. *Headache* 2010;50:943-52.
12. Tobin J, Flitman S. Occipital nerve blocks: when and what to inject? *Headache* 2009;49:1521-33.
13. Blumenfeld A, Silberstein SD, Dodick DW, et al. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache* 2010;50:1406-18.
14. Nicholson RA, Buse DC, Andrasik F, et al. Nonpharmacologic treatments for migraine and tension-type headache: how to choose and when to use. *Curr Treat Options Neurol* 2011;13:28-40.
15. Kosinki M, Bayliss MS, Bjorner JB, et al. A six item short form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12:963-74.
16. Andrasik F. Biofeedback in headache: an overview of approaches and evidence. *Cleve Clin J Med* 2010;77:S72-6.
17. The study of pain association in Thailand: The Development of Acute Pain. Edition 1, Bangkok.
18. Sauro KM, Becker WJ. Multidisciplinary treatment for headache in the Canadian healthcare setting. *Can J Neurol* Sci 2008;35:46-56.

Late Anterior Hip Dislocation after Metasul Metal-on-Metal Total Hip Arthroplasty for 13 Years: A Case Report

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Keywords:
total hip arthroplasty, hip dislocation, hip replacement

Hip dislocation after total hip arthroplasty can be classified into anterior and posterior dislocation, and immediate post-op and late dislocation. The most common dislocation is posterior dislocation which depends on a primary surgical approach because the resection of the posterior capsule takes part in the direction of hip dislocation. However, surgical technique, components orientation and soft tissue tension have a major role in hip stability. We report a case of a 52-year-old man who suffered from an unstable hip after having a normal hip functional score for 13 years without any traumatic events. Radiographic findings did not show any sign of loosening or radiolucency. The causes of late hip dislocation and treatment are also described.

Case Report

A 52-year-old man who worked as a flight attendant developed chronic right hip pain for 13 years with a diagnosis of avascular necrosis of the right femoral head. After the efforts of many conservative treatments for 6 months, the pain was in progression. The first surgeon decided to do a femoral head decompression. After the surgery, he could not walk well, and had slipped and fallen down many times. Then a derotation proximal femoral osteotomy was further performed. However, the patient developed uneven pain occasionally and later progressed to constant pain on his right hip. He decided to seek a second opinion. The x-ray showed segmental collapse of the right femoral head with a normal left hip. Total hip replacement (THA) was performed with Sportono acetabular cup and stem with 28mm Metal-on-Metal (MoM) articulation. After the successful operation, the patient could go back to work on board. He could sit low into a squat position and stand upright normally. He had a very active normal life with full functional score for 13 years after the right THA.

One and a half years later, he felt a clunk inside his right groin with minimal pain. He could do hip reduction by himself. There were about 8-9 times in a year that he had hip subluxation and spontaneous reduction. The most common position when he sensed the clunk was sitting with the right hip crossing the leg with the knee in flexion and a fully external rotation. He did self reduction by standing up and turning his foot in internal rotation.

One month ago, when standing up from a chair, he immediately felt severe pain in his right hip. Without any traumatic event, at that time he could not do self reduction. Then he was brought to the hospital. The x-ray confirmed that he had right hip prosthesis dislocation. Closed reduction under general anesthesia was successfully done without difficulty and it was stable at 75-80 degrees of flexion without any dislocation. The pre-operative

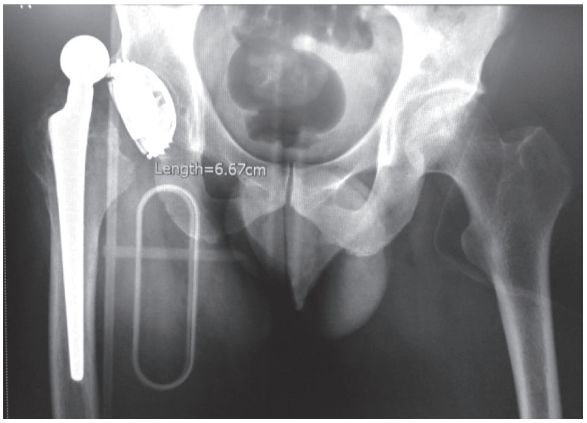

***Figure 1A**: Nontraumatic anterior hip dislocation fully exposed lesser trochanter in external rotation. Femoral stem and cup shell were still well fixed without any sign of osteolysis.*

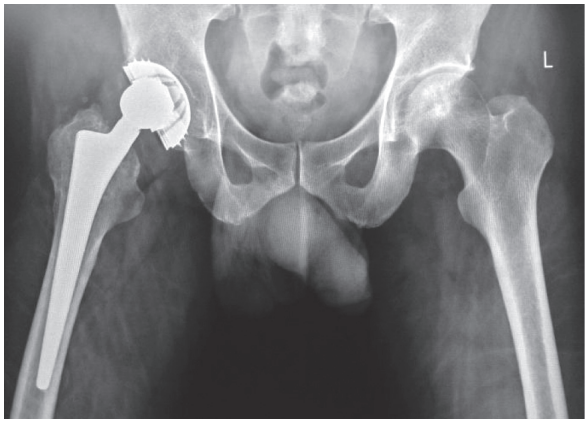

***Figure 1B**: After close reduction head was well seated into metal liner, both leg lengths were equal. Soft tissue tension was proper after telescoping test.*

x-ray showed hip dislocation and the post-operative x-ray after reduction at 75-80 degrees of flexion demonstrated normal position of the right femoral head dislocation (Figure 1). Despite successful hip reduction with some degree of stable hip, the patient still felt very unconfident with his right hip, he was afraid that if his hip dislocated again while he was working on board, it would be very painful and no one could do hip reduction for him.

Approaching and Pre-operative Planning

According to the history of subluxation and the incidence of dislocation after having normal function after 12 years post THA, a critical analysis of the post reduction x-ray was done. There was no sign of component loosening in both acetabulum and femoral stem components. Femoral component position was normal without any subsidence. Acetabular cup had about 65 degrees abduction angle with no excessive abnormal rotation. No positional change was detected. Considering that hip dislocation was not immediately post-operative event, but happened 13 years later, the high abduction cup angle should not be the major cause of this late hip dislocation. From the x-ray, both legs were equal in length so we could expect that soft tissue tension was normal and should not be the cause of hip dislocation in this patient.

After a meticulous study of the x-ray, we could detect a small change on the x-ray and this was a very important point that led to the definitive treatment. In Figure 2, the arrow sign shows the evidence of migration of metal liner over polyethylene liner. However, we could not evaluate the status of the locking mechanism between polyethylene and metal back shell. It might be broken already and this was not known until we were in the operative field. The positional change in metal liner that changed the degree of anteversion can explain why he had late hip dislocation.

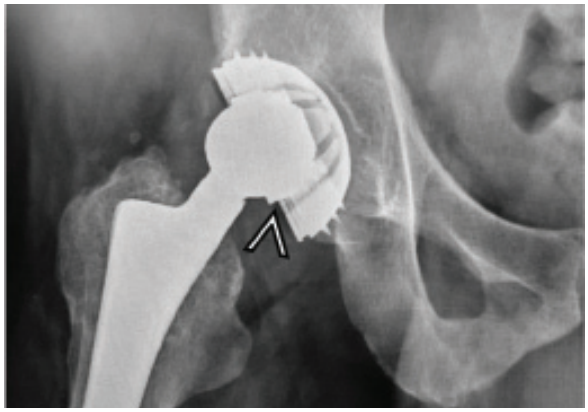

***Figure 2**: From a careful analysis on the post reduction x-ray, elevated metal liner was seen at the inferior junction of metal-polyethylene liner interface.*

During the pre-operative preparation, Metasul liner had stopped marketing and there had been no more implant stock in Thailand for 8 years, so the order for these liners from Switzerland had to be done. From the x-ray, the metal shell was a Spotorno cup and the distributor still had the equipment available.

The causes for the hip dislocation in this case should be from the separated bonding between metal liner and polyethylene and the migration of the metal liner over polyethylene that changed the degree of anteversion, so the metal liner could not cover the femoral head in the extreme position. However, we did not know whether or not the locking mechanism between the metal cup shell and the polyethylene liner was dislodged. The final decision should be made based on intra-operative findings. With this limited information, we prepared a step-by-step approach algorithm. The decision to use the posterior approach instead of the

previous anterior approach, was due to less scar tissue remaining and an easy to identify anatomical structure, was determined. In addition, the preservation of the anterior structure may decrease the incidence of the anterior hip dislocation in this revision surgery. If the cup shell had no sign of loosening after removal of the liner, only the polyethylene cup of the same size would be replaced by turning into the thread of the cup shell. In case the cup shell was loosened, acetabulum cup revision with new metal shell and new x-link polyethylene would be replaced. If a femoral component was loosened, we planned to perform femoral stem revision with a longer stem and 32 or 36 femoral head with a new bearing surface such as metal on x-link polyethylene.

Results

During the operation, the patient was placed in the lateral decubitus position. A lateral curvilinear over greater trochanter incision was done. Tensor fascia lata and previous fibrous tissue were split. Short external rotators were cut step by step then a posterior capsulotomy was performed. The femoral component was well fixed. Soft tissue and granulation tissue with very little metallosis around the acetabular cup were removed as shown in Figure 3. Then the liner was removed from the metal shell by using a special removal instrument twisting in an anti-clockwise direction, as shown in Figure 4 and 5. The spiral lock mechanism was checked and found that the locking system was still in good condition. New polyethylene was inserted into the spiral lock by a clockwise twist. The femoral head was then reduced and hip stability was tested. Closure of the wound was performed layer by layer with a vacuum drain inserted. The next day after surgery, the patient was allowed to have a full weight bearing walk with axillary crutches. He was discharged after 4 days of hospital admission and continued receiving physical therapy. After 1 month, he went back to work for the airline.

***Figure 3**: Shows a small amount of necrotic tissue around the impingement area. Very little metallosis is detected.*

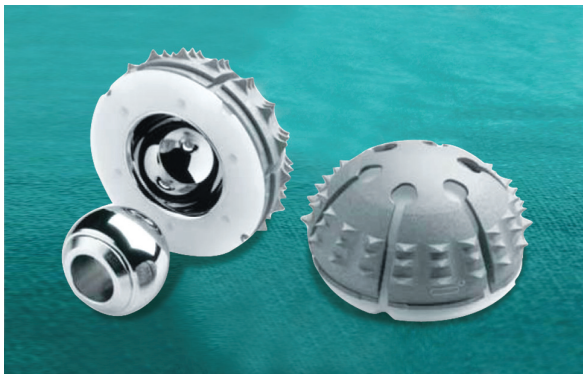

***Figure 4A**: Spotorno metal shell cup and liner.*

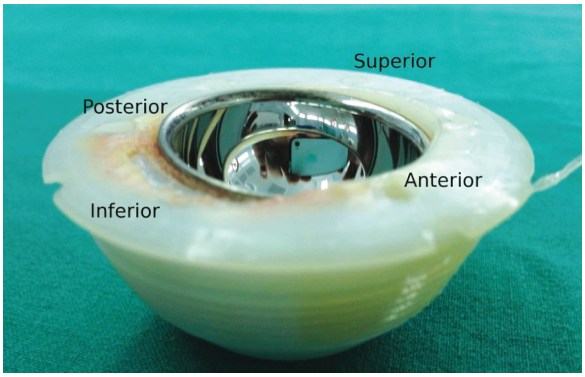

***Figure 4B**: Extracted Metasul liner shows inferior polyethylene surface with laminated wear. The change of metal liner position means polyethylene and metal liner disintegrated; however, they are well fixed together. The metal liner at anterosuperior is sunk. In the opposite direction, the posteroinferior border of metal liner is elevated.*

***Figure 5**: The back of the liner does not show wear out of locking mechanism. A small piece on the right of the liner comes from the extraction procedure.*

Table 1: Report of the number and causes of acetabular component revision

Study	Year	N	Mean follow up (years)	Acetabular component revision (N)	Cause of acetabular component failure
Streit MR[11]	2012	89	12	2	1 recurrent dislocation 1 unexplained pain
Hwang KT[12]	2012	227	12.3	2	Aseptic loosening
de Witte PB[13]	2011	102	11.8	10	9 aseptic loosening 1 recurrent dislocation
Müller LA[14]	2011	67	17	4	Aseptic loosening
Terré RA[15]	2010	171	17.9	19	Aseptic loosening

Discussion

Metal-on-metal (MoM) bearings in hips is not a new concept. Many long-lasting, successful cases more than 20 years with MoM were reported in several studies such as McKee-Farrar's prosthesis[1,2] and Peter Ring's prosthesis.[3] However, MoM was not popular because of the higher failure rate when compared to metal-on-polyethylene bearing (MoP). The major causes were big head and big neck designs that follow the design concept of Austin Moore prosthesis, so these designs could easily make impingement with the metal cup. One of the other causes was that metallurgy technology and quality control during that time were not as good as those at present. MoM hip with Metasul liner is the only 28mm head articulate with composite metal-polyethylene liner on the market that had a very successful track record,[4,5] especially when used with cementless acetabular and stem.[6] Spotorno cup is a cementless cup that was introduced and implanted in 1985. This special design features the basic conical shape and the large surface area of the self-tapping thread lamellae that give the cup excellent properties in terms of primary stability, biomechanics and secondary stability without press-fit or screw fixation.[7]

The cup placement in this case was 65 degrees abduction (Figure 2). Surgical technical limitation was a major cause in this vertical alignment. These constraints included the inadequate medial reaming and the cup placement which relied on the superolateral rim of the acetabulum. Retrospectively, if the surgeon just did more medial reaming, the abduction angle would be 40-45 degrees. In the case that abduction angle is more than 55 degrees, wear rate would increase up to 10 times within 5 years of implantation when compared to abduction angle at 45 degrees.[8] However, this patient used metalsul liner that was 28mm head MoM. The intra-operation findings showed very little metalosis (Figure 3). This evidence was correlated with the x-ray findings at 13 years postoperation, where there was no radiolucency or loosening signs in both femoral and cup shell components.

If this case used nearly anatomical head size such as hip resurfacing or big head MoM THA, worse results would be expected from high metal wear because in the high abduction angle cup, the fluid lubrication phenomenon would not occur but the boundary contact would happen instead.[9] The high level of metal ion production would have subsequent results of pseudo-tumor, early osteolysis and finally component loosening. A smaller head, like a 28mm head even in a normal abduction angle will not show the fluid lubrication phenomenon because it will perform much better when the diameter of a metal cup is more than 50mm (metal head size more than 44mm).[10] The evidence from these findings also supports that the smaller 28mm head MoM like Metasul tolerates volumetric wear better in a high abduction cup angle when compared to a big head MoM. On the other hand, metalsul does not rely on the fluid lubrication phenomenon and the boundary contact wear is lower in the small head metalsul than in the big head hip resurfacing.

There are studies reporting the failure of the acetabular cup in the Spotorno system. Most of them are aseptic loosening (Table 1). To our current knowledge, there is no report of the mode of failure like this case. The major cause of failure in this case was the impingement that resulted in hip dislocation. Even the cup abduction angle was too high but the anteversion was also low which provided stability of the artificial hip along 12 years of usage.[16] However, the high cup abduction angle also produced impingement at the anteroinferior sector of the cup especially when this patient worked in a squatting position on an airplane. This impingement force was not strong enough to make the metal cup shell immediately change its position because of the very strong initial bonding developed from the conical thread design of Spotorno and also the good bonding between the liner thread and inside the metal cup shell (Figure 5). When repetitive impingement happened again and again from routine airline work with a squatting position, the weaker de facto bonding between the inside metal liner and the outer polyethylene liner was dissociated. The anteroinferior sector of the inside metal liner changed its position and sunk

beneath the polyethylene liner. The repetitive impingement still happened; however, it impinged on the anteroinferior polyethylene liner instead of the metal liner because the metal liner had already sunk. This was why the laminated polyethylene wear was found at the anteroinferior sector in the same direction as the sinking metal liner. This anteroinferior defect was the cause of an unstable anterior hip dislocation in this patient. Fortunately, changing the inside metal liner was detected at the x-ray as in Figure 2. The appropriate pre-operative planning was prepared from this little change in the x-ray findings.

In conclusion, the major cause of the 13-year-later dislocation in well fixed cementless Spotorno total hip arthroplasty system in this case, was the anteroinferior impingement that later made an anterior defect. Despite the very high vertical cup placement (rim loading), there was no sign of massive metal wear in the standard head (28 mm) MoM bearing surface. This indicates the successful MoM articulation in a young active patient. A spiral thread design at the back of the Spotorno and at the polyethylene liner to the metal shell interface provide very high stable bonding both initially and subsequently.

Conflict of interest statement

The authors claim no conflict of interest associated with the manuscript.

References

1. Jacobsson SA, Djerf K, Wahlström O. Twenty-year results of McKee-Farrar versus Charnley prosthesis. *Clin Orthop Relat Res* 1996;329:60-8.
2. Brown SR, Davies WA, DeHeer DH, et al. Long-term survival of McKee-Farrar total hip prosthesis. *Clin Orthop Relat Res* 2002;402:157-63.
3. Ring PA. Press-fit Prosthesis Clinical Experience. In Freeman MAR, Reynolds DA (eds) Osteoarthitis and the Young Adult Hip. Edinburgh: Churchill Livingstone, 1989:220-32.
4. Eswaramoorthy V, Moonot P, Kalairajah Y, et al. The Metasul Metal-on-Metal articulation in primary total hip replacement: clinical and radiological results at ten years. *J Bone Joint Surg Br* 2008;90:1278-83.
5. Delaunay CP, Bonnomet F, Clavert P, et al. THA using Metal-on-Metal articulation in active patients younger than 50 years. *Clin Orthop Relat Res* 2008;466:340-6.
6. A Grubl, C Chiari, M Bruber. Cementless total hip arthroplasty with a taperd, rectangular titanium stem and threaded cup. A minimum ten-year follow up. *J Bone Joint Surg Am* 2002; 84:425-31.
7. Zweymuller KA, Steindl M, Schwarzinger U. Good stability and minimal osteolysis with a biconical threaded cup at 10 years. *Clin Orthop Relat Res* 2007;463:128-37.
8. De Haan R, Pyttyn C, Gill HS. Correlation of inclination of acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br* 2008;90:1291-7.
9. Jin ZM. Analysis of mixed lubrication mechanism in Metal-on-Metal hip joint replacements. *Proc Inst Mech Eng H* 2002;216:85-9.
10. Chan FW, Bobyn JD, Medley JB, et al. The Otto Aufranc Award. Wear and lubrication of metal-on-metal hip implants. *Clin Orthop Relat Res* 1999;369:10-24.
11. Streit MR, Schröder K, Körber M, et al. High survival in young patients using a second generation uncemented total hip replacement. *Int Orthop* 2012;36:1129-36.
12. Hwang KT, Kim YH, Kim YS, et al. Total Hip Arthroplasty Using Cementless Grit-Blasted Femoral Component: A Minimum 10-Year Follow-Up Study. *J Arthroplasty* 2012;27:1554-61.
13. de Witte PB, Brand R, Vermeer HG, et al. Mid-term results of total hip arthroplasty with the Cement-Less Spotorno (CLS) system. *J Bone Joint Surg Am* 2011;93:1249-55.
14. Müller LA, Wenger N, Schramm M, et al. 17-year follow -up of the rough-blasted threaded Weill cup in uncemented total hip arthroplasty. *Arch Orthop Trauma Surg* 2011;131:557-61.
15. Terré RA. Estimated survival probability of the Spotorno total hip arthroplasty after a 15- to 21-year follow-up: one surgeon's results. Hip Int 2010;20:70-8.
16. Goergen TG, Resnick D. Evaluation of acetabular anteversion following total hip arthroplasty: necessity of proper centering. *Br J Radio* 1975;48:259-60.

Case Report

Non Conspicuity of Biliary Tract by Magnetic Resonance Cholangiopancreatography (MRCP) in Hemobilia post Sphincterotomy

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Keywords:
hemobilia, MRCP, ERCP, sphincterotomy, the sphincter of Oddie

The diagnosis of hemobilia by non invasive magnetic resonance cholangiopancreatography (MRCP) can be difficult to interpret due to the technical procedures involved, surrounding tissue, respiratory artifacts and other factors. On many occasions, endoscopic retrograde cholangiopancreatography (ERCP) is attempted before MRCP. We presented a case of hemobilia identified using two dimension (2D) and three dimension (3D) MRCP findings to inform the physician in cases when ERCP alone cannot predict this condition.

Case Report

A 45-year-old man developed chest pain for one day with no discernable underlying cause. ECG showed transient ischemia. The coronary angiogram showed severe arteriosclerosis with a narrowing of the left anterior descending (LAD) and circumflex arteries. Coronary arterial stents were performed successfully. He was administered thrombolytic drugs post-stenting. The blood examination including coagulation was within normal limits. After stenting for 48 hours, he developed fever, jaundice and colicky pain, and acute cholecystitis with ascending cholangitis. A stone in the common bile duct (CBD) was diagnosed clinically. A Computed Tomography (CT) without contrast study showed a suspected stone in the CBD. The patient underwent ERCP, but no stone could be seen in the CBD with turbid bile. A sphincterotomy was performed. Twenty four hours later he developed severe colicky abdominal pain which required morphine medication. MRCP was performed using two techniques namely:

1. Single-Short Rapid Acquisition with Relaxation Enhancement (RARE) (Figure 1). This study showed non conspicuity of biliary tract and gallbladder but the pancreatic duct was depicted.

2. Multiple-Slice Half-Fourier Acquisition Single-short Turbo-spin Echo (HASTE) showed the same finding as the RARE technique (Figure 2).

The patient then underwent an explorative cholecystectomy and ERCP was performed intraoperatively. ERCP showed a bloody bile stain with a blood clot from the opening of the common bile duct. He had an uneventful post operative course.

Discussion

The non invasive method to view the pancreatobiliary tract by MRCP is difficult because of the structures located in multiple planes and varying size. The content in the biliary tract is variable with viscosity, sludge, stones and/or blood clots. In addition, surrounding tissue contains: fluids such as stomach juice, duodenal

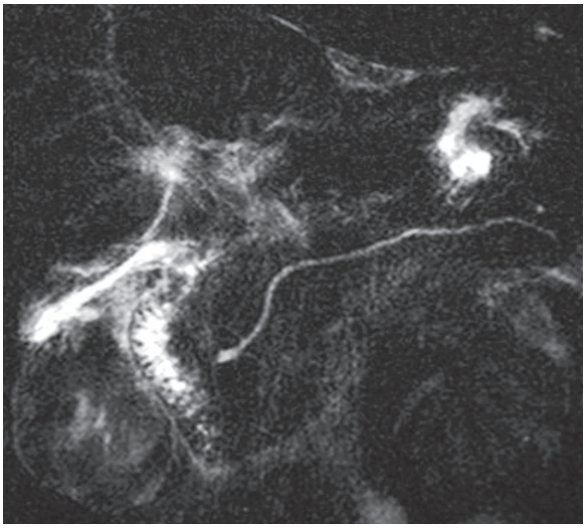

Figure 1*: RARE technique shows non conspicuity of gall bladder, intrahepatic ducts and common bile duct (CBD). It depicts the pancreatic duct.*

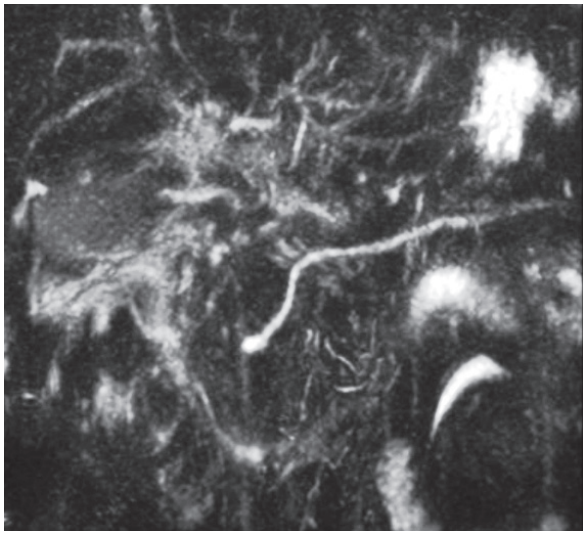

Figure 2*: HASTE technique shows the same result as the RARE technique.*

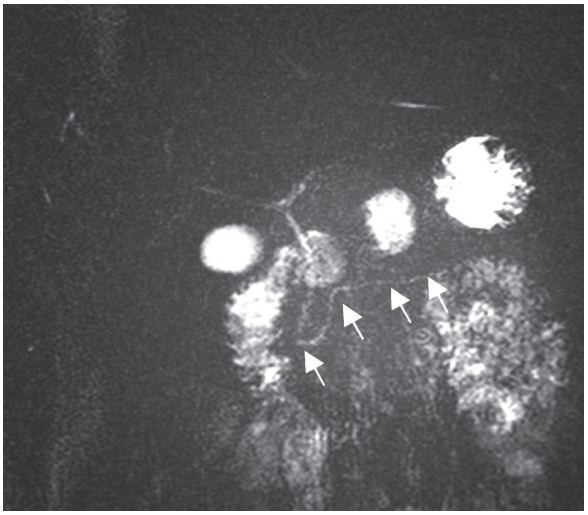

Figure 3*: Normal MRCP using RARE technique. It shows a good image of pancreatic biliary ducts conspicuity (arrows). A few artifacts in the surrounding tissue are observed.*

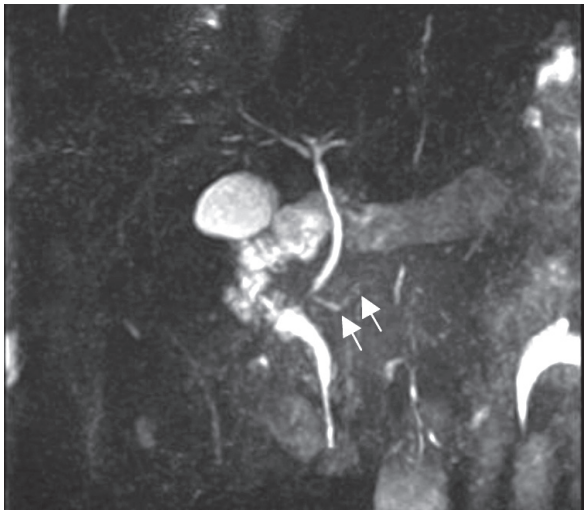

Figure 4*: Normal MRCP using HASTE technique. There is less conspicuity of the pancreatic duct. More artifacts are seen in surrounding tissue (arrows).*

loop, the right pelvocalyceal system, inferior vena cava, aorta, superior mesenteric vessels, respiratory movement and occasionally metallic clips from previous surgery. These produce artifacts for MRCP study. Morrin MM et al.[1], however, have applied two techniques of MRCP to overcome these factors as follows:

1. Single-Short Rapid Acquisition with Relaxation Enhancement (RARE)

This technique is applicable for the duration of a single breath hold, a very long echo time (> 500 ms.) and multi-slices are performed at various angles (360°). This provides better pancreatic and intrahepatic ducts conspicuity (Figure 3).

2. Multiple-slice Half-Fourier Acquisition Single-short Turbo-spin Echo (HASTE)

This technique is a 3D reconstruction, with normal breathing. Irie H et al.[2] claimed that it was better to detect a small choledocholithiasis. In our personal opinion, there are some cases when the visualization of the pancreatic duct is not sufficient (Figure 4).

For our case the clinical diagnosis of cholecystitis with ascending cholangitis and probably a stone in the common bile duct was suspected. Hence, a CT of the upper abdomen was performed. It showed a distended gallbladder containing small stones and a suspected small stone probably dislodged from the gallbladder into the common bile duct. We then decided to perform MRCP using the two techniques of RARE and HASTE studies. The findings showed non conspicuity of the gallbladder, intrahepatic duct and common bile duct but the pancreatic duct was depicted more clearly with the RARE technique. This effect can explain the basis of blood in the biliary tract which contains a hemoglobin-caused paramagnetic effect, amount of bile excretion, viscosity and components of bile fluid. MRCP will show hypointensity in gallbladder and CBD. In contrast, the pancreatic duct will show high intensity because of no bloody fluid. MRCP is a static study. The image may be inferior to ERCP which is a dynamic study. But MRCP is still required in cases requiring an examination by ERCP for many clinical indications. That said, MRCP is a non-invasive method and it is superior to ERCP in the case of hemobilia as shown in this case. The radiologist and radiographer should understand all potential pitfalls of MRCP and the use of various study techniques. This may help avoid an ERCP which may often be unnecessary.[3]

Conclusion

The diagnosis of hemobilia by MRCP using either RARE or HASTE techniques is very helpful. The paramagnetic property of hemoglobin, content and viscosity bile could explain the non depiction of the biliary tract. In some cases, however, HASTE may lead to a false negative result.

We recommend applying both techniques of MRCP in the case of a suspected hemobilia instead of ERCP as this cannot diagnose this entity.

References

1. Morrin MM, Farrell RJ, McEntee G, et al. MR cholangiopancreatography of pancreaticobiliary diseases: comparison of single-shot RARE and multislice HASTE sequences. *Clin Radiol* 2000;55:866-73.
2. Irie H, Honda H, Kuroiwa T, et al. Pitfalls in MR cholangiopancratographic interpretation. *Radiographics* 2001;21:23-37.
3. Sahni VA, Mortele KJ. Magnetic resonance cholangiopancreatography: current use and future applications. *Clin Gastroenterol Hepatol* 2008;6:967-77.

Case Report

Hand-Foot Syndrome or Palmar-Plantar Erythrodysesthesia (PPE)

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Keywords:
hand-foot syndrome, HFS, palmar-plantar erythrodysesthesia, PPE

Case Report

A 32-year-old man was found to have a low normal range of hematocrit (41.6-42.5%) for a period of 2 years. During a yearly check up the patient was found to be anemic with an anemia level of 31.5% (normal range, 43.5-53%). A colonoscopy examination discovered an ulcerated lesion with the medical aspect of the cecum just distal to the ileocecal junction. The biopsy specimen showed moderately differentiated adenocarcinoma. The patient underwent an exploratory laparotomy. There was no evidence of metastasis and a right hemicolectomy was performed. The pathological diagnosis revealed moderately differentiated adenocarcinoma involving the cecum with 25 negative regional lymph nodes. The tumor affected the mucosa, the submucosa, the muscular layer as well as the serosa.

He received a dose of chemotherapy: 2,000mg of Xeloda® in the morning and 1,500mg in the evening for 2 weeks. He then discontinued the medication for a week. The treatment plan was medication administered for a period of 6 months. At around 4 to 5 weeks post medication, the patient developed a tingling sensation in his fingers and toes and experienced discoloration of the skin (Figure 1,2).

The diagnosis of painful erythema and paresthesia affecting the palms and soles includes a cutaneous reaction caused by several chemotherapeutic agents and targeted therapy, graft-versus-host disease, toxic epidermal necrolysis, and necrolytic acral erythema associated with hepatitis C infection or zinc deficiency.

Discussion

This case demonstrates the skin changes to hands and feet when Xeloda® is administered immediately after a right hemicolectomy for Cancer cecum has been performed. The most likely diagnosis of this patient's condition is Hand Foot Syndrome (HFS) or palmer - plantar erythrodysesthesia (PPE) which is a relatively common cutaneous reaction caused by several chemotherapeutic agents with the associated targeted treatment.[1] (Table 1)

The symptomatic and histopathological findings of this disease are suggestive of direct cytotoxicity affecting the eccrine glands (the areas of highest eccrine density are on the palms and soles). This is caused by a high concentration of a chemotherapeutic agent. The clinical picture is divided into 3 grades according to severity.

Table 1: Chemotherapeutic Agents and Targeted Treatment that could cause HFS or PPE

Chemotherapeutic Agents	Targeted Treatment
Capecitabine (Xeloda®)	Sunitinib (Sutent®)
Cytarabine (Cytosar-U®)	Sorafenib (Nexavar®)
Floxuridine (FuDR®)	Pazopanib (Votrient®)
Fluorouracil (5-FU®, Adrucil)	Vemurafenib (Zelboraf)
Idarubicin (Idamycin)	Ixabepilone (Ixempra®)
Liposomal doxorubicin (Doxil®)	Lapatrinib (Lapatinib)
Doxorubicin (Adriamycin)	

The National Cancer Institute (NCI) grades and definitions of the disease are as follows:

1. Skin changes or dermatitis without pain (e.g. erythema, peeling).
2. Skin changes, with pain. No interference of function.
3. Skin changes, with pain and interference of function.

The most common treatments include:[2]

1. Avoid extremes of temperature, pressure and friction on the skin.
2. Administer pyridoxine (50mg) twice a day.
3. Apply topical treatments such as a cold compress, emollient and topical steroids.

Conclusion

General practitioners should be aware of this condition in their normal general practice. Patients may experience skin changes to the hands and feet after chemotherapy medication (Xeloda®) has been administered.

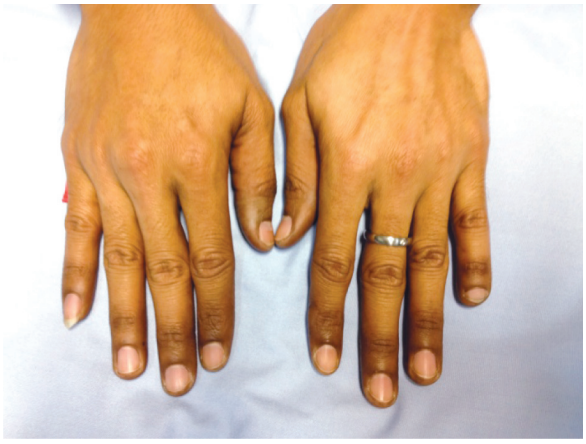

***Figure 1**: Patient's fingers are discoloured*

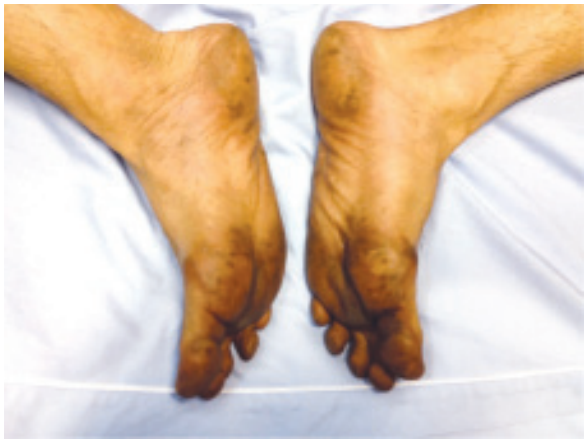

***Figure 2**: Patient's toes are discoloured*

References

1. Hand-Foot Syndrome or Palmar-Plantar Erythrodysesthesia. Reviewed and approved by the ©2005-2012 American Society of Clinical Oncology (ASCO). Last Updated: January 23, 2012.
2. Hand-Foot Syndrome (HFS) or Palmar-Plantar Erythrodysesthesia (PPE). ©2012 Breastcancer.org (Page last modified: September 17, 2012, at http://www.breastcancer.org/treatment/side_effects/hand_foot_synd)

Iodide Mumps

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Keywords:
iodine mumps, adverse contrast reaction, salivary gland, submandibular gland

Iodide mumps, a swelling of the salivary glands after a contrast medium injection, is a rare adverse reaction. This article considered a case of a 57-year-old male with a history of renal cell carcinoma who developed progressive swelling of the bilateral submandibular glands several hours after a intravenous (IV) contrast enhanced computed tomography (CT) imaging study was conducted during a routine tumour surveillance. After supportive medical treatment, the swelling of the glands gradually regressed and returned to normal within a few days.

Case Report

A 57-year-old male patient had a history of renal cell carcinoma and a right nephrectomy for six months. He was sent for a follow up CT scan for routine tumor surveillance. Prior to the surgery, he had had experience of IV contrast enhanced CT imaging without any kind of complication. This CT study was done by intravenous administration of 100 ml. low-osmolality nonionic iodinated contrast media. After finishing the study, no acute adverse reaction was observed within 30 minutes. Several hours later, though, the patient developed progressive swelling of both submandibular glands without any other symptoms. He came back to the hospital and a diagnosis of iodide mumps was given. After supportive treatment by corticosteroids and antihistamine, the swelling of the glands gradually regressed and returned to normal within a few days.

Discussion

Iodide mumps is an abnormal swelling of the salivary glands linked to an intravascular administration of iodine containing contrast material. This adverse reaction is rare. There are fewer adverse reactions when low-osmolality agents are administered. That said, the incidence of iodism, including iodide mumps, is the same for low and high osmolar contrast agents.[1] The ultrasound findings of the iodide mumps showed a diffuse swelling of the bilateral submandibular glands with prominent internal low echoic septa without increased vascularity[2] (Figure 1).

The prognosis of iodine mumps is relatively benign. The onset varies from within a few minutes to up to 5 days after contrast medium administration.[3] Associated adverse reactions with iodide mumps are facial nerve paralysis, severe allergic vasculitis, skin erythema, enlargement of the thyroid and lacrimal glands. However, no life threatening reaction has been reported.[3] The current management of iodide mumps is supportive therapy. In almost half of the reported cases recovery occurred without treatment.[3]

In this case, the reaction is classified as a delayed adverse reaction because the symptoms occurred several hours after contrast exposure. Most of delayed contrast reactions are cutaneous symptoms such as urticarial and/or a persistent rash. Other rare delayed adverse reactions like iodine mumps and acute polyarthropathy have been reported.[4] Although the pathogenesis of delayed reactions is not well understood, it appears that many are T-cell-mediated reactions. Predisposing factors for delayed reactions include previous experience of delayed reactions and interleukin-2 therapy.[5]

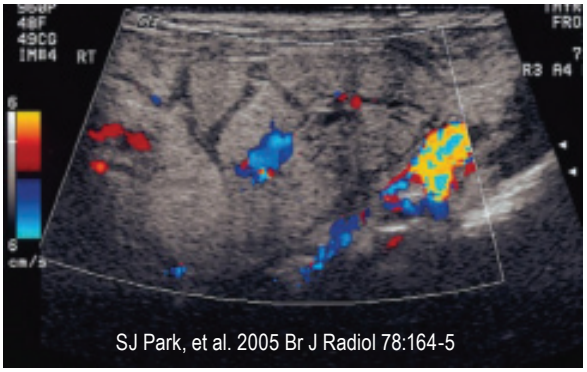

***Figure 1**: The color Doppler ultrasound shows a diffuse swelling of the submandibular gland with prominent internal low echoic septa and without increased vascularity.[2]*

Conclusion

Intravenous iodinated contrast agents are generally safe. Though the frequency of side effects has fallen significantly since the introduction of nonionic, monomeric contrast agents, side effects remain an important issue. Iodide mumps is a rare adverse reaction which is non-life threatening and requires only supportive measures and reassurance. Knowledge about this condition is important for appropriate management. Since the reaction may be due to T-cell-mediated hypersensitivity, the recurrence of a reaction may happen with re-exposure to contrast media. To avoid a more severe reaction, intravenous iodinated contrast agents should be avoided in patients who have already experienced an adverse reaction.

References

1. Berman HL, Delaney V. Iodide mumps due to low-osmolality contrast material. *AJR Am J Roentgenol* 1992;159: 1099-100.
2. Park SJ, Hong HS, Lee HK, et al. Ultrasound findings of iodide mumps. *Br J Radiol* 2005;78:164-5.
3. Christensen J. Iodide mumps after intravascular administration of a nonionic contrast medium. *Acta Radiol* 1995;36:82-4.
4. Adverse Events of Iodinated Contrast Media: ACR Manual on contrast Media-Version 8, 2012. Available from http://www.acr.org/.
5. Webb JA, Stacul F, Thomsen HS, et al. Late adverse reaction to intravascular iodinated contrast media. *Eur Radiol* 2003;13:181-4.

The FIFA Futsal World Cup Thailand 2012: Injuries to Athletes

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Keywords:
futsal world cup, Bangkok Hospital Academy of Sports and Exercise Medicine, BASEM, FIFA, soccer, athlete, sportinjury

Futsal is a variant of soccer played indoors and was approved by FIFA (Fédération Internationale de Football Association) in 1962.[1] It has become increasingly popular worldwide and there are less severe injuries to players that at soccer tournaments. There are fewer tackles in futsal than in soccer. Players who are in their early teens are most susceptible to injury, especially damage to knees, legs and ankles. Futsal players can often be injured because they have not warmed up sufficiently before starting to play, or because of sudden acceleration and deceleration moves that cause muscle tears. Plantar fasciitis is a painful swelling caused by a minor tear of the plantar fasci (a connective tissue on the sole of a foot) and is the most common injury in futsal players.[2,3]

In July 2012, the Bangkok Hospital opened the Bangkok Academy of Sports Exercise Medicine (BASEM). This new center contains a wide array of advanced diagnostic technologies and exercise equipment designed to optimize athletic performance and to aid faster rehabilitation. The unit also helps athletes to improve their fitness levels. BASEM is an accredited FIFA medical center of excellence and provides the same high standard of care at multiple centres worldwide in Europe, the United States, Australia, South Africa, Japan and Qatar.

BASEM is well equipped with top of the line sports exercise medical equipment. When injuries happen, BASEM can offer medical services and advanced treatment for many sports injuries. Treatments include tennis elbow release, knee arthroscopy for anterior cruciate ligament (ACL), posterior cruciate ligament (PCL) and meniscectomy, knee arthroscopy debridement for osteoarthritis (OA), shoulder arthroscopic decompressions and shoulder arthroscopic rotator repair. Specialists, including post-operative physiotherapists, are available around the clock.

The last futsal world tournament took place in Thailand from November 1-18, 2012. At the tournament, three futsal players sustained serious injuries and were treated by the team at BASEM.

Case Report # 1

A 35-year-old man presented with a painful left leg after taking part in the futsal 2012 competition. The magnetic resonance imaging (MRI) of the left leg revealed a grade 2 partial muscle tear of a deep section of the soleus muscle (Figure 1A, B) and a tear at the superficial section of the flexor hallucis longus muscle. A thin layer of fluid (2.5mm wide, Figure 1C) could be seen along the interfascial plane.

At the fascia there was no tendon involvement, and there was increased signal intensity in the anterior surface of solens muscle. The patient responded well to symptomatic and conservative management.

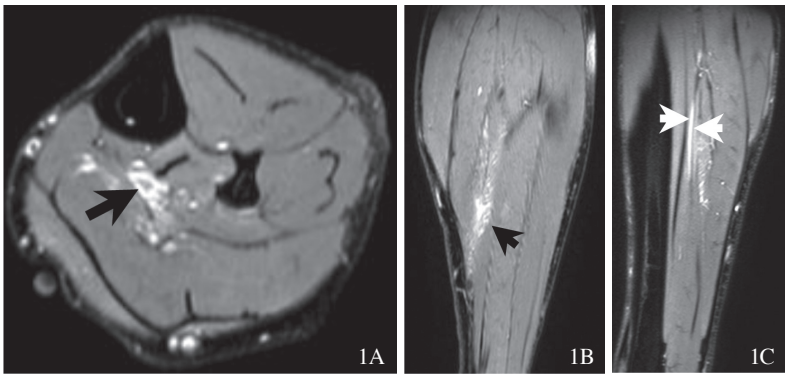

***Figure 1 A,B**: A thin layer of fluid can be seen along the interfascial plane (black arrow).*
***Figure 1C**: A thin layer of fluid can be seen along the interfascial plane (white arrow).*

Case Report # 2

A 31-year-old futsal player sustained a blunt injury to the left leg. He developed a painful swelling in his left calf for two days. The MRI of the left leg revealed a grade 1 partial tear of the muscle (Figure 2A) and of the musculotendineous junction of the medial gastrocnemius muscle. A thin layer of fluid (4mm wide, Figure 2B) was seen along the superficial fascia.

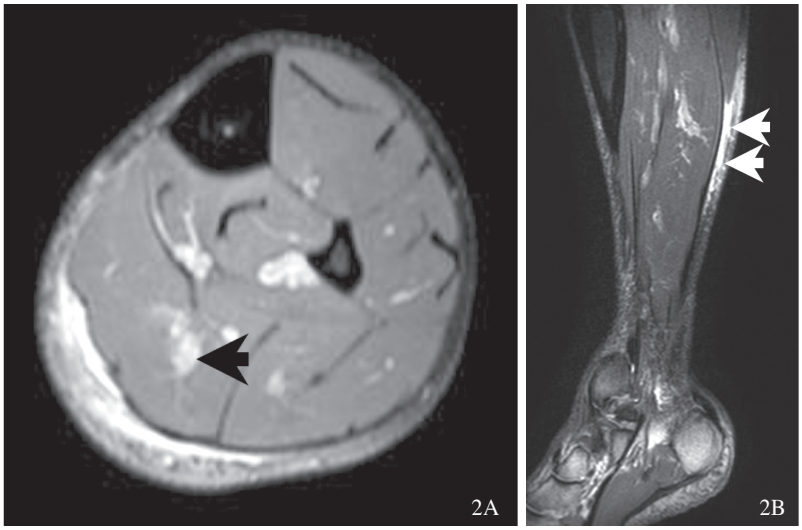

***Figure 2A**: MRI imaging shows a grade 1 partial muscle tear of the musculotendineous junction of the medial gastrocnemius muscle (black arrow).*
***Figure 2B**: A thin layer of fluid can be seen along the interfascial plane (white arrow).*

Case Report # 3

A 31-year-old futsal player sustained a blunt injury above the left thigh. He developed localized pain and tenderness. The MRI of the pelvis showed a grade 1 partial tear of the left adductor longus muscle and tendon (Figure 3) at the superior pubic ramus insertion with fluid (1.5cm wide) along the superficial fascia of the muscle. He responded well to conservative management.

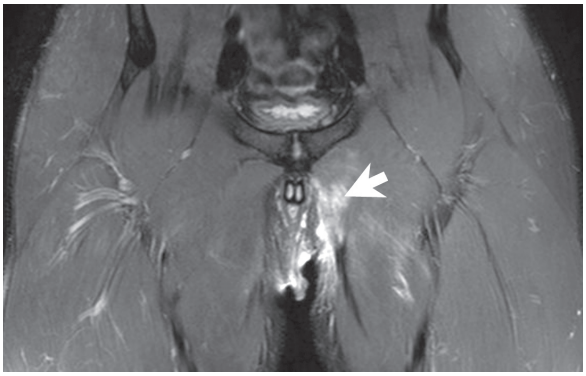

Figure 3*: MRI imaging shows a grade 1 partial muscle tear of the left adductor longus muscle and tendon at the superior pubic ramus insertion with fluid (1.5cm wide) along the superficial fascia.*

Discussion

The risk of injury when playing futsal is lower than playing soccer. This is due to stricter rules in futsal. For example, in futsal, slide tackles are prohibited. Players are recommended to stop the ball by chesting the ball rather than heading it. This can help prevent head and neck injuries.[1,2]

Although there are fewer futsal injuries than soccer injuries there are typical injuries seen in futsal. Junge A and Dvorak J[4] analyzed player injuries during three consecutive futsal world cups. There were a total of 165 injuries from 127 matches, or 130 injuries per 1,000 player matches. The majority of injuries were caused by contact with other players and 35% occurred during non-contact with other players. Most injuries affected the lower extremities (70%), head and neck (13%) and upper extremities (10%) and trunk (7%). The most frequent injuries were contusions of the lower leg (11%) ankle sprains (10%) and groin strains (8%). These were caused by contact with other players and by foul play.

The most recent futsal world cup was held in Thailand in November 2012. There were only three serious injury cases reported from all matches, with other less serious injuries reported, including minor strains and abrasions. Futsal injuries are mainly caused by contact with the ground or other players. To prevent fractures of the lower extremities, shin pads and straps are essential to protect the lower thigh, knee and ankle.

Conclusion

In the FIFA Futsal World Cup Thailand 2012, Brazil defended their title, winning it for the fifth time by defeating Spain. All the players who experienced serious injuries during the tournament were attended by the BASEM center of the Bangkok Hospital. The injuries involved two cases of grade 1 and one case of grade 2 leg muscle tears which responded well to conservative and symptomatic management. BASEM is an accredited FIFA medical center of excellence.

References

1. Horwitz s. Guide to futsal injury prevention. (Accessed January 10, 2013 at www.DCSportsInjury.com)
2. Futsal's World: Prevent Injuries in Futsal. (Accessed January 10, 2013 at http://simonfutsworld.blogspot.com/2012/04/prevent-injuries-in-futsal.html)
3. Analysis of the incidence and factors related to ankle sprains in adolescent athletes of soccer and futsal. A comparative study. (Accessed January 10, 2013 at http://futsal4all.com/2018/06/so-you-think-futsal-causes-way-more-injuries-than-football-think-again.html)
4. Junge A, Dvorak J. Injury risk of playing football in Futsal World Cups. *Br J Sports Med* 2010;44:1089-92.

Review Article

Painful Diabetic Neuropathy (PDN): An Update for Clinicians

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Keywords:
diabetic neuropathy, neuropathic pain, PDN pain syndrome

Neuropathy is one of the most common complications in both type I and type II diabetes mellitus. It can present in various forms, either focal or symmetrical.[1] The most common form is a chronic, symmetrical, length dependent axonal sensorimotor polyneuropathy. This disease can also affect the autonomic nervous system and plays an important role in other subsequent complications. Some patients are asymptomatic, but many patients have sensory symptoms, either negative or positive ones. These symptoms may fluctuate over time. Some of them also have pain associated with neuropathy, so called painful diabetic neuropathy (PDN).[2] As Jambart et al noted about Middle Eastern patients: *"The odds of painful DPN were highest among patients with peripheral vascular disease, diabetic retinopathy and diabetic nephropathy.[3]"*

Diabetes mellitus is also the most common cause of distal symmetric polyneuropathy.[4] Therefore, it is the most common cause of neuropathic pain.[5] The prevalence of neuropathic pain in the diabetic population varies enormously according to different studies which estimate a range between 3% and 50% of patients.[3,6] A recent survey in the United Kingdom revealed the prevalence of 26.4% and 80% of patients reporting moderate to severe pain.[7] Having PDN has a significant negative effect on the quality of life, especially the physical aspect, and a significantly worse trajectory of quality of life outcomes over time and long-term increased total costs.[7,8]

PDN pain syndrome

The diagnosis of PDN is a clinical one, which relies on the patient's description of pain. The symptoms are distal, symmetrical, often associated with nocturnal exacerbations, and commonly described as prickling, deep aching, sharp, like an electric shock, and burning with hyperalgesia and frequently allodynia upon examination.[1,9] The symptoms are usually associated with the clinical signs of peripheral neuropathy, although occasionally in acute painful diabetic peripheral neuropathy (DPN), the symptoms may occur in the absence of signs.

Common painful symptoms also include sharp or lancinating pain attacks, allodynia, cramping and gnawing.[10,11] These symptoms are commonly used in rating scales and standard pain questionnaires to assess frequency and severity of painful symptoms, and treatment response. Moreover, since each type of pain is believed to be caused by a different pathophysiological mechanism, therefore, each neuropathic pain medication might have a different effect on sensory symptoms.[12]

Despite the advances in neurophysiologic studies, diagnosis cannot be made without taking a full history and giving a physical examination. Incorporating standard pain questionnaires in clinical evaluation will also aid earlier diagnosis and better management in these patients.[11] In our study,[13] we used the DN4 questionnaire, which has been validated as a reliable screening tool for neuropathic pain in diabetic patients.[14] The questionnaires can be used to screen and differentiate between neuropathic and non-neuropathic pain.[15] Almost all patients had more than one type of pain which adds more complexity to the clinical evaluation.[13] This may imply that the mechanism of pain is most likely due to small nerve fibers, rather than large fiber dysfunction. Previous clinical and electrophysiological studies also confirmed that the neuropathic pain in diabetic polyneuropathy is not associated with the degree of involvement of large diameter sensory fibers or the severity of the diabetes.[16,17] Interestingly, when looking at sharp pain, the duration of diabetes was not associated with painful symptoms.[13] This was due to the natural history of small fiber neuropathy which can occur in the pre-diabetes stage.[18] Although the pain of PDN may resolve completely over time in some patients, in those in whom painful neuropathic symptoms had persisted over 5 years, no significant improvement in pain intensity was observed.[19]

Impact of PDN upon quality of life

The presence of PDN significantly affected patients' quality of life, especially physical function. Moreover, it was associated with a significantly worse trajectory of quality of life outcomes over time and long-term increased total costs, when comparing to patients with non-painful diabetic polyneuropathy. The presence and severity of neuropathic pain were associated with greater impairments in a number of important Health Related Quality of Life (HRQoL) domains.[8,16,20,21] Regarding the SF-36 subcategories, pain symptoms had more effect on physical function and role-physical, than social function and emotional well-being.[13] This data was in line with previous reports in diabetic patients whether they had PDN or not.[22-24] When comparing to other diabetic populations and other diseases, PDN patients had a poorer physical function than those with other chronic neurological illnesses or the general diabetic population.[25] Their QOL was similar to that of diabetic foot ulcer patients, which indicated severe disability.

A recent American Academy of Neurology evidence-based review has used Visual Analog Scale (VAS) as a primary measure and physical function and QOL, e.g. SF-36 as guidelines for efficacious assessment, in order to formulate recommendations for pharmacological treatment of painful diabetic polyneuropathy.[26] However, in clinical trial situations, Quantitative Sensory Testing (QST) is still necessary for a more objective measurement of outcome, as well as HRQoL.[21, 27]

Treatment of PDN

Regarding the symptomatic treatment of this condition, Thai and international guidelines recommend the use of tricyclic antidepressants (TCA) e.g. amitriptyline, nortriptyline and calcium channel ligands (e.g. gabapentin, pregabalin) as first line treatments.[5,9,26,28] The second and third line medications are selective norepinephrine serotonin reuptake inhibitors (SNRIs) e.g. venlafaxine and duloxetine and opioids (e.g. tramadol, oxycodone and morphine). However, using strong opioids in this indication should be reserved for severe and refractory cases under pain specialist supervision. Capsaicin cream and percutaneous electrical nerve stimulation can also be used as adjunctive treatments, with less systemic side effects.[5, 26]

When comparing the efficacy of each medication according to number needed to treat (NNT) for 50% pain reduction, TCA and opioid are slightly more effective than other groups. They are followed by calcium channel ligands and SNRIs.[29] The medication selection should also consider other factors, such as type of pain, pharmacokinetics, co-existing symptoms or diseases, side effects and price. Recommended medications and dosage of neuropathic pain medication were summarized in Table 1.

Despite the improvement in treatment modalities for chronic pain in recent years, patients with PDN continue to be inadequately treated. The different profiles of pain quality and spatial characteristics suggest that assessing patterns of pain symptoms might contribute to the identification of distinct pathophysiologic mechanisms, subgroups of patients and the development of mechanism -based treatment approaches.[31,32] This will eventually improve the outcome and qualities of life in these patients.

Conclusion

Neuropathy is one of the most common complications in both type I and type II diabetes patients. The most common form is the chronic, symmetrical, length dependent, axonal sensorimotor polyneuropathy which affects either large or small sensory nerve fibers, or autonomic nerve fibers. Many patients suffer from neuropathic pain due to this condition, so called painful diabetic neuropathy. Generally, various types of pain can occur in the same patient in moderate to severe degree. Symptomatic treatment and pain control are the main therapeutic strategies. Many national and international organizations have recommended tricyclic antidepressants and calcium channel ligands as first line treatment options. This will eventually prevent other related complications and should improve the patient's quality of life.

Table 1: Common neuropathic pain medications

Medication	Initial dose and titration	Recommended dose
Antidepressants		
Tricyclic antidepressants		
Amitriptyline	10 mg/d, increase 10 mg/wk	25 to 75 mg/d
Nortriptyline	10 mg/d, increase 10 mg/wk	25 to 75 mg/d
Other antidepressants		
Venlafaxine	37.5 mg/d, increase 37.5mg/wk	75-225 mg/d
Duloxetine	30 mg/d	60 mg/d
Anticonvulsants		
Carbamazepine	200 mg/d, increase 200 mg/wk	600-1,200 mg/d
Oxcarbazepine	300 mg/d, increase 300 mg/wk	600-2,400 mg/d
Gabapentin	300 mg/d, increase 300 mg/wk	900-2,400 mg/d
Pregabalin	75 mg/d, increase 75 mg/wk	150-600 mg/d
Non-narcotic analgesics		
Tramadol	100 mg/d, increase 50 mg/wk	100-400 mg/d
Narcotic analgesics		
Morphine (oral)	15-30 mg/d in divided dose	30-120 mg/d
Topical agents		
0.075% capsaicin cream/gel	Apply locally	3-4 times/d

References

1. Dyck PJ, Albers JW, Andersen H, et al. Diabetic Polyneuropathies: Update on Research Definition, Diagnostic Criteria and Estimation of Severity. *Diabetes Metab Res Rev* 2011 Jun 21. doi: 10.1002/dmrr.1226. [Epub ahead of print]
2. Tesfaye S, Vileikyte L, Rayman G, et al. Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management. *Diabetes Metab Res Rev* 2011 Jun 21. doi: 10.1002/dmrr.1225. [Epub ahead of print]
3. Jambart S, Ammarche Z, Haddad F, et al. Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. *J Int Med Res* 2011;39:366-77.
4. England JD, Gronseth G, Franklin G, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review): Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;72:185-92.
5. Attal N, Cruccu GG, Baron R, et al. European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:1113-88.
6. Boulton AJ, Malik RA, Arezzo JC, et al. Diabetic somatic neuropathies. *Diabetes Care* 2004;27:1458-86.
7. Davies M, Brophy S, Williams R, et al. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2006;29: 1518-22.
8. daCosta DiBonaventura M, Cappelleri JC, Joshi AV. A longitudinal assessment of painful diabetic peripheral neuropathy on health status, productivity, and health care utilization and cost. *Pain Medicine* 2011;12:118-26.
9. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010;33:2285-93.
10. Baron R, Tolle TR, Gockel U, et al. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. *Pain* 2009;146 :34-40.
11. Petrikonis K, Sciupokas A, Samušytė G, et al. Importance of pain evaluation for more accurate diagnosis of painful diabetic polyneuropathy. *Medicina (Kaunas)* 2010;46: 735-42.
12. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010;9:807-19.
13. Kulkantrakorn K, Lorsuwansiri J. Sensory profile and its impact on quality of life in patients with painful diabetic polyneuropathy. *Neurol Sci* 2012 (submitted).

14. Spallone V, Monganti R, D'Amato C, et al. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med* 2012;29:578-85.
15. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; 152:14-27.
16. Erbas T, Ertas M, Yucel A, et al. Prevalence of peripheral neuropathy and painful peripheral neuropathy in Turkish diabetic patients. *J Clin Neurophysiol* 2011;28:51-5.
17. Mondelli M, Aretini A, Baldasseroni A. Distal symmetric polyneuropathy in diabetes: difference between patients with and without neuropathic pain. *Exp Clin Endocrinol Diabetes* 2012;120:45-50.
18. Tavee J. Zhou L. Small fiber neuropathy: A burning problem. *Cleve Clin J Med* 2009;76:297-305.
19. Daousi C, Benbow SJ, Woodward A, et al. The natural history of chronic painful peripheral neuropathy in a community diabetes population. *Diabet Med* 2006;23:1021-4.
20. Taylor RS. Epidemiology of refractory neuropathic pain. *Pain Pract* 2006;6:22-6.
21. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life : review and implications. *Neurology* 2007;68:1178-82.
22. Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. *Clin J Pain* 2004;20:174-8.
23. Rerkasem K, Kosachunhanun N, Tongprasert S, et al. A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. *Int J Low Extrem Wounds* 2009;8:153-6.
24. Swislocki A, Orth M, Bales M, et al. A randomized clinical trial of the effectiveness of photon stimulation on pain, sensation, and quality of life in patients with diabetic peripheral neuropathy. *Pain Symptom Manage* 2010;39: 88-99.
25. Hermann BP, Vickrey B, Hays RD, et al. A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Res* 1996;25: 113-8.
26. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758-65.
27. Backonja MM, Walk D, Edwards RR, et al. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *Clin J Pain* 2009;25:641-7.
28. Thai Association for the Study of Pain. Clinical Practice Guideline for Neuropathic Pain 2008. Bangkok, Thailand, Beyond Enterprise Publishing, 2008.
29. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573-81.
30. Kulkantrakorn K. Diabetic neuropathy. *Clinic* 2012;28:15-21.
31. Dworkin RH, Jensen MP, Gammaitoni AR, et al. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* 2007;8:118-26.
32. Koroschetz J, Rehm SE, Gockel U, et al. Fibromyalgia and neuropathic pain - differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. *BMC Neurology* 2011;11:55.

Review Article

Update on Migraine Prophylaxis: Things that can help your migraine patients

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Keywords:
migraine prophylaxis, migraine headache, migraine prevention

Migraine is a common chronic neurological disorder characterized by recurrent episodes of disabling headaches. It is also known as one of the most debilitating disorders. Approximately 90% of migraineurs experience moderate to severe pain, and 75% have impaired function during migraine attacks and 53% reported severe impairment or require bed rest during their attacks.[1,2] Approximately one third of migraineurs had missed at least one day of work or school in the last year and often have decreased productivity by at least one half.[3-5] Hypersensitivity to light (photophobia), sound (phonophobia), smell (osmophobia), and head movement, along with nausea and vomiting are associated with the attack.[6]

The pathophysiology of migraine is still not fully understood but the vascular theory has been discarded. Central nervous system dysfunctions, including brain excitability and abnormality in pain modulating circuits in the brain stem, have been recently proposed as contributory factors.[7,8] Functional neuroimaging studies of migraineurs suggest dynamic dysfunction between the periaqueductal gray matter (PAG) and several brain areas within nociceptive and somatosensory processing pathways. The impairment of the descending pain modulatory circuit causes loss of pain inhibition and hyperexcitability along both spinal and trigeminal nociceptive pathways, leading to a migraine attack.[9,10]

This review covers the pharmacological treatments of episodic migraine according to guidelines from the 2012 American Academy of Neurology (AAN) and the American Headache Society (AHS) and the European Federation Neurology Society (EFNS). In addition, an emerging treatment in chronic migraine, Botulinum toxin type A, is reviewed.

Migraine Burden

Migraine was ranked the 12th most disabling medical disorder in women and the 19th in men by the World Health Organization (WHO) in 2005. With the publication of the World Health Report 2001 with evidence of the high burden of migraine, WHO recognized headache disorders as a high-priority public-health problem.[11]

Global prevalence of migraine was 10% and life-time prevalence for migraine was 14% according to a study by Stovner et al in 2007.[12] The American Migraine Prevalence and Prevention (AMPP) study, the largest population based study of migraine, demonstrated a high prevalence of migraine in the general population. The prevalence estimate of unadjusted 1-year period migraine is 11.7%, with a higher prevalence among women than men (17.1% for women vs. 5.6% for men).

The prevalence of migraine was highest in those aged 30-39 years for both men (7.4%), and women (24.4%). This study also showed that migraine remained underrecognized and undertreated.[1]

Approximately 90% of migraineurs have moderate to severe pain, 75% have reduced ability to function during headache attacks, and 30% require bed rest during their attacks.[13] Most migraineurs use only acute medication for their headaches. Approximately 40% of migraineurs are eligible for migraine prevention measures, but only 13% are currently receiving it.[1,14-16]

Preventive therapies can decrease the occurrence of migraine by 50-80%, reducing the severity and duration of migraine, and also improve acute medication responsiveness.[1,17] These therapies may help prevent the progression of episodic migraine to chronic migraine with a resulting reduction of health care cost.[18,19] The quality of life of migraine patients is also improved.[20]

Migraine Prevention

Preventive treatment should be considered for all migraineurs whose attacks have an impact on their working productivity, school, familial and social activities despite an appropriate use of acute medications. The main aim of prophylaxis is to reduce the attack frequency to ≥ 50%. Prophylaxis may also reduce headache intensity, duration and disability, and improve the response to acute medication. Patients with ≥ 2 disabling attacks per month, who failed to adequately respond to acute medications, should start a prophylactic treatment.[21-24]

The United State (U.S.) evidence-based guidelines for migraine and EFNS guidelines on the drug treatment of migraine have established the circumstances that might warrant preventive treatment (Table 1).[21-24]

Table 1: Guidelines for starting pharmacotherapy in migraine prophylaxis[21-24]

- Recurring migraine attacks that significantly interfere with daily routines, despite appropriate acute treatment.
- Severely impair quality of life, business duties, or school attendance.
- Frequent headaches (> 4 attacks/month in U.S. guidelines, ≥ 2 attacks/month in EFNS guidelines)
- Acute medication is contraindicated, ineffective, overused, or not tolerated.
- Patient preference.
- Frequent, very long or uncomfortable auras.
- Uncommon migraine conditions, including hemiplegic migraine, basilar type migraine, migraine with prolonged aura, or migrainous infarction.

General considerations in preventive treatment

Guidelines suggest starting preventive medicines at a low dose and to increase the dosage slowly every 1-2 weeks or more until there is a therapeutic effect and to test the patient's tolerance to side effects from the medications. An adequate trial duration of 2-6 months with an appropriate dosage is necessary to determine the efficacy of treatment. Efficacy is often first noted at 4 weeks. Medication overuse should be monitored regularly. Patients' progress and symptoms should be monitored with a headache calendar or diary. Comorbid conditions such as depression, anxiety, epilepsy, cardiovascular disease, and obesity should be factored in. Women of child bearing age should be alerted to the side effects of medication during pregnancy. Once the headaches become under control for 6-12 months, the preventive medicines should be slowly tapered off.[21-24]

A longer period of preventive treatment (lasting more than 12 months) is suggested for patients who are at risk for migraine progression such as: high attack frequency (> 6 attacks/month), medication overuse (> 10 tablets/month), obesity (BMI > 30), history of a head injury, snoring or experience of a stressful life event.[25-31]

Preventive medications

The choice of preventive medication has to be carefully discussed with the patient. The efficacy of any agent, its potential side effects and experience of previous treatment trials, interaction with other drugs, and comorbidities should be considered for each individual patient. The updated 2012 guidelines from the American Academy of Neurology (AAN) and the American Headache Society (AHS) classify preventive agents on 4 levels based on published clinical trial evidence: Level A (established efficacy), Level B (probable efficacy), Level C (possible efficacy) and Level U (inadequate or conflicting data).[32,33]

Level A medications for episodic migraine prevention include antiepileptics (divalproex sodium/sodium valproate, topiramate), beta-blockers (metoprolol, propranolol, timolol), and herbal remedies (butterbur). The guidelines' authors suggest that Level A drugs should be offered to patients who required prophylaxis for migraine.

Level B medications include several non-steroidal anti-inflammatory drugs - NSAIDs (naproxen/naproxen sodium, ibuprofen, ketoprofen, fenoprofen), antidepressants (amitriptyline, venlafaxine), histamines (subcutaneous histamine), herbal remedies (feverfew), vitamins (riboflavin), and minerals (magnesium). Level B drugs should be considered for patients who require prophylaxis for migraine.

Level C medications include 11 drugs that may be considered for patients requiring migraine prophylaxis. Two antihypertensive medications (candesartan and lisinopril) are included in this class. NSAIDs (mefenamic acid, flurbiprofen), antihistamines (cyproheptadine), beta-blockers (nebivilol, pindolol), and minerals (co-enzyme Q-10) are also in this class.

Classifications of medicines in migraine prevention are shown in Table 2. The recommended dosage and levels of evidence of efficacy of migraine preventive medicines are shown in Table 3.

Table 2: Classifications in migraine preventive medicines

- Antiepileptics
- Beta-blockers
- Calcium channel blockers
- Antidepressants
- Histamine/Antihistamine
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Angiotensin-converting enzyme inhibitors (ACEI)/ Angiotensin II receptor antagonists (ARB)
- Herbal remedies, Vitamins, and Minerals
- Miscellaneous

Antiepileptics

Meta-analysis suggests that antiepileptics are an effective prophylaxis for migraine. Mean migraine frequency is significantly reduced by 1.3 attacks per 28 days compared with placebo (weapon of mass destruction (WMD) -1.31; -1.99, -0.63). Patients are 2.3 times more likely to have a ≥ 50% reduction in frequency with antiepileptics than with placebo (relative risk (RR) 2.25).[34] Topiramate and sodium valproate are approved by the U.S. Food and Drug Administration (U.S. FDA) for prophylaxis with strong evidence of efficacy. The updated AHS/AAN 2012 guidelines also classify topiramate and sodium valproate as level A medications.

Topiramate

Topiramate is a voltage-activated Ca2+ and Na+ channel blocker, it enhances gamma-aminobutyrate (GABA) at GABA-A receptors, it modulates the AMPA/kainate subtype of glutamate receptors, and it inhibits carbonic anhydrase (with selectivity for CA II and CA IV isoenzymes).[35] Topiramate significantly inhibits trigeminovascular activity in the trigeminothalamic pathway via the kainate receptor.[36]

A dosage of between 100-200 milligrams per day (mg/d) has been shown to be superior to a placebo in the prevention of episodic, chronic, refractory, pediatric migraine, and migraine with medication overuse.[34,37-39] Slow titration from 12.5mg to 25mg may improve tolerance. Common adverse effects are: paresthesia on extremities, weight loss, anorexia, taste interference, memory problems (slow cognitive processes and delayed word retrieval), nausea, and fatigue. Patients with renal stones or a history of renal stone conditions should avoid this medication. Topiramate has recently been reclassified as a category D medication in pregnancy due to the risk of oral cleft lip/cleft palate abnormalities (RR 5.4; 95% CI = 1.5-20.1).[40] The idiosyncratic syndrome of myopia with secondary glaucoma is a rare but potentially severe complication. Immediate discontinuation and emergency ophthalmic consultation can prevent permanent visual loss.[41]

Sodium valproate

Sodium valproate increases GABA levels in synapses, it increases potassium conductance and produces neuronal hyperpolarization, with an attenuation of low threshold T-type Ca2+ channels, a blocking of voltage-dependent Na+ channels and an attenuation of plasma extravasation.[42] Valproate turns off the firing of serotonergic neurons (5-HT) of the dorsal raphe; this is implicated in headache control.

In clinical trials, the dosage varies from 500mg to 1,500mg/d. Begin with a dose of 250mg at bedtime and slowly increase to 1,000mg/d, although some patients may benefit from a dosage of up to 1,500mg/d. Valproate led to a significant reduction in migraine frequency and a 50% respondent rate which is significantly superior to the placebo. The most frequent adverse effects include nausea, vomiting, alopecia, tremors, weight gain, and dizziness.[34,37,39,42]

Valproate has also been associated with encephalopathy, an elevation of liver enzymes, pancreatitis and agranulocytosis. Before administering sodium valproate, special attention must be paid to hepatic, hematologic and bleeding abnormalities.

Baseline laboratory studies and follow up studies including valproate levels, liver enzymes (LFT), and complete blood count (CBC) are needed. Absolute contraindications to valproate are: pregnancy or the chance of falling pregnant, any history of pancreatitis, hepatic disorders, and hematologic disorders (thrombocytopenia, pancytopenia, and bleeding disorders).[43]

Beta-blockers

Beta-blockers are a first-line drug in migraine prophylaxis. The main mechanism of beta-blockers in migraine prevention is considered to be mediated by the inhibition of central beta-1 receptors and consequently the inhibition of Na+ release and tyrosine hydroxylase activity. It also reduces the noradrenergic neuronal firing rate in locus coeruleus, it regulates the firing rate of PAG and it blocks 5-HT2C and 5-HT2B receptors.[44]

Clinical trials support the efficacy of propranolol

Table 3: The recommended dosage and levels of evidence of efficacy of migraine preventive medicines.[24,32,33]

Medicines	Daily usual dosage	Evidence Level	Common side effects	Contraindications
Antiepileptic Drugs				
Sodium valproate	400-1000 mg	A	Drowsiness, weight gain, nausea, tremor, hair loss, hematological or liver abnormalities, fetal abnormalities	Hepatic disease, pancreatitis,pregnancy, urea cycle disorders, thrombocytopenia
Topiramate	25-200 mg	A	Paresthesia, cognitive dysfunction, weight loss, fatigue, secondary glaucoma, nephrolithiasis	Hypersensitivity
Beta Blockers				
Propranolol	120-240 mg	A	Exercise intolerance, tiredness, postural symptoms; contraindicated in asthma	Asthma, peripheral vascular disease, heart block, congestive heart failure, diabetes
Metoprolol	50-200 mg	A	Reduced energy, tiredness, postural symptoms; contraindicated in asthma	
Calcium Channel Blockers				
Flunarizine	5–10 mg	A	Drowsiness, weight gain, depression, parkinsonism	Severe depression, Parkinson's disease
Antidepressants				
Amitriptyline	25-150 mg	B	Drowsiness, urinary retention, arrhythmias	Recent myocardial infarction, cisapride use, monoamine oxidase inhibitor use, hypersensitivity to tricyclic antidepressants
Nortriptyline	20-10 mg	Not included in evidence review	Drowsiness, urinary retention, arrhythmias	
Venlafaxine extended release	150 mg	B	Nausea, insomnia, drowsiness, sweating, dry mouth, agitation, impotence, decrease libido, decreased seizure threshold	Concomitant use of monoamine oxidase inhibitors, caution in lactating mothers
Histamine/Antihistamine				
Histamine SC	1-10 ng twice a week	A	Local reaction at injected site (itching)	Hypersensitivity
Cyproheptadine	4 mg	C	Drowsiness, weight gain	
ACEI/ARB				
Lisinopril	10-20 mg	C	Cough, dizziness, fatigue, muscle cramp, angioedema	Hereditary or idiopathic angioedema, anuria, or hypersensitivity to other sulfonamide-derived drugs
Candesartan	16 mg	C	Hypotension, birth defects and fetal death	Hypersensitivity, pregnancy and Lactation
Herbals, Vitamins and Minerals				
Petasites (Butterbur)	50–75 mg bid	A	Elevation of liver enzymes, nausea, bloating	Hypersensitivity, pregnancy and lactation
Feverfew (MIG-99)	6,25 mg tid	B	Gastrointestinal disorders	
Riboflavin	400 mg	B	Diarrhea, polyuria, abdominal cramp	
Magnesium	600 mg (24 mmol)	B	Diarrhea, gastric irritation	
Coenzyme Q10	300 mg	C	No side effect was reported	
Miscellaneous				
Onabotulinum toxin A (for chronic migraine)	155-195 units every 12 weeks	Not included in evidence review	Muscle weakness, neck pain, ptosis, flu-like symptom	Myasthenia gravis and other disorders of neuromuscular transmission
Clonidine	25-50µg tid	C	Nausea, drowsiness	

ng = nano grams µg = micrograms bid = bis in die (twice a day) tid = ter in die (three times a day)

(120-240mg/d), metoprolol (50-200mg/d), timolol (10-15mg bid), and atenolol (50-100mg/d). Propranolol is superior to a placebo in reducing migraine frequency by ≥ 50% (OR 1.94, 95% CI = 1.61-2.35, $p < 0.00001$).[45]

In a clinical study of propranolol, the dropout rate due to adverse effects was 5.3%.[45] Common adverse effects are fatigue, exercise intolerance, drowsiness, insomnia, nightmares, nausea, dizziness and depression.

Metoprolol, propranolol, and timolol are all level A medications as recommended in the latest guidelines.[32]

Calcium channel blockers

Flunarizine, a non-specific calcium channel blocker, has show effectiveness in migraine prophylaxis in several studies.[46,47] The mechanism in migraine prophylaxis could be due to the blocking of serotonin release and the attenuation of dural vasodilatation or probably by the blocking of L-type Ca2+ and Na+ channels and a reduction in NO synthesis.[44] The dosage is 5-10mg/d, and female patients seem to benefit from a lower dose than males.[48] Meta-analysis showed a significant reduction in the frequency of attacks with flunarizine 10mg vs a placebo (95% CI = 0.215-0.895; $p = 0.002$).[49] Antiserotonergic effects such as sedation and weight gain are the most frequent side effects. Flunarizine should be avoided by the elderly due to a risk of extrapyramidal side effects (parkinsonism). Flunarizine is not approved for migraine prophylaxis in many countries including the U.S. However in EFNS guidelines, flunarizine was recommended as one of the first choice medications for migraine prophylaxis (level A).[24]

Verapamil, an L-type calcium channel blocker, is used in both migraine and cluster headache prevention. A dosage of between 120-180mg/d is commonly prescribed. Side effects include constipation, dizziness, hypotension, and cardiac conduction block. Verapamil was downgraded to a level U medication in the 2012 guidelines due to data conflict.

Antidepressants

Antidepressants have been commonly used in migraine and tension-type headache prevention. Amitriptyline, the tricyclic antidepressant (TCA), has had several small but non controlled studies. Amitriptyline blocks the neuronal uptake of both serotonin and norepinephrine, and also inhibits the activation of the trigeminovascular system.

TCAs are more effective than placebos in reducing migraine frequency (mean difference -0.7, 95% CI = -0.93 to -0.48) but are not superior to selective serotonin reuptake inhibitors (SSRIs). Both TCAs and SSRIs reduce the intensity of migraine ≥ 50% than a placebo (OR 1.8, 95% CI = 1.24-2.62 for tricyclics and OR 1.72, 95% CI = 1.15-2.55 for SSRI).[50] A recent large randomized control trial of amitriptyline, with a dosage of 25-100mg/d for 20 weeks, showed a statistically significant superiority of amitriptyline over a placebo in migraine prophylaxis at 8 weeks (25% vs. 5%, $p = 0.031$) and at 16 weeks (46% vs. 9%, $p = 0.043$) but not at 12 or 20 weeks.[51] Common side effects are dry mucous membrane, somnolence, constipation, dizziness and urinary retention.

A dosage of between 25-150mg/d of amitriptyline and 100mg/d of nortriptyline showed benefits in migraine prevention. Some patients can tolerate and respond to a very low dose of 2.5-5mg/d. TCAs can be useful in patients with insomnia or fragmented sleep. On the other hand, prolonged sedation in the morning is a common adverse effect that can be improved by administering the medication in the early evening.

Extended release Venlafaxine, is a selective serotonin norepinephrine reuptake inhibitor (SNRI). The dosage of 150mg/d for 2 months showed a statistically significant reduction in the number of headache attacks compared to a placebo ($p = 0.006$) throughout the treatment period. Patient satisfaction was significantly different in the active group when compared to the placebo group ($p = 0.001$ at visit 2 and visit 6). The treatment benefits were rated good or very good in 80% of patients in the 75mg group and 88.2% of the patients in the 150mg group.[52] Adverse effects include nausea, vomiting, insomnia, nervousness, and decreased seizure threshold.

Histamine/Antihistamine

Histamine

Histamine showed efficacy in migraine prevention in three class II studies.[53-55] N-alpha-methyl histamine, 1-10 nano grams (ng) subcutaneous injection (SC) twice a week reduced headache frequency from 3.8 at baseline to 0.5 in the histamine group at 4 weeks of treatment ($p < 0.0001$). Histamine was superior to the placebo in the reduction of migraine frequency, severity and duration through 12 weeks of treatment ($p < 0.0001$). The reported adverse side effect of histamine SC was only a short lived itchiness at the injection site.[53]

The second study showed an equivalent efficacy of a 500mg daily sodium valproate dosage when compared to a 1-10ng for 2 times/week histamine SC injection. Headache frequency, duration, and intensity improved after only 8 weeks of treatment ($p < 0.05$). No adverse side effect was reported in the histamine group. Conversely, the sodium valproate group reported nausea 37%, tremors 34%, weight gain 24% and alopecia 12%.[54]

The third study of topiramate (100mg/d) was compared to a dosage of histamine 1-10ng for 2 times/ week SC. Both active groups showed improvement over the baseline in attack frequency, intensity, and the use of rescue medication. Eleven percent of the histamine group withdrew from treatment due to a lack of satisfaction with the speed of results.[55]

Antihistamine

Cyproheptadine, the antagonist of the histamine H1 receptor, 5-HT2, L-type calcium channel and muscarinic cholinergic receptor, is commonly used in childhood migraine prophylaxis. Cyproheptadine (4mg/d) was as effective as propranolol (80mg/d) in reducing migraine frequency and severity. A combination of cyproheptadine and propranolol was more effective than monotherapy.[56] Common side effects reported include drowsiness, weight gain, dry mouth, nausea, diarrhoea, and ankle oedema.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Some NSAIDs including naproxen sodium, ibuprofen, ketoprofen and fenoprofen have modest but significant migraine prophylaxis properties.[33,57] However, the regular use of NSAIDs for migraine prevention may exacerbate medication overuse, headache, and other adverse side effects including gastrointestinal disturbances, renal toxicity and increased cardiovascular risk. NSAIDs are more suitable for short term prophylaxis such as in menstrual-related migraine.

Aspirin (ASA) has been used in migraine prevention, but its efficacy remains controversial. A study comparing 300mg of ASA to 200mg of metoprolol in migraine patients showed metoprolol was more effective than aspirin (respondent rate 56.9% vs. 42.7%).[58] In another study, ASA 100mg given in combination with vitamin E 600 IU compared with a placebo in combination with vitamin E showed no difference in migraine frequency or severity of migraine at 12 months and 36 months.[59]

In the updated 2012 guidelines naproxen/naproxen sodium, ibuprofen, ketoprofen, and fenoprofen are classified as level B medications. Mefenamic acid and flubiprofen are classified as level C medications.

Angiotensin-converting enzyme inhibitors (ACEI) and Angiotensin II receptor antagonists (ARB)

Lisinopril (10mg twice a day (bid)) and candesartan (16mg/d) showed prophylaxis properties in migraine patients. They have been graded as level C medications as per recommendations in the latest updated AHS/AAN guidelines.

The mechanism of ACEI and ARB for migraine prophylaxis might be an attenuation of the central sympathetic tone, inhibition of oxidative stress, promotion of degradation of pro-inflammatory factors such as substance P, encephalin, and bradykinin and probably modulation of endogenous opioid systems.[44]

Lisinopril

Lisinopril, an angiotensin converting enzyme inhibitor (ACEI), was studied in a double-blind placebo-controlled test as a migraine prophylaxis. The treatment period was 12 weeks with 10mg/d lisinopril for 1 week then 10mg twice daily for 11 weeks, followed by 2 weeks wash-out period compared to a placebo. Headache hours, headache days, migraine days, and the headache severity index were significantly reduced by 20% (95% CI = 5-36%), 17% (95% CI = 5-30%), 21% (95% CI = 9-34%), and 20% (95% CI = 3-37%) respectively in the lisinopril group. Adverse effects include: arterial hypotension, a dry cough, and fatigue.[60]

Candesartan

Candesartan, an angiotensin II receptor antagonist (ARB), showed efficacy in reducing headache days in a randomized, double-blind, placebo controlled, cross-over study of candesartan (16mg/d) over 20 weeks (4 weeks of run-in period, 12 weeks of treatment, and 4 weeks of washout). During the 12 weeks treatment period, the mean number of days with headaches was statistically reduced (13.6 vs. 18.5 days, $p < 0.001$). The number of candesartan respondents (reduction of 50% compared to the placebo) was 31.6% for days with headache, and 40.4% for days with migraine. The tolerability profile of candesartan was comparable with the placebo.[61]

Herbal remedies, Vitamins, and Minerals

Petasites

Petasites (butterbur) is a purified extract from the Petasites hybridus root. Two studies by Grossman et al.[62] in 2001 and by Lipton et al.[63] in 2004 showed Petasites (50-75mg bid) was effective in reducing migraine attack frequency. In the first study, the frequency of migraine attacks decreased by a maximum of 60% versus the baseline and a significant reduction in the number of migraine attacks compared with the placebo ($p \leq 0.05$). In the second study, over a 4 months treatment period, migraine attack frequency was reduced by 26% in the placebo, and by 48% with Petasites extract (75mg bid) ($p = 0.0012$ vs. placebo), and 36% in Petasites 50mg bid ($p = 0.127$ vs. placebo). The most frequent adverse effects were: mild gastrointestinal events, predominantly burping. The currently updated guidelines considered

butterbur effective (Level A) for the prevention of episodic migraine headaches in adults.[32,33]

MIG-99 (Feverfew)

MIG-99 is extracted from tanacetum parthenium (feverfew). Two studies by Pfaffenrath et al.[64] in 2002 and Diener et al.[65] in 2005 showed the benefit of MIG-99 in migraine prophylaxis. In the first study (class I study), migraine frequency decreased from 4.76 by 1.9 attacks per month in the MIG-99 group and by 1.3 attacks in the placebo group (p =0.0456). A logistic regression analysis of respondent rate showed an odd ratio of 3.4 in favor of MIG-99 (p = 0.0049). Adverse events were similar to the placebo, and the most common symptoms are gastrointestinal and respiratory system disorders.[64]

The second study (class II study), confirmed the efficacy of MIG-99 (6.25mg three times a day (tid)) in reducing the mean number of migraine attacks versus the placebo (1.8 vs. 0.3 attacks/month, p = 0.02, 95% CI = 1.07-2.49).[65]

Riboflavin (vitamin B2)

Mitochondrial dysfunction resulting in impaired oxygen metabolism may play a role in migraine pathogenesis.[66] Riboflavin is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the electron transport chain. Riboflavin improved abnormalities in mitochondrial encephalomyopathies and this has been studied in migraine prophylaxis.[67-69]

A high dose of vitamin B2 (400mg) was significantly superior to the placebo in reducing the attack frequency (p = 0.005), headache days (p = 0.012), and migraine index (p = 0.012). The number needed to treat (NNT) was 2.3. Adverse effects are transient mild diarrhea and polyuria.[70]

Magnesium

A prospective study of oral magnesium (trimagnesium dicitrate) (600mg (24mmol) or a placebo daily for 12 weeks in migraine patients showed that the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group at week 9-12 compared to the baseline ($p < 0.05$). Migraine days and symptomatic drug use also decreased significantly in the magnesium group. Adverse effects were diarrhea (18.6%) and gastric irritation (4.7%).[71]

A combination of magnesium (300mg), riboflavin (400mg), and MIG-99 (100mg) was studied compared with the placebo (25mg of riboflavin). Both treatment groups showed improvement over the baseline, but no between-group differences were noted (42% respondents in the treatment group versus 44% in the placebo group; $p = 0.87$).[72]

Coenzyme Q10 (water-soluble disbursable form of Co-Q10)

Coenzyme Q10 is a mitochondrial cofactor involved in energy generation. Deficiency of coenzyme Q10 was found in 33% of childhood migraines.[73] In an open label study, 61.3% of patients who received coenzyme Q10 (150mg/d) had a greater than 50% reduction in number of days with migraine. No side effect was noted.[74] A double-blind placebo-controlled trial of coenzyme Q10 (100mg tid) for 4 months showed that the 50% responder rate was 47.6% compared with 14.3% by placebo (p = 0.02) (number-needed-to-treat = 3). The side effects reported were insomnia and dyspepsia.[75]

Miscellaneous Prophylaxis Drugs

Botulinum toxin type A

Botulinum toxin type A (BTA) inhibits acetylcholine release at motor nerve terminals.[76] Experimental studies in rats showed anti-nociceptive properties.[77,78] BTA is approved by the U.S. FDA for chronic migraine, defined as 15 or more headaches per month for at least 3 consecutive months, with clinical features of migraine without aura for at least 8 of those 15 days.[79] Two phase 3 studies of BTA in chronic migraine have been completed: The Phase III Research Evaluating Migraine Prophylaxis Therapy with BTA 155-195 units (U) every 12 weeks with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase (PREEMPT 1 and PREEMPT 2).[80,81]

In the PREEMPT 1 study, the primary end point (change in number of headache episodes from the baseline) was similar in BTA and placebo groups (-5.2 vs. -5.3 episodes; p = 0.344), however the secondary endpoints are significantly different between the two groups, there is significant reduction in headache days (p = 0.006) and migraine days (p = 0.002) with the BTA group.[80]

The PREEMPT 2 study was reported to have achieved both primary and secondary endpoints. BTA was statistically significantly superior to the placebo for reducing the frequency of headache days per 28 days relative to the baseline (-9.0 vs. -6.7 days; $p < 0.001$).[81]

The pooled results from PREEMPT 1 and PREEMPT 2 also showed a statistically significant benefit of BTA over the placebo in reducing the frequency of headache days at 24 weeks (-8.4 vs. -6.6; $p < 0.001$). Adverse events

Table 4: Drug Recommended for Short-Term Prevention of Migraine Associated With Menstruation

Medicines	Usual dosage	Evidence Level	Common side effects	Contraindications
Triptans				
Frovatriptan	2.5 mg bid perimenstrually	A	Dizziness, chest pain, difficulty breathing, fatigue, flushing	Ischaemic heart disease, stroke, uncontrolled hypertension, peripheral vascular disease, hemiplegic and basilar migraine
Naratriptan	1 mg bid for 5 days perimenstrually	B	Flushing, drowsiness, dizziness, paresthesia, neck/ throat tightness	
Zolmitriptan	2.5 mg bid or tid perimenstrually	B	Neck/ throat/ jaw pain/ tightness, dizziness, paresthesia, somnolence, chest heaviness	
Hormonal therapy				
Estrogen	1.5 mg estradiol in gel QD for 7 days perimenstrually	C	breast pain or tenderness, upset stomach, vomiting, heartburn, leg cramps, nervousness, loss of appetite	Caution in migraine with aura, cardiovascular risk factors, stroke, myocardium infraction, venous thromboembolism, endometrial cancer

QD = quaque die (every day) bid = bis in die (twice daily) tid = ter in die (three times a day)

were mild to moderate in severity and only a few patients discontinued (BTA 3.8%, placebo 1.2%) due to adverse effects.[82]

Pooled analyses of the 56 weeks PREEMPT clinical trials showed that BTA was statistically significant in reducing the frequency of headache days in patients with chronic migraine at week 56 when compared to the placebo (-11.7 vs. -10.8; $p = 0.019$). Several secondary efficacy variables at week 56 were also statistically significantly reduced in the BTA group, including frequencies of migraine (-11.2 vs. -10.3; $p = 0.018$) and moderate/severe headache days (-10.7 vs. -9.9; $p = 0.027$) and cumulative headache hours on headache days (-169.1 vs. -145.7; $p = 0.018$). BTA was safe and well tolerated, with few treatments related to adverse effects.[83] BTA is also effective in the subgroup of patients with medication overuse.[84]

α-adrenergic agonists

The centrally acting α2-adrenergic agonists clonidine and guanfacine have been used in migraine prophylaxis. Clonidine inhibits the firing of locus coeruleus neurons induced by activating presynaptic inhibitory α2 receptors. Clinical trials showed variable evidence and very few benefits.[85,86] Clonidine and guanfacine have been classified as level C agents in the latest updated guidelines.[32]

Short-term prophylaxis treatment

Short-term prophylaxis may be useful in migraine associated with menstruation. Menstrual migraine is defined as attacks occuring during the 5 day interval of time extending from 2 days before through 3 days after the onset of menses.[3] Drugs that have been used include NSAIDs, triptans, estrogen, magnesium, and ergot.[87]

Naproxen sodium (550mg oral bid) was the most commonly used NSAIDs for short-term prevention.[88] However, NSAIDs are not mentioned in the latest updated guidelines.

Triptans seem effectivce in the abortive management of menstrual migraines.[89] Systematic review of short-term prevention in perimenstrual migraine suggests frovatriptan (2.5mg bid) for 6 days perimenstrually (level A), naratriptan (1 mg bid) for 5 days starting 2 days before the expected onset of menses (level B), and transcutaneous estrogen 1.5 mg QD for 7 days (level C).[90] The AHS/AAN migraine prevention guidelines for short-term prevention of migraine associated with menstruation is shown in Table 4.

Conclusion

Migraine is a chronic debilitating disorder that affects the patients' quality of life. Migraine prevention should be considered for patients with frequent disabling migraine attacks (≥2 attacks/month), not controlled by acute medication, and complicated migraines. Preventive therapies include medication, behavioral, and alternative treatments. Topiramate, sodium valproate, metoprolol, propranolol, timolol, and butterbur are recommended as effective prophylaxis level A medications. Treatments and side effects of the treatments have to be discussed. Comorbidity should be considered and treated together.

Migraineurs need to have realistic expectations of success and be aware of the time needed for medication to take effect and the proposed duration of treatment. The goal of preventive therapy is to reduce the frequency, duration, and severity of migraine attack, to reduce disability, to improve patient functioning and to improve the responsiveness of acute attack medications in the future. Education is an important part of any successful treatment. Patients need to be informed about the nature of the disease, its progression, the need for changes in lifestyle including the avoidance of known triggers, getting regular sleep, eating regular meals, and effective stress management. Non-pharmacologic interventions such as biofeedback, relaxation training, aerobic exercise, rehabilitation, and acupuncture can be considered for migraine patients.

References

1. Lipton RB, Bigal ME, Diamond M, et al, for the AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68:343-9.
2. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001;41:646-57.
3. Ferrari MD. The economic burden of migraine to society. *Pharmacoeconomics* 1998;13:667-76.
4. Stewart WF, Lipton RB, Simon D. Work-related disability: results from the American Migraine study. *Cephalalgia* 1996;16:231-8.
5. Michel P, Dartigues JF, Lindousli A, et al. Loss of productivity and quality of life in migraineurs among French workers: results from the GAZEL cohort. *Headache* 1997;37:71-8.
6. Headache Classification Committee of the International Headache Society, The International Classification of Headache Disorders: 2nd edition, *Cephalalgia* 2004;24 (Suppl 1):9-160.
7. Schoenen J. Neurophysiological features of the migrainous brain. *Neurol Sci* 2006;27:77-81.
8. Olesen J, Burstein R, Ashina M, et al. Origin of pain in migraine: evidence for peripheral sensitisation. *Lancet* Neurol 2009; 8:679-90.
9. Maizels M, Aurora S, Heinricher M. Beyond Neurovascular: Migraine as a Dysfunctional Neurolimbic Pain Network. *Headache* 2012 Jul 3. doi: 10.1111/j.1526-4610. 2012.02209.x. [Epub ahead of print]
10. Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol* 2011;70:838-45.
11. Leonardi M, Steiner TJ, Scher AI, et al. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache and Pain* 2005; 6:429-40.
12. Stovner Lj, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27:193-210.
13. Edmeads J, Mackell JA. The economic impact of migraine: an analysis of direct and indirect costs. *Headache* 2002;42:501-9.
14. Ferrari MD. The economic burden of migraine to society. *Pharmacoeconomics* 1998;13:667-76.
15. Stewart WF, Lipton RB, Simon D. Work-related disability: results from the American Migraine study. *Cephalalgia* 1996;16:231-8.
16. Michel P, Dartigues JF, Lindousli A, et al. Loss of productivity and quality of life in migraineurs among French workers: results from the GAZEL cohort. *Headache* 1997;37:71-8.
17. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache* 2003;43:171-8.
18. Silberstein SD. Preventive treatment of migraine: an overview. *Cephalalgia* 1997;17:67-72.
19. Brown JS, Papadopoulos G, Neumann PJ, et al. Cost-effectiveness of topiramate in migraine prevention: Results from a pharmacoeconomic model of topiramate treatment. *Headache* 2005;45:1012-22.
20. D'Amico D, Solari A, Usai S, et al. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudi- nal multicentre study. *Cephalalgia* 2006;26:691-6.
21. Silberstein SD, for the US Headache Consortium Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-62.
22. Silberstein SD, Rosenberg J. Multispecialty consensus on diagnosis and treatment of headache. *Neurology* 2000;54: 1553.
23. Schroeder BM. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. *Am Fam Physician* 2003;67:1392,1395-7.
24. Evers S, Afra J, Frese A, et al. European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *Eur J Neurol* 2009;16:968-81.
25. Bigal ME, Lipton RB. Migraine chronification. *Curr Neurol Neurosci Rep* 2011;11(2):139-48.
26. Evans RW, Loder E, Biondi DM. When can successful migraine prophylaxis be discontinued? *Headache* 2004; 44:1040-2.
27. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. *Neurology* 2009;72(Suppl 5):S3-7.
28. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008;48:1157-68.
29. Bigal ME, Lipton RB, Holland PR, et al. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. *Neurology* 2007;68:1851-61.
30. Scher AI, Lipton RB, Stewart WF. Habitual snoring as a risk factor for chronic daily headache. *Neurology* 2003;60:1366-8.

31. Scher AI, Stewart WF, Buse D, et al. Major life changes before and after the onset of chronic daily headache: a population-based study. *Cephalalgia* 2008;28:868-76.
32. Silberstein SD, Holland S, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1337-45.
33. Holland S, Silberstein SD, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78: 1346-53.
34. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* 2008;28: 585-97.
35. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia* 2000;41(Suppl 1):S35-9.
36. Andreou AP, Goadsby PJ. Topiramate in the treatment of migraine: a kainate (glutamate) receptor antagonist within the trigeminothalamic pathway. *Cephalalgia* 2011;31: 1343-58.
37. Schürks M, Diener HC, Goadsby P. Update on the prophylaxis of migraine. *Curr Treat Options Neurol* 2008; 10:20-9.
38. Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. *CMAJ* 2010;182:E269-76.
39. Barbanti P, Aurilia C, Egeo G, et al. Migraine prophylaxis: what is new and what we need? *Neurol Sci* 2011;32 (Suppl 1):S111-5.
40. Margulis AV, Mitchell AA, Gilboa SM, et al. National Birth Defects Prevention Study. Use of topiramate in pregnancy and risk of oral clefts. *Am J Obstet Gynecol* 2012;207:405.e1-7.
41. Abtahi MA, Abtahi SH, Fazel F, et al. Topiramate and the vision: a systematic review. *Clin Ophthalmol* 2012;6: 117-31.
42. Vikelis M, Rapoport AM. Role of antiepileptic drugs as preventive agents for migraine. *CNS Drugs* 2010;24: 21-33.
43. Silberstein SD, Wilmore LJ. Divalproex sodium: migraine treatment and monitoring. *Headache* 1996;36:239-42.
44. Galletti F, Cupini LM, Corbelli I, et al. Pathophysiological basis of migraine prophylaxis. *Prog Neurobiol* 2009;89: 176-92.
45. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;CD003225.
46. Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002;22:209-21.
47. Leone M, Grazzi L, Mantia LL, et al. Flunarizine in migraine: a mini review. *Headache* 1991;31: 388-91.
48. Diener H, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002;22:209-21.
49. Reveiz-Herault L, Cardona AF, Ospina EG, et al. Effectiveness of flunarizine in the prophylaxis of migraine: a meta-analytical review of the literature. *Rev Neurol* 2003;36:907-12.
50. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* 2010;341:c5222.
51. Couch JR. Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache* 2011;51:33-51.
52. Ozyalcin SN, Talu GK, Kiziltan E, et al. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005;45:144-52.
53. Milla´n-Guerrero RO, Isais-Milla´n R, Benjamín TH, et al. N-alpha-methyl histamine safety and efficacy in migraine prophylaxis: phase III study. *Can J Neurol Sci* 2006;33:195-9.
54. Milla´n-Guerrero RO, Isais-Milla´n R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus sodium valproate in migraine prophylaxis: a randomized, controlled, doubleblind study. *Eur J Neurol* 2007;14:1079-84.
55. Milla´n-Guerrero RO, Isais-Milla´n R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus topiramate in migraine prophylaxis: a double-blind study. *Eur Neurol* 2008;59:237-42.
56. Rao BS, Das DG, Taraknath VR, et al. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. *Neurol India* 2000;48:223-6.
57. Welch KMA: Naproxen sodium in the treatment of migraine. *Cephalalgia* 1986;6:85-92.
58. Diener HC, Hartung E, Chrubasik J, et al. A comparative study of acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomised, controlled, double-blind, parallel group phase III study. *Cephalalgia* 2001;21:140-4.
59. Benseñor IM, Cook NR, Lee IM, et al. Low-dose aspirin for migraine prophylaxis in women. *Cephalalgia* 2001;21: 175-83.
60. Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001;322:19-22.
61. Tronvik E, Stovner L, Helde G, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. J*AMA* 2003;289: 65-9.
62. Grossman W, Schmidramsl H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. *Altern Med Rev* 2001;6:303-10.
63. Lipton RB, Gobel H, Einhaupl KM, et al. Petasites hybridus root (butterbur) is an effective preven-tive treatment for migraine. *Neurology* 2004;63:2240-4.

64. Pfaffenrath V, Diener HC, Fischer M, et al. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis–a double-blind, multicentre, randomized placebo- controlled dose-response study. *Cephalalgia* 2002;22:523-32.
65. Diener HC, Pfaffenrath V, Schnitker J, et al. Efficacy and safety of 6.25 mg tid feverfew CO2-extract (MIG-99) in migraine prevention–a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 2005; 25:1031-41.
66. Watanabe H, Kuwabara T, Ohkubo M, et al. Elevation of cerebral lactate detected by localized 1H-magnetic resonance spectroscopy in migraine during the interictal period. *Neurology* 1996;47:1093-5.
67. Penn AMW, Lee JWK, Thuillier P, et al. MELAS syndrome with mitochondrial tRNALeu (UUR) mutation: correlation of clinical state, nerve conduction, and muscle 31P magnetic resonance spectroscopy during treatment with nicotinamide and riboflavin. *Neurology* 1992;42: 2147-52.
68. Nishikawa Y, Takahashi M, Yorifuji S, et al. Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome c oxidase deficiency: a 31P NMR study. *Neurology* 1989;39:399-403.
69. Montagna P. High-dose riboflavin as a prophylactic treatment. *Cephalalgia* 1994;14:317.
70. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50:466-70.
71. Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996;16: 257-63.
72. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004;44: 885-90.
73. Hershey AD, Powers SW, Vockell A-LB, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache* 2007;47: 73-80.
74. Rozen TD, Oshinsky ML, Gebeline CA, et al. Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia* 2002;22:137-41.
75. Sándor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005;64:713-5.
76. Simpson LL.The origin, structure, and pharmacological activity of botulinum toxin. *Pharmacol Rev* 1981;33: 155-88.
77. Cui M, Khanijou S, Rubino J, et al. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain* 2004;107(1-2):125-33.
78. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology* 2005;26(5):785-93.
79. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26:742-6.
80. Aurora SK, Dodick DW, Turkel CC, et al. PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30:793-803.
81. Diener HC, Dodick DW, Aurora SK, et al. PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30:804-14.
82. Dodick DW, Turkel CC, DeGryse RE, et a. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010;50: 921-36.
83. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 2011;51:1358-73.
84. Sandrini G, Perrotta A, Tassorelli C, et al. Botulinum tox in type-A in the prophylactic treatment of medication-overusel headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. *J Headache Pain* 2011;12:427-33.
85. Stensrud P, Skaug OE, Sjaastad O. Clinical trial of MY-25 (1-methyl-ergotamine-bitartrate) in migraine prophylaxis. *Headache* 1971;11:128-31.
86. Kallanranta T, Hakkarainen H, Hokkanen E, et al. Clonidine in migraine prophylaxis. *Headache* 1977;17: 169-72.
87. Martin VT. Menstrual migraine: a review of prophylactic therapies. *Curr Pain Headache Rep* 2004;8:229-37.
88. Sances G, Martignoni E, Fioroni L, et al. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990;30:705-9.
89. Sullivan E, Bushnell C. Management of menstrual migraine: a review of current abortive and prophylactic therapies. *Curr Pain Headache Rep* 2010;14:376-84.
90. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. *Neurology* 2008 22;70:1555-63.

Tomosynthesis-Improved Breast Cancer Screening and Diagnosis

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Keywords:
tomosynthesis, breast cancer, cancer screening

Since its introduction in 2000, digital mammography has become an accepted standard of care in breast cancer screening and has paved the way for a new groundbreaking technology-breast tomosynthesis. With breast tomosynthesis, images of a breast are acquired at multiple angles during a short scan. The individual images are then reconstructed into a series of thin, high-resolution slices typically 1mm thick, which can be displayed individually or in a dynamic ciné mode. A tomosynthesis data set virtually eliminates detection challenges associated with overlapping structures in the breast, which is the primary drawback of conventional two dimensional (2D) mammography. Figure 1 illustrates the basic principle. As is known from standard computed tomography (CT) body imaging, three dimensional cross sectional slices often improve visibility through the reduction of superimposed structures.

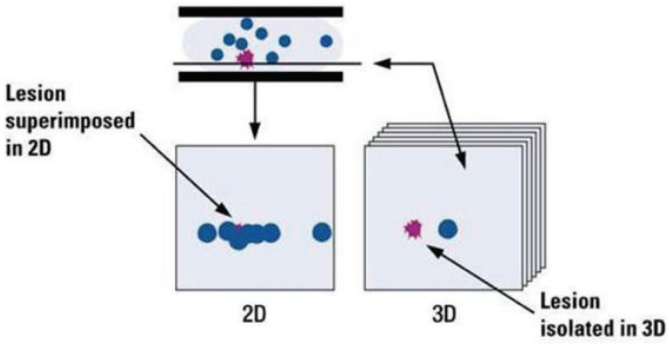

Figure 1: *Overlapping structures hides lesions in two dimensional (2D) that can be clearly seen in a three dimensional (3D) cross sectional slice.*

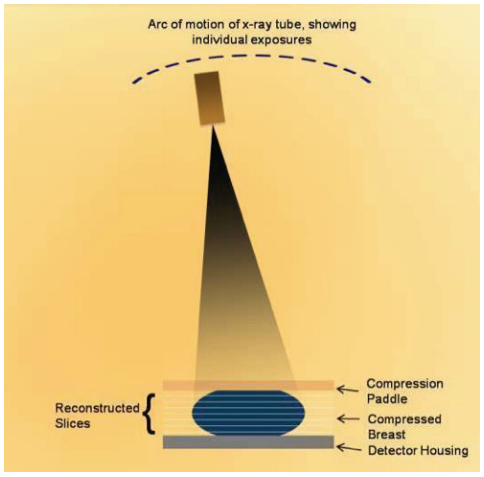

Figure 2: *Schematic shows principle of operation of tomosynthesis system.*

Figure 2 shows the geometry used in tomosynthesis imaging. The breast is compressed in a standard way as is done in conventional mammography. While the breast is compressed, the x-ray tube rotates around the breast in a limited angular sweep, acquiring a number of low-dose projection mammograms. These are then reconstructed into the cross-sectional slices, typically 1mm in separation. Each slice is parallel to the detector housing. Different manufacturers use different acquisition geometries, but all share a common method of performing limited angle tomography. Table 1 shows the system details for four systems. They differ in the scan angle, number of projections, and the scan time.

Table 1: Scan parameters used in some tomosynthesis systems.

System	Scan Angle (degrees)	Projections	Scan Time (sec)
Hologic	15	15	3.7
Siemens	50	25	25
General Electric	25	9	10
Sectra	11	21	10

Breast tomosynthesis systems from several major manufacturers have been available in Europe and other countries recognizing the CE mark since 2008. In February 2011, Hologic's Selenia® Dimensions® tomosynthesis system was the first commercial system approved by the United States (U.S.). Food and Drug Administration (FDA). The FDA approved the system for use in the same clinical indications as 2D mammography including breast cancer screening and diagnosis. Other manufacturers have announced plans to bring tomosynthesis to the U.S. but as of today, Hologic is the only vender with a commercial system in the U.S.

This article reviews the results of a number of clinical trials of tomosynthesis systems.

Initial Clinical Trials

The first multi-center tomosynthesis trial was the one performed by Hologic in support of their FDA submission. This trial compared the performance of 2D digital mammography plus tomosynthesis imaging (combo-mode) to that of 2D mammography alone. All subjects in the trial had bilateral 2-view mammograms (mediolateral oblique (MLO) and craniocaudal (CC) in both 2D and tomosynthesis imaging modes).

Two reader studies were conducted by Hologic using images from the initial clinical trial data set. The reader study results were analyzed using Receiver Operating Characteristics (ROC) methodology, with the area under the curve measuring the ability of individual radiologists (readers) to correctly characterize the presence or absence of disease.

Results from the first reader study were presented by Rafferty at the Radiological Society of North America (RSNA) annual conference in 2007, and both reader studies were presented at an FDA panel meeting in September 2010.[1,2] In both studies, the performance of 2D mammography plus tomosynthesis was shown to be significantly superior to the performance of 2D alone. In addition, both studies showed a reduced non-cancer recall rate. These results were consistent with those of an independent third reader study from University of Pittsburgh researchers who found a 7% improvement in the area under the ROC curve for 2D plus tomosynthesis compared to 2D alone.[3]

The clinical benefits of tomosynthesis as demonstrated by Hologic's clinical trials and independent trials conducted by a variety of researchers world-wide are discussed below.

Improved Sensitivity

Hologic's clinical trials showed that radiologists reading in combo-mode compared to 2D alone demonstrated improved sensitivity in the measure of how many cancers are detected. The figure below shows a hypothetical example of ROC curves based on 2D plus tomosynthesis imaging.

Hypothetical ROC Analysis

A Comparison of the Ability of Readers to Correctly Characterize the Presence or Absence of Cancer with Conventional 2D Mammography and 2D Mammography Plus Tomosynthesis.

The first trial results on improved cancer detection in a screening environment were presented by Skaane at the RSNA 2011 conference.[4] In an analysis of the first 3,500 patients entering a prospective trial of over 20,000 women, Skaane observed a relative increase of 47% in cancer detection using tomosynthesis compared to 2D mammography alone.

Reduced Recall Rate

A reduction in recall rates was reported for 2D plus tomosynthesis compared to 2D alone in the two Hologic reader studies and the reader study by Gur et al.[5] The Gur reader study suggested that the use of tomosynthesis during baseline screening mammography may reduce the recall rate by 28%. Rafferty[1], in her 2007 RSNA presentation, estimated the recall reduction rate to be over 40%. Subsequent studies have also found a significant reduction in recall rates with tomosynthesis.

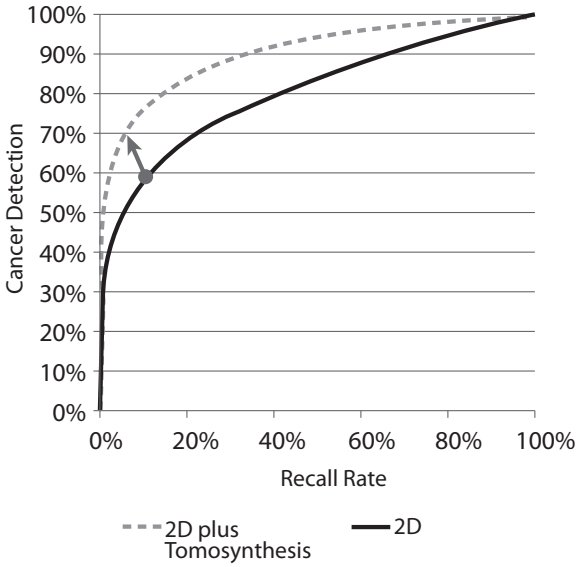

***Figure 3**: The diagonal arrow shows how an individual's cancer detection rate can be improved and their recall rate reduced using a technology that has a higher ROC curve.*

Greater Performance Using Two-View Tomosynthesis

The three reader studies referenced above used two-view mammography for both 2D and tomosynthesis imaging. One of the reader studies also investigated a 3rd arm: single-view tomosynthesis (MLO) imaging in combination with 2-view (CC and MLO) 2D imaging.[2] In this reader study, the performance of 2D imaging plus tomosynthesis MLO showed that the tomosynthesis MLO-only arm performed better than 2D imaging alone, but not as well as 2D plus both tomosynthesis views.

These results are consistent with several other studies, illustrating that MLO-only tomosynthesis is likely to be inferior to two-view tomosynthesis:

- Rafferty[6] found that 12% of lesions were better seen on the tomosynthesis MLO image, 15% better seen on tomo CC and 9% of lesions were visible only on tomo CC.

- Similar results were reported by Baker[7], who found 8% of lesions were visible only on the tomosynthesis CC view and 1.4% only on the tomo MLO.

Performance in Calcifications, Masses and Distortions

The clinical trial data in Hologic's reader studies has been analyzed by separating the image sets into calcification and non-calcification cases. Rafferty[1] found that 2D plus tomosynthesis offered a very significant increase in performance relative to 2D imaging for cases involving masses and distortions. For the imaging of cases involving microcalcifications, there was a small, but not statistically significant, improvement in the ROC performance with the addition of tomosynthesis.

Other studies have looked at calcifications and their visibility with tomosynthesis. For example, Kopans[8] found that the characterization of calcifications in tomosynthesis was equal or superior to their characterization in conventional digital mammography in 92% of the cases studied.

Performance in Fatty and Dense Breasts

Tomosynthesis has been shown to improve the performance of mammography in both fatty and dense breasts. Researchers have performed an analysis on cases following their grouping into fatty breast (defined as Breast Imaging-Reporting and Data System (BI-RADS) 1 and 2) and dense breast (defined as BI-RADS 3 and 4) sub-groups. Rafferty[9] studied the performance of tomosynthesis in women with dense breasts and found an increase in the recall for cancer cases and a reduction in the recall rate for non-cancer cases.

In a separate study, Rafferty[10] found that 2D plus tomosynthesis was significantly better than 2D mammography alone in ROC performance for both fatty and dense breasts. While there was a gain in the area under the ROC curve in both breast density types, the gain was 2-3 times higher in dense breasts than it was in fatty breasts. Rafferty[10] also reported large recall rate reductions in both fatty and dense breast types.

Tomosynthesis Performance in the Evaluation of Symptomatic Patients

The use of tomosynthesis in diagnostic assessment offers the opportunity for both improved performance and a reduction in the number of x-ray images needed, as well as superior performance compared to 2D mammography in predicting tumor size, demonstrating margins, extents of lesions, and in staging.

Zuley et al.[11] found comparable sensitivity and specificity in the use of two-view tomo imaging in place of the additional diagnostic 2D views typically taken.

Tagliafico[12] found that tomosynthesis could replace spot compression views, lowering both radiation dose and offering the potential to reduce biopsies on nonmalignant lesions.

Svahn[13] showed that the combined diagnostic performance of digital mammography and tomosynthesis is superior to either digital mammography or tomosynthesis alone.

Michell[14] showed that tomosynthesis is superior to 2D mammography in predicting the histological tumor size because tomosynthesis demonstrates the margins and extents of the mammographic lesions more clearly.

Fornvik[15] found breast tomosynthesis superior to digital mammography in the assessment of breast tumor size and stage.

Meacock[16] found that tomosynthesis was more accurate than 2D in tumor size measurement.

2D vs. Tomosynthesis (3D) Imaging

Early investigators using tomosynthesis hypothesized that three dimensional (3D) breast imaging would replace 2D imaging. That may yet happen, but so far the best clinical performance of tomosynthesis imaging has been shown when combined together with a 2D exam, i.e. 2D plus 3D imaging.

There are several reasons why acquiring both a 2D mammography and tomosynthesis image together are useful, especially in screening. It is well known that comparison of current images with prior images is standard mammography practice and critical to perceive subtle changes which may be associated with a cancer. Obtaining a 2D exam along with the tomosynthesis exam allows direct comparison of current 2D images with prior 2D images.

The 2D exam is also useful for the rapid detection of calcifications. Clusters of calcifications are more easily and quickly appreciated with 2D because all the calcifications appear together in one image.

The tomosynthesis portion of the 2D plus 3D exam is also critical. The tomosynthesis image reduces structure overlap, minimizing recalls for overlapped structures and better demonstrates masses and architectural distortions. Thus we see that 2D and Tomo are complementary and acquired together offers an advantage in clinical use.

There may be methods to eliminate the need to separately acquire the 2D exam through mathematical algorithms that generate a synthesized 2D image reconstructed from the Tomo dataset. This approach is being evaluated in a screening clinical trial in Oslo, Norway, with principal investigator Per Skaane.

Conclusion

Breast tomosynthesis is an exciting new technology that offers the potential for improvements in both breast cancer screening and diagnostic evaluations. Clinical trial results demonstrate that:

- 2D mammography plus tomosynthesis is superior to 2D alone
- The sensitivity of 2D mammography plus tomosynthesis is higher than 2D alone
- The screening recall rate of 2D mammography plus tomosynthesis is lower than that of 2D alone
- Performance using both tomo CC and MLO views was greater than tomo MLO alone
- 2D mammography plus tomosynthesis provides improved performance in both fatty and dense breasts, compared to 2D alone, with the performance gain in dense breasts higher than in fatty breasts.
- Tomosynthesis is useful in diagnostic imaging of the symptomatic patient. Tomosynthesis has the potential to reduce the number of exposures needed for diagnostic imaging and provide other diagnostic benefits including enhanced performance in assessing tumor size and stage and more clearly demonstrating margins and extent of lesions.

Opinion: Digital Tomosynthesis of the Breast

A 42-year-old female presented with a small mobile mass on the inner aspect of the left breast for a period of two months. Previously her annual mammogram check-ups were negative. The 2D mammogram reveals a heterogeneous dense breast with a craniocaudal (CC) view, and no abnormality is seen (Figure 6). The 3D breast tomosynthesis shows a well defined mass on the upper inner quadrant, the size is 16x18mm (Figure 7). The ultrasound is inconclusive in identifying the mass (Figure 8).

The biopsy revealed a benign intraductal papilloma. No evidence of malignancy was observed. The 3D breast tomosynthesis is very helpful to ensure more accuracy and to give physicians additional information in the case of a dense breast.[1-4] This modality will reduce the number of recalls and also reduce further sophisticated investigations in the case of clear cut criteria of imaging by BI-RADS.

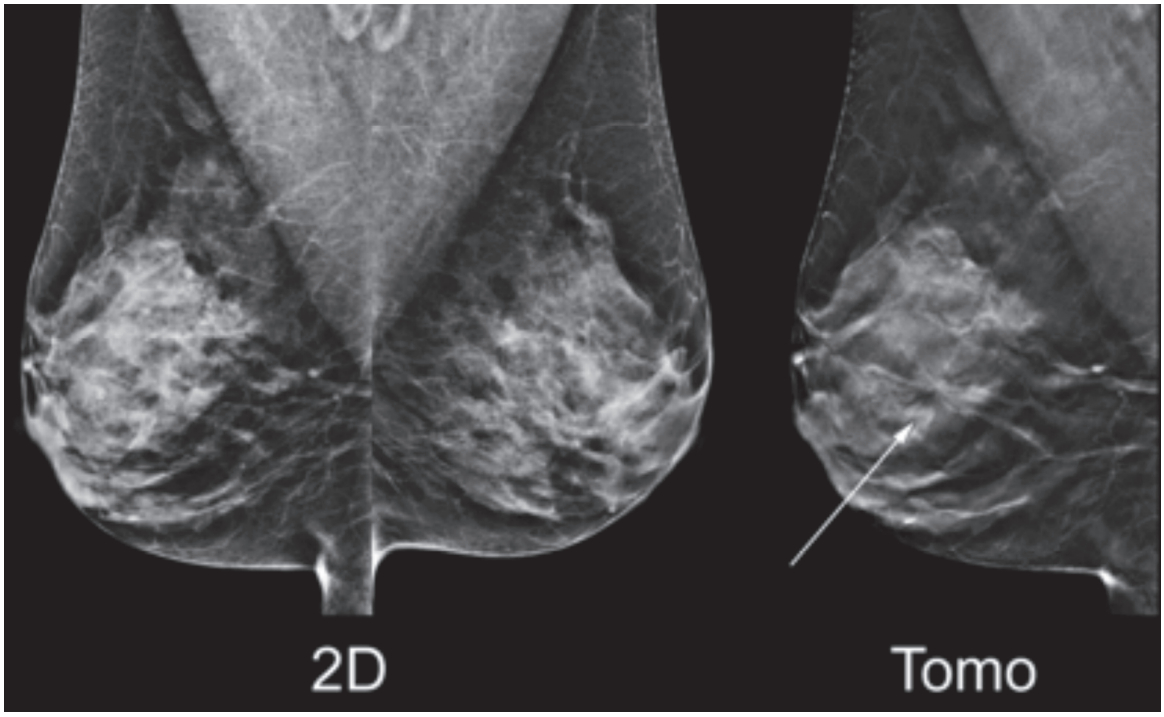

Figure 4: *Increased cancer detection: the tomosynthesis reconstructed slice shown on the right reveals a definitive spiculated mass that is only faintly revealed in the 2D image shown on the left. (Diagnosis: Invasive Ductal Carcinoma)*

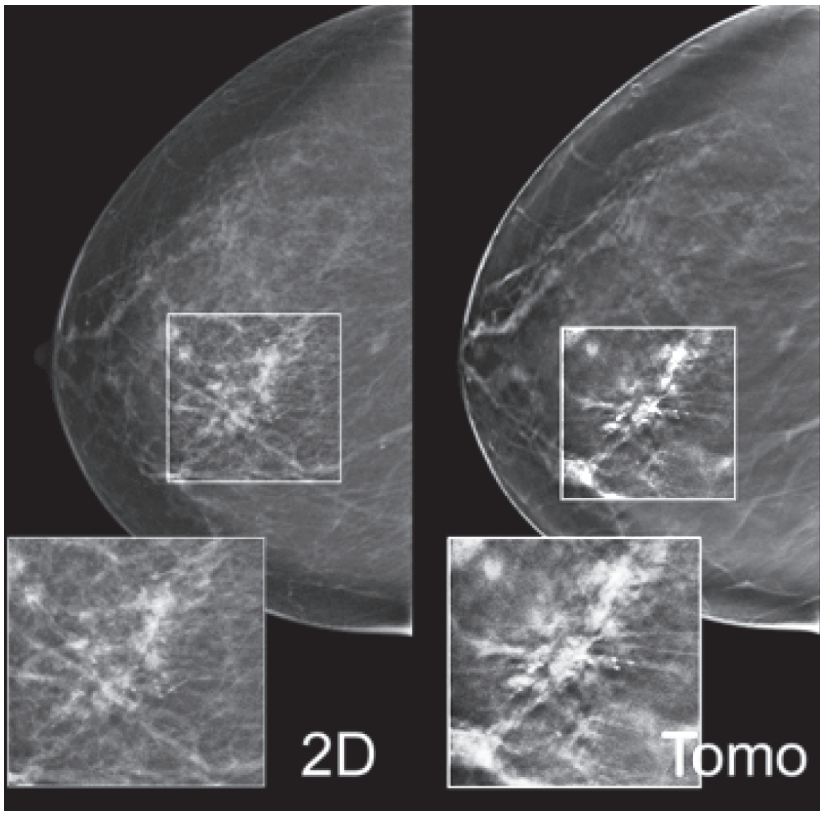

Figure 5: *Added value for calcifications: the 2D mammogram on the left shows right medial microcalcifications. The tomosynthesis reconstructed slice on the right illustrates the associated architectural distortion only revealed on the CC tomosynthesis image and not shown on the mammogram. (Diagnosis: Ductal Carcinoma In-situ/High Grade)*

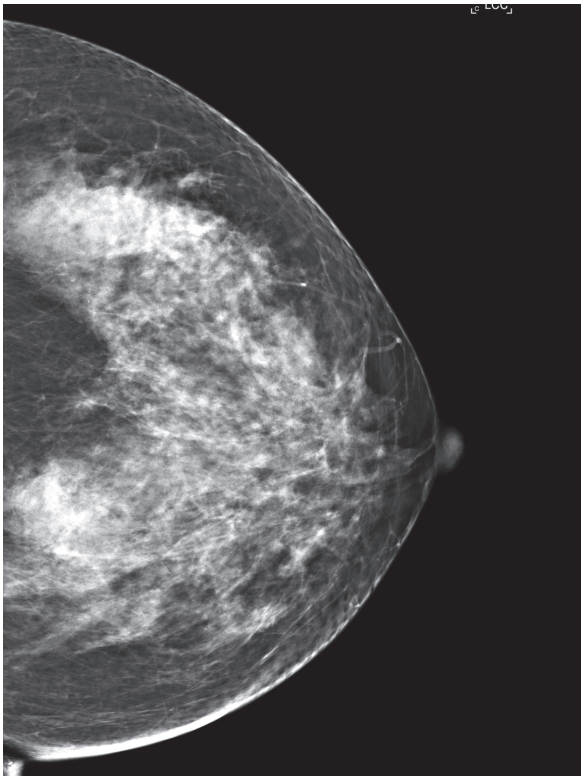

Figure 6: *The 2D mammogram reveals a heterogeneous dense breast with a craniocaudal (CC) view.*

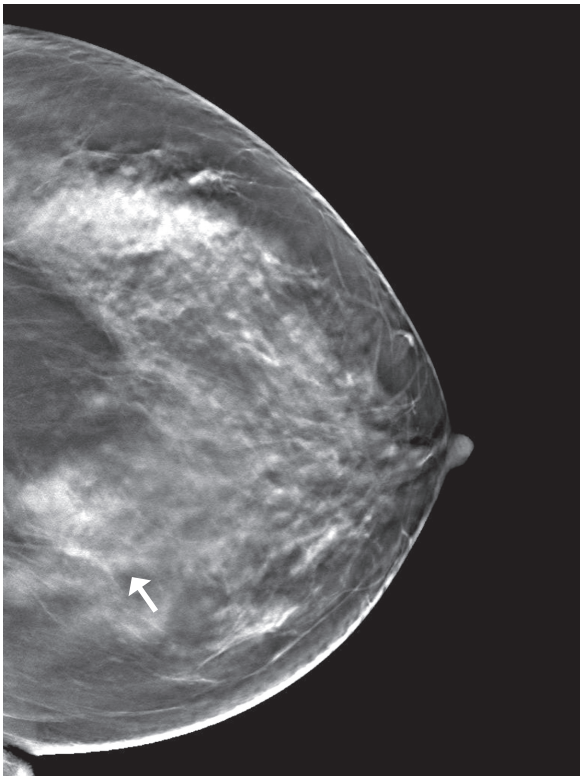

Figure 7: *The 3D breast tomosynthesis shows a well defined mass on the upper inner quadrant; the size is 16x18mm (arrow).*

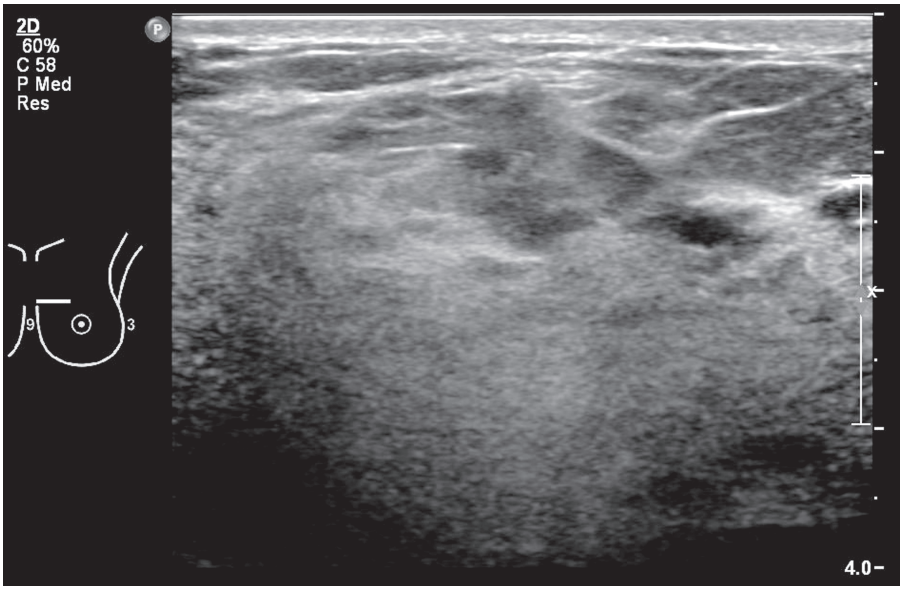

Figure 8: *The ultrasound is inconclusive in identifying the mass*

References

1. Rafferty E, Niklason L, Halpern E, et al. Assessing radiologist performance using combined full-field digital mammography and breast tomosynthesis versus full-field digital mammography alone: results of a multi-center multi-reader trial. Radiological Society of North America annual meeting. Chicago, 2007.
2. http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080003b.pdf
3. Gur D, Bandos AI, Rockette He, et al. Is an ROC-type response truly always better than a binary response in observer performance studies? *Acad Radiol* 2010;5:639-45.
4. Skaane P, Gullien R, Eben EB, et al. Reading time of FFDM and tomosynthesis in a population-based screening program. Radiological Society of North America annual meeting. *Chicago*, 2011.
5. Gur D, Sumkin J, Zuley R, et al. Recall rate reduction with tomosynthesis during baseline examinations - preliminary assessment from a prospective screening trial. Radiological Society of North America annual meeting. *Chicago*, 2011
6. Rafferty E, Niklason L, Jameson-Meehan L. Breast tomosynthesis: one view or two? Radiological Society of North America annual meeting. *Chicago*, 2006.
7. Baker JA, Lo JY. Breast tomosynthesis: state-of-the-art and review of the literature. *Acad Radiol* 2011;18: 1298-310.
8. Kopans D, Moore R. Calcifications in digital breast omosynthesis (DBT). Radiological Society of North America annual meeting. *Chicago*, 2008.
9. Rafferty EA, Niklason L. FFDM versus FFDM with tomosynthesis for women with radiologically dense breasts: an enriched retrospective reader study. Radiological Society of North America annual meeting. *Chicago*, 2011.
10. Rafferty EA, Niklason L, Smith A. Comparison of FFDM with breast tomosynthesis to FFDM alone: performance in fatty and dense breasts. Tomosynthesis Imaging Symposium, Duke University, 2009.
11. Zuley M, Sumkin J, Ganott M, et al. Digital breast tomosynthesis vs. supplemental diagnostic mammography images for the evaluation of non-calcified breast lesions. Radiological Society of North America annual meeting. Chicago, 2011.
12. Tagliafico A, Astengo D, Cavagnetto F, et al. One-to-one comparison between digital spot compression view and digital breast tomosynthesis. *Eur Radiol* 2012;22:539-44.
13. Savhn T, Andersson I, Chakraborty D, et al. The diagnostic accuracy of dual-view digital mammography, single-view tomosynthesis and adual-view combination of breast tomosynthesis and digital mammography in a free-response observer performance study. *Radiat Prot Dosimetry* 2010;139:113-7.
14. Michell M, Iqbal A, Wasan R, et al. A comparison of the accuracy of digital breast tomosynthesis with two dimension digital mammography in measurement of breast tumour size. Radiological Society of North America annual meeting. *Chicago*, 2010.
15. Fornvik D, Zackrisson S, Ljunberg O, et al. Breast Tomosynthesis: Accuracy of tumor measurement compared with digital mammography and ultrasonography. *Acta Radiol* 2010;3:240-7.
16. Meacock LM, et al. The accuracy of breast cancer size measurement: Digital breast tomosynthesis (DBT vs. 2D digital mammography). European College of Radiology annual meeting. Vienna, Austria, 2010.

Review Article

Anticoagulant agents for Acute Coronary Syndromes

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Keywords:
anticoagulant, acute coronary syndromes, ACS, heparin, STEMI

The classical recommendations for efficient and safe use of fibrinolytic agents have been described in detail in The Bangkok Medical Journal; February 2012, Volume 3. This article is an up to date description of how to use anticoagulant agents in acute coronary syndrome.

Intravenous and subcutaneous anticoagulants

It is generally agreed that short-time administration of an anticoagulant in the acute phase of an acute coronary syndrome (ACS) is beneficial. There is however ongoing debate about the best choice of intravenous or subcutaneous anticoagulant therapy for acute-phase management of ACS patients. Current recommendations for the use of unfractionated heparin (UFH), enoxaparin, fondaparinux, or bivalirudin vary depending on whether or not patients are undergoing fibrinolysis, Percutaneous Coronary Intervention (PCI), or surgical revascularization, and on individual patient characteristics, including ischemic and bleeding risk.

UFH is still widely used, but a systematic overview of enoxaparin studies involving non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients (with or without PCI) showed a statistically significant reduction in the composite endpoint of death or nonfatal myocardial infarction (MI) at 30 days with enoxaparin compared with UFH.[1] Furthermore, individual responses to UFH vary considerably, necessitating careful monitoring of activated clotting times.[2] In ST-segment elevation myocardial infarction (STEMI) populations, trials showed that enoxaparin reduced cardiovascular event rates compared with UFH in patients receiving fibrinolysis[3] or undergoing primary PCI (ATOLL trial)[4] but not in those who were unsuitable for revascularization (TETAMI trial).[5] There is also evidence of an increased risk of bleeding with enoxaparin compared with UFH (e.g. ExTRACT-TIMI253, TIMI 11B-ESSENCE meta-analysis, and SYNERG.[6,7] It should be noted that pre-randomization anticoagulation treatment in these trials may have led to an excess of bleeding in some cases. Nevertheless, careful dose adjustment of enoxaparin and other low molecular weight heparins (LMWHs) is necessary in patients who are older, underweight, or have renal failure. Both UFH and LMWHs carry a potential risk of *'heparin rebound'* after stopping treatment, resulting in increased thrombin generation (i.e., above baseline levels), but this tends not to be a serious clinical issue. Heparin-induced thrombocytopenia is an uncommon but serious complication.[2]

The selective Factor Xa inhibitor fondaparinux has been shown to achieve a comparable reduction in cardiovascular events to that achieved with enoxaparin in patients with NSTE-ACS, with a significant reduction in major bleeding, leading to improved long-term

mortality and morbidity in the fondaparinux group (OASIS-5 trial).[8] Although the bleeding rates due to dose choice of enoxaparin were higher than in previous studies with this agent, similar results were seen in a secondary analysis of patients in this study who underwent PCI.[9] However, guiding catheter thromboses were more common in the fondaparinux group (0.9% vs. 0.4%), except in those who also received open-label UFH after fondaparinux.[9] In a study in STEMI patients, fondaparinux was found to reduce cardiovascular endpoints compared with placebo in those without an indication for heparin, and compared with UFH in those with an indication for heparin, with no differences in major bleeding between the treatment groups (OASIS-6 trial).[10] It should be noted that most patients who did not undergo primary PCI in this study were treated with streptokinase, and only a minority with fibrin-specific agents. As in the OASIS-5 trial, there was an increased rate of guiding catheter thrombosis with fondaparinux compared with UFH in patients undergoing PCI. A Cochrane Database systematic review of fondaparinux randomized controlled trials (RCTs) in patients with ACS found that it was associated with a reduced risk of all-cause mortality at 90-180 days compared with UFH or enoxaparin, and with a reduced incidence of major and minor bleeding compared with enoxaparin (but not UFH).[11]

Bivalirudin is a direct thrombin inhibitor that has demonstrated comparable efficacy to heparin (UFH or enoxaparin) plus a glycoprotein (GP) IIb/IIIa inhibitor in NSTE-ACS patients, including those undergoing PCI, with similar rates of major bleeding (ACUITY trial).[12,13] Bivalirudin was associated with a significant reduction in major bleeding compared with heparin and a GpIIb/IIIa inhibitor, with similar rates of ischemic endpoints. Subsequent analysis of PCI patients from the ACUITY trial suggested that timing of clopidogrel therapy was important in this context.[14] That is, bivalirudin without a GPIIb/IIIa inhibitor may actually be associated with worse outcomes than with heparin in patients who only received clopidogrel more than 30 minutes after PCI or not at all, as opposed to before or within 30 minutes of PCI. On the other hand, bivalirudin may be particularly suitable for elderly patients with NSTE-ACS because bleeding complications were significantly less frequent in patients aged 75 years or more treated with bivalirudin alone compared with heparin plus GPIIb/IIIa inhibitor, but with similar rates of ischemic outcomes.[15] In the recently published ISAR-REACT 4 studies in NSTEMI patients undergoing PCI, bivalirudin was also found to be associated with significantly less bleeding than heparin plus abciximab, with comparable ischemic event rates.[16]

A study evaluating bivalirudin in STEMI patients undergoing PCI also demonstrated comparable efficacy and reduced rates of major bleeding compared with UFH plus a GPIIb/IIIa inhibitor (HORIZONS-AMI trial).[17] Patients treated with a clopidogrel 600mg loading dose in this study had significantly reduced 30 days ischemic adverse and bleeding event rates compared with those who received a clopidogrel 300mg loading dose.[18] The 3-year mortality was significantly less in bivalirudin-treated patients.[19]

New oral anticoagulants

The oral factor Xa inhibitors rivaroxaban, apixaban, and darexaban have all been evaluated on top of standard therapy in ACS, with varying degrees of benefit and a consistent increase in bleeding risk versus placebo. Development of darexaban has actually been discontinued for all indications[20] following disappointing results in a phase II trial in ACS, which showed increased bleeding with no reduction of ischemic events with various darexaban regimens on top of dual antiplatelet therapy (RUBY-1 trial).[21]

A phase III trial with apixaban in ACS was terminated prematurely after enrollment of 7,392 patients (out of a planned 10,800) because of an increased bleeding risk with apixaban versus placebo, with no reduction in recurrent ischemic events (APPRAISE-2 trial).[22] A phase II Japanese study (NCT00852397) with apixaban has also been stopped.

The oral direct thrombin inhibitor dabigatran has also been evaluated in a phase II study in ACS patients, but showed a dose-related increase in major bleeding at 6 months without a convincing signal for a reduction in ischemic events (RE-DEEM trial).[23]

However, a phase III trial with rivaroxaban in ACS reported a statistically significant reduction in the primary composite endpoint of cardiovascular death, MI, and stroke compared with standard therapy plus placebo (ATLAS ACS 2-TIMI 51 trial).[24] The low-dose rivaroxaban arm (2.5mg twice a day (bid)) showed a significant reduction in total mortality. There was an increased risk of major and intracranial bleeding with rivaroxaban, but no increased risk of fatal bleeding.

Implications for guidelines

The latest ESC (the European Society of Cardiology) guidelines for NSTE-ACS recommend the use of fondaparinux as a first-line anticoagulant, because it has the best efficacy-safety profile.[25] For patients undergoing PCI, they also recommend the use of a single bolus of UFH. Subsequent choices are enoxaparin and then UFH; although bivalirudin without a GPIIb/IIIa inhibitor is recommended as an alternative for patients with an early invasive strategy, particularly if the bleeding risk is high.[25] The current STEMI guidelines also recommend UFH or bivalirudin during primary PCI. Whether rivaroxaban on top of dual antiplatelet therapy will be recommended in future guidelines will depend on further analyses of the ATLAS ACS 2 study.

References

1. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes. A systematic overview. *JAMA* 2004;292:89-96.
2. Sakhuja R, Yeh RW, Bhatt DL. Anticoagulant agents in acute coronary syndromes. *Curr Probl Cardiol* 2011; 36:127-68.
3. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; 354:1477-88.
4. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction : the international randomised open-label ATOLL trial. *Lancet* 2011;378:693-703.
5. Cohen M, Gensini GF, Maritz F, et al. The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute ST-segment elevation myocardial infarction patients ineligible for reperfusion (TETAMI): a randomized trial. *J Am Coll Cardiol* 2003;42:1348-56.
6. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/ non-Q-wave myocardial infarction TIMI 11B–ESSENCE meta-analysis. *Circulation* 1999;100:1602-8.
7. White HD, Kleiman NS, Mahaffey KW, et al. Efficacy and safety of enoxaparin compared with unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial. *Am Heart J* 2006; 152:1042-50.
8. Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464-76.
9. Mehta RH, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007;50:1742-51.
10. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295:1519-30.
11. Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes. *Cochrane Database Syst. Rev* 2011;Jan 19(1):CD007038.
12. Stone GW, McLaurin BlT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203-16.
13. Stone GW, Ware JH, Bertrand ME, et al. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007;298:2497-506.
14. Lincoff AM, Steinhubl SR, Manoukian SV, et al. Influence of timing of clopidogrel treatment on the efficacy and safety of bivalirudin in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention: an analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *JACC Cardiovasc Interv* 2008;1: 639-46.
15. Lopes RD, Alexander KP, Manoukian SV, et al. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *J Am Coll Cardiol* 2009;53:1021-30.
16. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 2011;365:1980-9.
17. Mehran R, Lansky AJ, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarctions (HORIZONS-AMI): 1-year results of a randomized controlled trial. *Lancet* 2009;374:1149-59.
18. Dangas G, Mehran R, Guagliumi G, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 2009;54: 1436-46.
19. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 2011;377:2193-204.
20. Astellas Pharma Inc. Astellas Pharma Inc. discontinues development of darexaban (YM150), an oral direct Factor Xa inhibitor. http://www.astellas.com/en/corporate/news/detail/astellas-pharma-inc-discontinu.html (Accessed 5 January 2012).
21. Steg PG, Mehta SR, Jukema W, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. *Eur Heart J* 2011;32:2541-54.
22. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndromes. *N Engl J Med* 2011;365:699-708.
23 .Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011;32:2781-9.
24. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-12.
25. Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.

Gene in Multiple Cancers

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Keywords:
cancer, gene, multiple cancers

Genes are the determinants of individual appearance or phenotype. Several studies reveal the clinical association between genes and cancer. To study the genes and their relationship to cancer is the present focus in clinical oncology. In this specific brief review, the author would like to introduce a group of genes that are associated with multiple cancers.

In carcinogenesis, a complex process has to occur.[1, 2] Briefly, there are two main contributing factors that lead to cancer development. One is genetic and the other is environmental.[3-7] Genes are the determinant of individual appearance or phenotype. Several studies reveal the clinical association between genes and cancer. To study the genes and their relationship to cancer is the present focus in clinical oncology. With advancements in post-genomic bioinformatics technology, many new gene profiling techniques allow medical scientists to measure the expressions of many genes. Also, informatics can help clarify and predict the association between gene disorders and development as well as progression of malignancy.

Studying the relationship between genes and cancer can provide much useful data in clinical oncology. The derived data can be used for diagnosis, therapy and prognosis predictions. Briefly, there are three groups of genes which are classified according to their known relationship to cancer.[8,9] The first group is the genes with confirmed evidence that they relate to cancer. The second group is the genes with confirmed evidence that they do not relate to cancer. The last group is the genes without clear evidence for their relationship to cancer. The genes which are being focused on by biomedical researchers at present are those in the first group.

In this specific brief review, the author would like to introduce a group of genes that are associated with multiple cancers. It is the case that one gene mutation can result in multiple cancers in a patient.

Multiple cancers: an interesting pathology

Put simply, cancer is the uncontrolled growth of cells that can invade nearby structures as well as migrate to remote organs (metastasis). Due to the invasive nature of cancer, it can result in death. Generally, a patient might develop malignancy if the required genetic and environmental disorders are fulfilled.[3] In general, the malignancy in a patient is usually due to a single cancer (with or without metastasis). This means there is only one primary focus of the malignancy that causes the disease in the patient. However, in some uncommon cases, there might be more than one foci in a patient. This is called multiple cancers.

Table 1: Some interesting reports on multiple cancers

Authors	Combination
Capaldo et al.[12]	Ovarian carcinoid tumor, mucinous cystadenoma of low malignant potential tumor of left ovary, and adenocarcinoma of colon[12]
Demandante et al.[13]	Synchronous ureteral/bladder/urethral transitional cell carcinoma and prostatic adenocarcinoma[13]
Kobayashi et al.[14]	Uterus, stomach, breast cancer and glioblastoma multiforme[14], uterus, stomach cancer and glioblastoma[14]
Klochikhin et al.[15]	Neoplasm of the laryngopharynx and stomach[15]
Sielanczyk et al.[16]	Endometrial uterus cancer, breast cancer and thyroid cancer[16]

Multiple cancers is an interesting pathology. Below are some pathological descriptions of multiple cancers:[10, 11]

- Primary cancers that appear in a patient in different organs at the same time
- Cancer found in both sides of paired organs such as breast and kidney is not considered as a cancer in different organs
- Different kinds of malignancies in the same organ are considered as a cancer in the same organ
- The uterus with adnexa and the lower intestine are each classified as single organs
- There must be histological confirmation of malignant nature
- Metastatic lesions are not considered as a new primary cancer
- The malignancy must not be the result of previous cancer therapy (chemotherapy or radiotherapy)

These criteria are called *"Werthamer criteria"*.[10] Multiple cancers is classified as a rare syndrome that can be seen in less than 1 % of cancerous patients. Some rare combinations are sporadically reported in literature[12-16] (Table 1). Focusing on the natural history of multiple cancers, Schoenberg[17] analyzed the Connecticut data during 1935-1964 and concluded that *"individuals with one malignant neoplasm have 1.29 times the risk of developing a new independent primary tumor when compared to individuals who never had cancer"*. However, the increased risk seems to be site dependent. According to another newer study by Ray et al.[18], no increased risk could be observed for prostate cancer. Similar findings were also reported for laryngeal cancer.[19] Also, in this work[19], the size and site of the laryngeal tumor was shown to have no relationship to the occurrence of other primary cancers. Patients with multiple cancers usually have a family history of cancers. However, no family history can also be seen.[16]

Role of genes in hereditary multiple cancer syndrome

As noted, genetic defects is an important basic requirement for carcinogenesis. For some cancers such as retinoblastoma, there is already copious information on the underlying gene mutations that cause the cancers. For multiple cancers, the genes that have correlation are of interest. There are several, specific groups of multiple cancers that have strong evidence of genetic inheritance. The so called hereditary multiple cancer syndrome is the name of those disorders.[20-22] Indeed, one-twentieth of overall cancers have a clear hereditary pattern. Those cancers are proved for passing from one to the next generation. Hence, the role of gene defect can be proven. Well-known hereditary syndromes include hereditary breast and ovarian cancer syndrome, Cowden syndrome and multiple endocrine neoplasia. The details of some important hereditary multiple cancer syndrome will be further discussed.

A. Von Hippel-Lindau disease

Von Hippel-Lindau disease (VHL) is a rare disease that involves many organ systems. The main disorders can be seen in the vascular system. It can be benign or malignant. In benign cases, the abnormalities might be angiomas. In malignant cases, hemangioblastomas can be seen. The malignant hemangioblastomas in VHL are common at retina, brain and spinal cord.[23-25] The concomitant primary tumors include adrenal tumor, kidney cancer and pancreas cancer.[23-25] Hence, it is a rule to completely investigate for these possible cancers in patients presenting with the VHL.

Focusing on the genetic defect in the VHL, the widely mentioned gene is the VHL gene. Mutations within the VHL gene can be seen in almost all patients with VHL. Generally, the VHL gene is responsible for the production of a specific protein, namely pVHL (213 amino acid residues, molecular weight of 24 to 30 kDa).[26] Normally, this derived protein helps inhibit the hypoxia-inducible factor (HIF) via post-translational prolyl hydroxylation with use of a conserved family of Egl-nine enzymes and further targeting HIF for ubiquitin-mediated degradation.[26-27] Aberration of the protein function is believed to be the starting point of carcinogenesis.[26] This is well observed in the case of renal cell carcinoma.[26, 28, 29]

B. Cowden syndrome

Cowden syndrome (CS) is another rare multiple cancer syndrome whereby its underlying genetic pathology has been proven. The nature of this disease is the

development of multiple tumor-like growths (hamartomas) of the skin and mucous membranes. Sometimes, abnormal growth can also be seen at the gastrointestinal tract or central nervous system. There are also reports on the increased risk of breast, uterus and thyroid cancers.[30-33]

Focusing on the genetic defect in CS, the widely mentioned gene is PTEN gene.[34,35] The mutations within PTEN gene can be seen in almost all patients with PTEN. Generally, PTEN is a tumor suppressor gene on 10q23.3 which corresponds to encoding a lipid phosphatase that lies upstream of protein kinase B (Akt).[35,36] PTEN negatively regulates cell interactions with the extracellular matrix and the aberration of this normal function can result in carcinogenesis.[35]

C. Li-Fraumeni Syndrome

Li-Fraumeni Syndrome (LFS) is another rare disorder with onset in the young. Increased risk of many cancers is observed in LFS. The problematic cancers include soft tissue sarcomas, breast cancer, leukemia, lung cancer, adrenocortical cancer and brain cancer.[37-39]

Focusing on the genetic defect in CS, the widely mentioned gene is the TP53 gene.[40,41] The mutations within the TP53 gene can be seen in approximately 50% of the cases and common mutations are missense mutations, located between exon 5 and exon 8, within the DNA-binding domain of TP53.[41] At present, the investigation for TP53 is more widely available. It is recommended for testing in any case with a tumor in the general population, belonging to LFS.[41]

D. Lynch syndrome

Lynch syndrome or hereditary non-polyposis colorectal cancer syndrome is another rate genetic disorder presenting with early age onset colorectal cancer, endometrial cancer and other extracolonic malignancies.[42-44] The mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6 or PMS2) have a proven relationship to Lynch syndrome.[42-44] Due to the high incidence of colorectal cancer in the West, attempts to launch the screening investigation for Lynch syndrome have been widely mentioned and have been approved for their cost effectiveness.[45] For screening, a combination of various genetic and immunohistochemical tests are used.[46]

E. Muir Torre syndrome

Muir Torre syndrome is a variant of Lynch syndrome. It is strongly related to skin cancers. The genetic disorder is usually within one of the DNA mismatch repair genes and can be seen in up to 70 % of the cases.[47,48]

F. Turcot syndrome

Turcot syndrome is another variant of Lynch syndrome. It is strongly related to brain cancer (glioblastoma or astrocytoma).[49, 50]

G. Hereditary breast and ovarian cancer syndrome

Hereditary breast and ovarian cancer syndrome is a genetic disorder that has a proven relationship to mutations in the BRCA1 and BRCA2 genes. It is related to the increased risk of many cancers including breast cancer (in both sexes), ovarian cancer and prostate cancer. Also, there are some reports of a risk for pancreatic cancer and melanoma.[51,52]

Focusing on the risk, an 85% lifetime risk of breast cancer and up to a 46% lifetime risk ovarian cancer are reported.[53] Preconception counseling is recommended for this syndrome.[54]

Conclusion

Gene defects is an important underlying pathology in multiple cancers. There is already confirming evidence on the underlying abnormality of some genes in several multiple cancers. Investigation into those problematic genes can be a basic screening tool for early detection and recognition of the possible occurrence of multiple cancers in a cancerous patient. There is no doubt that many primary cancers might be concurrent in a patient but only one cancer might be initially detected. If it is affordable, screening should be performed in any cancerous patient as early as possible. Early diagnosis is the core concept in any cancer therapy, whether multiple or not.[55]

References

1. Graffi A. Observations on the theories of carcinogenesis. *Arch Geschwulstforsch* 1963;22:13-41.
2. Laerum OD. Current cancer theories and their scientific basis. *Tidsskr Nor Laegeforen* 1970;90:2067-70.
3. Brennan P. Gene-environment interaction and aetiology of cancer: what does it mean and how can we measure it? *Carcinogenesis* 2002;23:381-7.
4. Borek C. Molecular mechanisms in cancer induction and prevention. *Environ Health Perspect* 1993;101:237-45.
5. Sutherland JE, Costa M. Epigenetics and the environment. *Ann N Y Acad Sci* 2003;983:151-60.
6. Weber W. Cancer epigenetics. *Prog Mol Biol Transl Sci* 2010;95:299-349.
7. McMillan SC. Carcinogenesis. *Semin Oncol Nurs* 1992;8:10-9.
8. Knudson AG Jr. Overview: genes that predispose to cancer. *Mutat Res* 1991;247:185-90.
9. Knudson AG Jr. The genetic predisposition to cancer. *Birth Defects Orig Artic Ser* 1989;25:15-27.
10. Werthamer S, Jabush M, Schulman J. Multiple primary malignancies. *JAMA* 1961;175:558-62.
11. Luciani A, Balducci L. Multiple primary malignancies. *Semin Oncol* 2004;31:264-73.
12. Capaldo GR, Kunschner AJ, Amin RM. Multiple primary neoplasms. Ovarian carcinoid tumor, mucinous cystadenoma of low malignant potential tumor of left ovary, and adenocarcinoma of the colon. *Arch Pathol Lab Med* 1996;120:393-6.
13. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. *Am J Clin Oncol* 2003;26:79-83.
14. Kobayashi T, Takahashi T, Tanaka T, et al. Multiple primary neoplasm--glioblastoma combined with cancer of other organs. *No Shinkei Geka* 1987;15:1011-7.
15. Klochikhin AL, Markov GI, Shilenkova VV. A case of a cure of synchronous multiple primary neoplasm of the laryngopharynx and stomach. *Vestn Otorinolaringol* 1997;1:56.
16. Sielanczyk A, Jakubowska D, Sierón A. Multiple primary neoplasm without family history-case report. *Pol Merkur Lekarski* 2004;16:255-7.
17. Schoenberg BS. Multiple primary malignant neoplasms. The Connecticut experience, 1935-1964. *Recent Results Cancer Res* 1977;58:1-173.
18. Ray P, Guinan P, Sharifi R, et al. Prostate cancer and the multiple primary malignant neoplasm syndrome. *Prostate* 1983;4:513-22.
19. Esposito ED, Bevilacqua L, Guadagno MT. Multiple primary malignant neoplasm in patients with laryngeal carcinoma. *J Surg Oncol* 2000;74:83-6.
20. Lynch HT, Guirgis HA, Lynch PM, et al. Familial cancer syndromes: a survey. *Cancer* 1977;39:1867-81.
21. Li FP. Familial cancer syndromes and clusters. *Curr Probl Cancer* 1990;14:73-114.
22. Den Otter W, Koten JW, Van der Vegt BJ, et al. Hereditary cancer and its clinical implications: a view. *Anticancer Res* 1990;10:489-95.
23. Seitz ML, Shenker IR, Leonidas JC, et al. Von Hippel-Lindau disease in an adolescent. *Pediatrics* 1987;79:632-7.
24. Neumann HP. The von Hippel-Lindau syndrome. *Dtsch Med Wochenschr* 1991;116:28-34.
25. Neumann HP. Von Hippel-Lindau syndrome. *Nephrol Dial Transplant* 1994;9:313-5.
26. Arjumand W, Sultana S. Role of VHL gene mutation in human renal cell carcinoma. *Tumour Biol* 2012;33:9-16.
27. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. *J Clin Oncol* 2004;22:4991-5004.
28. Audenet F, Yates DR, Cancel-Tassin G, et al. Genetic pathways involved in carcinogenesis of clear cell renal cell carcinoma: genomics towards personalized medicine. *BJU Int* 2012;109:1864-70.
29. Arai E, Kanai Y. Genetic and epigenetic alterations during renal carcinogenesis. *Int J Clin Exp Pathol* 2010;4:58-73.
30. Monnier G, Mauduit G, Thivolet J. Cowden's disease. *Ann Dermatol Venereol* 1985;112:169-77.
31. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. *J Am Acad Dermatol* 1983;8:686-96.
32. Civatte J, Laufer J, Delort J, et al. Cowden's disease (multiple hamartoma syndrome). Review of the literature in connection with 1 case. *Ann Med Interne (Paris)* 1978;129:593-9.
33. Bardenstein DS, McLean IW, Nerney J, et al. Cowden's disease. *Ophthalmology* 1988;95:1038-41.
34. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nat Rev Cancer* 2011;11:289-301.
35. Romano C, Schepis C. PTEN Gene: A Model for Genetic Diseases in Dermatology. *Scientific World Journal* 2012;2012:252457.
36. Eng C. Role of PTEN, a lipid phosphatase upstream effector of protein kinase B, in epithelial thyroid carcinogenesis. *Ann N Y Acad Sci* 2002;968:213-21.
37. Palmero EI, Achatz MI, Ashton-Prolla P, et al. Tumor protein 53 mutations and inherited cancer: beyond Li-Fraumeni syndrome. *Curr Opin Oncol* 2010;22:64-9.
38. Evans SC, Lozano G. The Li-Fraumeni syndrome: an inherited susceptibility to cancer. *Mol Med Today* 1997;3:390-5.
39. Frebourg T. Li-Fraumeni syndrome. *Bull Cancer* 1997; 84:735-40.
40. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol* 2010;2:a001008.
41. Szymańska K, Hainaut P. TP53 and mutations in human cancer. *Acta Biochim Pol* 2003;50:231-8.

42. Bozzao C, Lastella P, Stella A. Anticipation in lynch syndrome: where we are where we go. *Curr Genomics* 2011;12:451-65.
43. Iwama T, Ishida H. Hereditary colorectal cancer; familial adenomatous polyposis, MUTYH associated polyposis and Lynch syndrome. *Nihon Rinsho* 2011; 69:59-64.
44. Gala M, Chung DC. Hereditary colon cancer syndromes. *Semin Oncol* 2011;38:490-9.
45. Gudgeon JM, Williams JL, Burt RW, et al. Lynch syndrome screening implementation: business analysis by a healthcare system. *Am J Manag Care* 2011;17:e288-300.
46. Weissman SM, Burt R, Church J, et al. Identification of Individuals at Risk for Lynch Syndrome Using Targeted Evaluations and Genetic Testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer Joint Practice Guideline. *J Genet Couns* 2011 Dec 14.
47. Mercader P. Muir-Torre syndrome. *Adv Exp Med Biol* 2010;685:186-95.
48. Kacerovská D, Kazakov DV, Cerná K, et al. Muir-Torre syndrome-a phenotypic variant of Lynch syndrome. *Cesk Patol* 2010;46:86-94.
49. Masuno M. Turcot syndrome. *Ryoikibetsu Shokogun Shirizu* 2001;(34 Pt 2):765-6.
50. Sunahara M, Nakagawara A. Turcot syndrome. *Nihon Rinsho* 2000;58:1484-9.
51. Shulman LP. Hereditary breast and ovarian cancer (HBOC): clinical features and counseling for BRCA1 and BRCA2, Lynch syndrome, Cowden syndrome, and Li-Fraumeni syndrome. *Obstet Gynecol Clin North Am* 2010;37:109-33.
52. Plevová P, Novotný J, Petráková K, et al. Hereditary breast and ovarian cancer syndrome. *Klin Onkol* 2009;22:S8-11.
53. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2007;107:159-62.
54. Beller U. Preconception counseling for the couple at risk preventing the hereditary breast and ovarian cancer syndrome. *Int J Gynecol Cancer* 2010;20:S29-30.
55. Wiwanitkit V. Cell, Gene and Molecular Therapy: New Concepts. New York: Nova Biomedical, 2009.

Review Article

PET Imaging in Alzheimer's Disease

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Keywords:
PET, FDG, amyloid, brain, dementia, Alzheimer's disease

Dementia is a common disease in the elderly with a rising incidence with increasing age. Diagnosis is crucial for determining patient care and directing the lines of treatment to decrease the rate of dementia progression.[1,2]

There are number of degenerative diseases that cause dementia including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD). There are also number of other neurodegenerative diseases that sometimes present with dementia such as Parkinson's disease (PD), other Parkinsonian disorders, and Creutzfeldt-Jakob disease (CJD). Dementia can also present in patients with other primary causes such as vascular dementia and AIDS dementia.[3] Diagnosis of AD has been based on clinical phenotypes together with pathological changes in the brain.[4] Since pathological diagnosis is difficult to obtain from a living patient, diagnosis of AD is predominantly a clinical entity with probabilistic diagnosis (probable or possible AD).[5] Since the criteria for AD diagnosis in 1984, there has been evidence that many in vivo biological markers can also accurately diagnose AD during the patient's lifetime. Thus, in 2007 a new research criterion was proposed, which permits diagnosis of AD with high accuracy.[6] Among the in vivo biomarkers, Positron Emission Tomography (PET) is one of the imaging methods that can be used. It is different from anatomical imaging (CT and MRI) which are mainly used to exclude other potential curative diseases that can cause cognitive impairment.[2,7] PET is an imaging that uses positron emitting isotopes labeled with human physiologic chemicals or analogues to qualitatively or quantitatively trace cerebral blood flow, metabolism, receptors, transporters, and enzymes within the patient's body. It is a sensitive tool for diagnosis of diseases even when there is no demonstrable anatomical change. It can also be used to follow disease progression.

PET Usage in Alzheimer's Disease

Several radiopharmaceuticals can be used in PET imaging for dementia with different purposes, for example, for early diagnosis or diagnosis confirmation, disease differentiation, or follow up of disease progression. (Table 1)

Table 1: PET radiopharmaceuticals and aims of use.

Radiopharmaceutical	Target	Aim of use
F18-FDG*	Glucose metabolism	Early diagnosis of dementia, Differentiate types of dementia, Follow up disease progression
F18-DOPA*	Pre-synaptic dopamine imaging	Confirm diagnosis of dementia with Lewy bodies/ Parkinson's dementia
C11-PiB *	β-Amyloid imaging	Early diagnosis of Alzheimer's disease
F18-florbetaben		
F18-florbetapir		
F18-flumetamol		
F18-FDDNP		

*Available in Thailand

Indications of PET in Alzheimer's disease (AD)

1. Diagnosis of AD in preclinical or presymptomatic stage

The National Institute on Aging-Alzheimer's Association in the United States has suggested that Alzheimer's disease would be optimally treated before significant cognitive impairment, defined as a *'presymptomatic'* or *'preclinical'* stage. For this purpose, the use of PET agents which detect amyloid aggregates are of advantage.[8] The most widely used agent is C11-PiB (Pittsburgh compound-B) which has a high affinity to amyloid-β peptide aggregates[9] and is available in Thailand.

In mild cognitive impairment (MCI) patients who subsequently converted to AD had a high C11-PiB uptake and the level of PiB uptake was comparable to those with AD. In a longitudinal study,[10] MCI patients showed serially increased PiB uptake while FDG uptake was serially decreased. In symptomatic AD, PiB uptake was stably high while FDG uptake was decreased in relation to cognitive decline. Thus, abnormal PiB and FDG-PET are detected early in MCI patients who will progress to AD and are predictive of those who will progress to AD.[10, 11]

In the preclinical stage, which is difficult to identify, F18-FDDNP was studied in those who are at high risk for developing AD.[12] Patients recruited were those with impaired cognitive status, older age, and APOE-4 genetic risk for AD, family history of dementia and less education. Impaired cognitive status, older age, and APOE-4 carrier status are associated with increased brain FDDNP-PET binding in persons without dementia, consistent with previous clinical and postmortem studies associating these risk factors with amyloid plaque and tau tangle accumulation.

2. Confirm clinical diagnosis of AD

From a meta-analysis, which analyzed studies which compared various biomarkers and imaging from 1990 to 2010,[13] it was demonstrated that FDG-PET was the best way to differentiate patients with AD from normal controls with an area under the ROC curve of 0.96, sensitivity of 90% and specificity of 89%.

In a multicenter study of patients that had pathologically verified dementia, FDG-PET showing typical parieto-temporal hypometabolism patterns improved the accuracy of *"Probable AD"* by clinical diagnosis from 73% to 82%.[14] Thus, FDG-PET is recommended for use in a patient with difficult-to-clinically-characterize dementia. C11-PiB can also be used to confirm AD pathology in patients with atypical presentations of dementia.[15]

3. Differentiate other dementia causes from AD

Other than confirming clinical AD diagnosis, PET can also differentiate other types of dementia causes because of the metabolic patterns typical in each abnormality. In the aforementioned meta-analysis, FDG-PET provided the best diagnostic accuracy in differentiating AD from other dementing diseases compared to other biomarkers or imaging methods with a sensitivity of 92% and a specificity of 78%.[13]

FDG-PET patterns in various dementing diseases are: hypometabolism at parietal, superior/posterior temporal, posterior cingulate and precuneus areas in AD[16,17] (Figure 1); hypometabolism at the frontal lobe and anterior temporal lobe in FTLD; hypometabolism in the same areas as AD with additional occipital lobe involvement in DLB; scattered hypometabolism in cortical and subcortical areas in vascular dementia.[3]

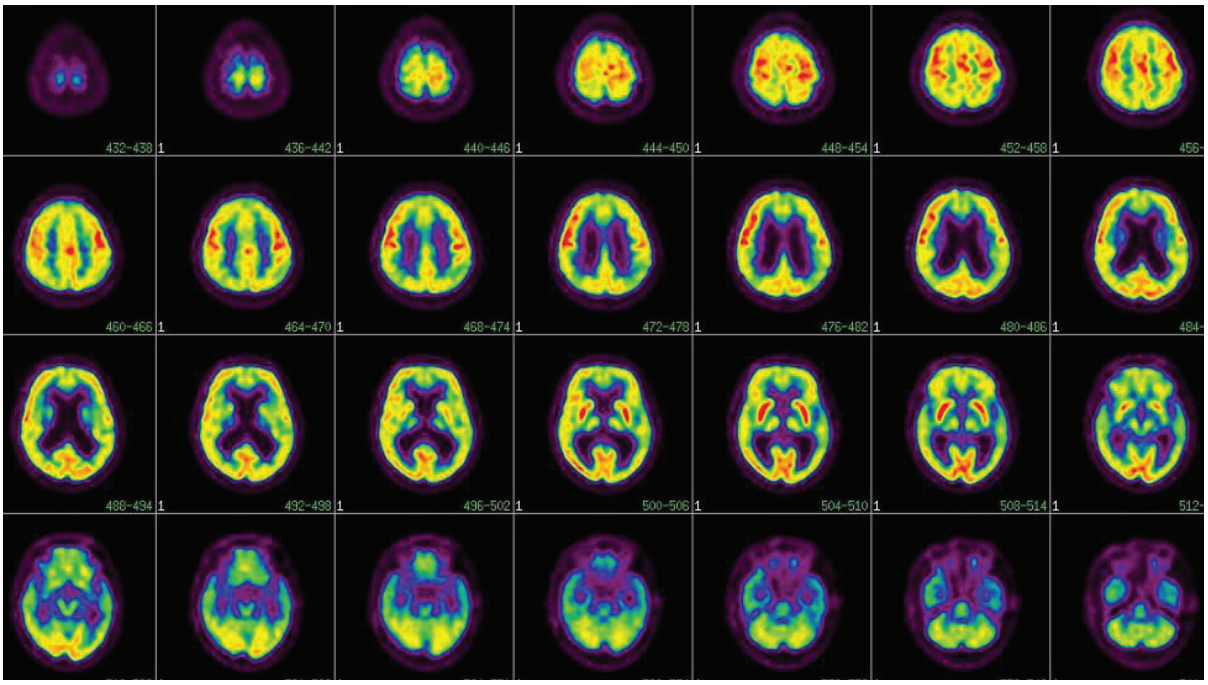

Figure 1: *Findings of hypometabolism seen on FDG-PET scan in AD: hypometabolism at bilateral parietal and temporal lobes posterior cingulate cortex and precuneus without abnormalities at primary sensorimotor area, occipital lobe, basal ganglia, thalami, and cerebellum. In advanced disease, hypometabolism at frontal lobes may be seen.*

To differentiate DLB or Parkinson's disease from dementia (PDD) from AD, a radiopharmaceutical that is taken up in the presynaptic site such as F18-DOPA can be used, in which DLB and PDD will show decreased uptake at striatum while AD shows no abnormality.[18] This can be applied in patients with suspected visual variant AD because there will be hypometabolism of FDG at occipital lobes confusing differentiation with DLB by using FDG-PET.[19]

4. Predict response to medications

Currently there are many promising treatment candidates which either slow down cognitive deterioration or even reverse the process of neurodegeneration. Biomarkers which can evaluate the effect of treatment are essential. FDG-PET has proven to be a sensitive biomarker to track these changes.[20-22] It can differentiate patients who will respond to particular treatment from those who will not.

Current status of brain PET in Thailand

The PET/CT scanner was installed in Bangkok in November 2005 at Wattanosoth Hospital. Until now (July 2012), there are 6 hospitals in Thailand (Chulabhorn Hospital, King Chulalongkorn Memorial Hospital, Siriraj Hospital, Bumrungrad Hospital, and Ramathibodi Hospital) that have PET/CT scanners. Currently F18-FDG, F18-DOPA, and C11-PiB are available in Thailand for brain dementia PET scan.

At Wattanosoth Hospital, to date we have performed 128 cases of brain PET, with 93 cases being performed for dementia indications. Others were for epilepsy, brain function in vegetative state, and other indications.

In King Chulalongkorn Memorial Hospital, brain PET scans are performed mainly for epilepsy and dementia.

Conclusion

PET has many roles in dementia diagnosis and management from early diagnosis of AD, confirming diagnosis of AD, differentiating dementia type and predicting responses to therapy. For diagnostic purposes, it should be used in high risk patients and difficult-to-diagnose cases. It can also potentially reduce the costs of long-term treatment in patients already diagnosed as AD.

References

1. Carpenter BD, Xiong C, Porensky EK, et al. Reaction to a dementia diagnosis in individuals with Alzheimer's disease and mild Cognitive Impairment. *J Am Geriatr Soc* 2008;56:405-12.
2. Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 2010;17:1236-48.
3. Tartaglia MC, Rosen HJ, Miller BL. Neuroimaging in dementia. *Neurotherapeutics* 2011;8:82-92.
4. Cummings JL. Alzheimer's disease. *N Engl J Med* 2004;351:56-67.
5. McKhann G, Drachman D, Folstein M et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-44.
6. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007;6:734-46.
7. Scheltens P. Imaging in Alzheimer's disease. *Dialogues Clin Neurosci* 2009;11:191-9.
8. Gelosa G, Brooks DJ. The prognostic value of amyloid imaging. *Eur J Nucl Med Mol Imaging* 2012;39:1207-19.
9. Mori T, Maeda J, Shimada H, et al. Molecular imaging of dementia. *Psychogeriatrics* 2012;12:106-14.
10. Forsberg A, Engler H, Almkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging* 2008;29:1456-65.
11. Drzezga A, Grimmer T, Riemenschneider M, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. *J Nucl Med* 2005;46:1625-32.
12. Small GW, Siddarth P, Burggren AC, et al. Influence of cognitive status, age, and APOE-4 genetic risk on brain FDDNP positron-emission tomography imaging in persons without dementia. *Arch Gen Psychiatry* 2009;66: 81-7.
13. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimers Dis* 2011; 26:627-45.
14. Hoffman JM, Welsh-Bohmer KA, Hanson M, et al. FDG PET imaging in patients with pathologically verified dementia. *J Nucl Med* 2000;41:1920-8.
15. Wolk DA, Price JC, Madeira C, et al. Amyloid imaging in dementias with atypical presentation. *Alzheimers Dement* 2012;8:389-98.
16. Silverman DH, Small GW, Phelps ME. Clinical Value of Neuroimaging in the Diagnosis of Dementia. Sensitivity and Specificity of Regional Cerebral Metabolic and Other Parameters for Early Identification of Alzheimer's Disease. *Clin Positron Imaging* 1999;2:119-30.
17. Small GW, Bookheimer SY, Thompson PM, et al. Current and future uses of neuroimaging for cognitively impaired patients. *Lancet Neurol* 2008;7:161-72.
18. Klein JC, Eggers C, Kalbe E, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology* 2010;74:885-92.
19. Nestor PJ, Caine D, Fryer TD, et al. The topography of metabolic deficits in posterior cortical atrophy (the visual variant of Alzheimer's disease) with FDG-PET. *J Neurol Neurosurg Psychiatry* 2003;74:1521-9.
20. Shimada A, Hashimoto H, Kawabe J, et al. Evaluation of therapeutic response to donepezil by positron emission tomography. *Osaka City Med J* 2011;57:11-9.
21. Martin-Moreno AM, Brera B, Spuch C, et al. Prolonged oral cannabinoid administration prevents neuroinflammation, lowers beta-amyloid levels and improves cognitive performance in Tg APP 2576 mice. *J Neuroinflammation* 2012;9:8.
22. Forster S, Buschert VC, Teipel SJ, et al. Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer's disease. *J Alzheimers Dis* 2011;26:337-48.

Review Article

FDG-PET and FDG production at Wattanosoth Hospital

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Keywords:
FDG-PET, FDG production, cancer, Wattanosoth Hospital

FDG-PET or Positron Emission Tomography with Fluorodeoxyglucose (fluorine-18-2-fluoro-2-deoxy-D-glucose [FDG]) for oncologic imaging both detects and effectively monitors the therapy of many malignancies. FDG-PET improves the detection and staging of cancer, disease management, therapy selection, and the assessment of appropriate therapeutic responses. Besides the use of FDG-PET in oncology, it can also be used in neurology and cardiology. The clinical use of FDG-PET has flourished over the past 15 years. This article is not meant to be exhaustive, but rather to give an overview and to share some information and experience of FDG-PET and FDG production at Wattanosoth Hospital. It will touch briefly on all aspects of FDG-PET and its production, namely an overview of radioisotope production of F-18, FDG synthesis and quality control.

Introduction – Overview of FDG and PET

In the mid-1970s, Wolf et al[1,2] successfully produced FDG, ^{18}F-FDG or 2-[^{18}F]fluoro-2-deoxy-D-glucose at the Brookhaven National Laboratory. It provides an impetus for the advancement of PET or Positron Emission Tomography which is now a powerful scientific and clinical tool for probing biochemical processes in human body. The medical community was excited by the possibilities of using FDG-PET in clinical applications, once the broad utility of this tracer had been demonstrated. Nowadays, FDG is the most widely used PET radiopharmaceutical. It is utilized largely in oncology, but also in cardiology and neurology and its use is steadily growing.[3]

FDG is a radiolabeled analog of glucose, in which the hydroxyl group on the 2-carbon of a glucose molecule is replaced by a fluoride atom. Just as glucose, it is taken up by glucose-using cells and phosphorylated by hexokinase as the first step toward glycolysis.[4] However, FDG cannot undergo further metabolism and becomes effectively trapped intracellularly as FDG-6-Phosphate.

Whole body PET imaging with FDG measures glucose metabolism in all organ systems with a single examination. Since cancer is a systemic disease, FDG-PET allows the early detection and quantification of metastasis. Therefore, it has found applications in the diagnosis, staging, and restaging of several clinical conditions such as lung cancer, colorectal cancer, lymphoma, melanoma, head and neck cancer, brain tumor, breast cancer, and oesophageal cancer etc.[5-7] Clinical applications of FDG-PET are also found in neurology, cardiology and inflammation/infection.

Table 1: Reimbursement of PET and PET/CT in the United States[9]

Indication	Medicare National Coverage
FDG-PET for Lung Cancer	Covered
FDG-PET for Esophageal Cancer	Covered
FDG-PET for Colorectal Cancer	Covered
FDG-PET for Lymphoma	Covered
FDG-PET for Melanoma	Covered
FDG-PET for Head and Neck Cancers	Covered
FDG-PET for Myocardial Viability	Covered for the determination of myocardial viability following an inconclusive SPECT test
FDG-PET for Refractory Seizures	Covered only for pre-surgical evaluation
FDG-PET for Breast Cancer	Covered
FDG-PET for Thyroid Cancer	Covered
FDG-PET for Soft Tissue Sarcoma	Covered
FDG-PET for Dementia and Neurodegenerative Diseases	Covered for either the differential diagnosis of FTD and AD, or in a CMS-approved practical clinical trial focused on the utility of FDG- PET in the diagnosis or treatment of dementia and neurodegenerative diseases
FDG-PET for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers	Covered
FDG-PET for All Other Cancer Indications Not Previously Specified	Covered

SPECT = Single-photon emission computed tomography FTD = Frontotemporal dementia
AD = Alzheimer's disease CMS = Centers for Medicare & Medicaid Services

Although the PET imaging technique has existed for more than 30 years, it has been used clinically for only the last 10-15 years. There were many reasons for the dramatic growth of clinical usage of PET. Such factors are the approval of using FDG-PET by the US FDA, the availability of reimbursement in the late 1990s, the availability of medical cyclotron to produce the necessary short-lived positron emitters, the advancement in synthesis and quality control of FDG, and the invention of the combination of a dedicated PET scanner and multi-slice helical CT (PET/CT). PET/CT enables integrated functional and high-resolution morphologic imaging.

Since it was introduced to clinical medicine in 2001, PET/CT has represented one of the largest growth diagnostic modalities worldwide[8]. In the United States, the Centers for Medicare and Medicaid Services (CMS) allow reimbursement for most clinical indications in oncology, such as staging and restaging of lung cancer; esophageal, colorectal, and other gastrointestinal tract cancers; breast cancer; kidney and other genitourinary cancers; melanoma; head and neck cancers; and malignant lymphoma (Table 1)[9]. CMS state that more indications will be added to the list of services covered, provided that all prospective clinical trials include examinations.

Buck et al.[10] reported on the current knowledge of economic evaluations of PET and PET/CT in oncologic applications. *"The clinical use of PET has been demonstrated to be cost effective for staging of non-small cell lung cancer, differential diagnosis of solitary pulmonary nodules, restaging of Hodgkin disease and non-Hodgkin lymphoma, and restaging of colorectal carcinoma"*. The use of PET in clinical routines seems justified from a health economic point of view. Diagnostic effectiveness has been demonstrated for many other clinical indications such as monitoring response to therapy or radiation treatment planning. Buck et al go on to state: *"PET and PET/CT are highly sensitive diagnostic tests to screen for metastatic tumor deposits in the entire body that may be missed by standard imaging modalities. The sensitivity for detection of lymph node metastases varies significantly among cancers and may be inferior compared with other techniques such as sentinel lymph node biopsy"*.

Public PET services are limited by high costs. Some countries such as Israel, France, Canada, Belgium and the United Kingdom (UK) rationalize public PET services by limiting the number of PET scanners based on population size.[11] The number of scanners is controlled, which effectively controls the volume of PET scans, provided that each scanner operates at maximum capacity. The Royal College of Radiologists in the UK proposed that one PET scanner should be provided for populations of 1 to 1.5 million people.[12] The World Health Organization (WHO) recommends two PET scanners for every million people. In 2009, approximately 2,000 PET/CT scanners were installed in the United States and approximately 350 were installed in Europe.[10] In Germany, there were about 1.2 scanners per million people. While in the States, there were about 6.5 scanners per million people. In Hong Kong there were a total of 11 PET scanners in 2010, which represented 1.6 scanners per million. In Canada, the number of PET scanners per million people was 0.83 in the year 2009.[13] A report on available PET scanners per million people as at 2007 (Table 2) is sourced from an international literature review on funding arrangements for diagnostic imaging services.[14]

In Thailand, there are total of 6 PET/CT scanners and 2 Cyclotron facilities in Bangkok since 2012. Two of PET/CT scanners are in private hospitals. There is one cyclotron facility the in public sector and another one is in private sector. According to United Nations Thailand, the estimated population of Thailand in 2012 is 64 million of which approximately 9.3 million live in Bangkok and its vicinities. Therefore, there is about one PET scanner per 10.7 million people in Thailand (or 0.09 PET scanner per million of population) which is far below many other countries. The number of PET exams in Thailand is growing slowly since the cost per PET exam is high and there are limited indications for reimbursement.

Table 2: Number of PET scanners per million people in various countries in 2007[14]

Country	PET scanners per million people
Denmark	3.7
Luxembourg	2.1
Korea	1.9
Ireland	1.4
Germany	1.0
France	1.0
Canada	0.9
Spain	0.7
Australia	0.7
Slovak Republic	0.6
Italy	0.6
Hungary	0.6
Czech Republic	0.5

FDG-PET at Wattanosoth Hospital

The first PET/CT in Thailand was installed at Wattanosoth Hospital, Bangkok Hospital Medical Center in November 2005. The PET/CT scanner at Wattanosoth Hospital is a Gemini GXL. Up to November 2012, more than 6,000 PET exams have been performed at Wattanosoth. Most of these were FDG-PET for oncologic imaging; about 3% of the scans were for neurology imaging. However, the trend for using PET imaging in neurology is growing.

Patient preparation

Patients are instructed to fast and not consume beverages, except for water, for at least 6 hours before the administration of FDG to decrease physiologic glucose levels and to reduce serum insulin levels to near basal levels. Intravenous fluids containing dextrose or parenteral feedings are also withheld for 6 hours. Patients are screened for a history of iodinated contrast material allergy, and renal disease, if intravenous contrast material is used. When the serum creatinine level is above 1.5 mg/dL, intravenous contrast material will not be used. Blood glucose levels are checked before FDG administration. If the blood glucose level is greater than 200mg/dL, the patient will be rescheduled. The patient may be asked to consult an endocrine physician to control their blood glucose levels.

Prior to the administration of FDG, patients are assessed for any history of diabetes, their fasting state, current medication, any recent infections, type and site of malignancy, dates of diagnosis and treatment etc. Any history of claustrophobia and the patient's ability to lie still for the duration of the acquisition (about 15-30 minutes) is investigated.

Adult patients will be intravenously administered about 6-14mCi of FDG according to their body weight. Children will receive about 6mCi of FDG intravenously. The radiation dose to the patient undergoing a PET/CT exam is the combination of the radiation dose from the PET radiopharmaceutical and the radiation dose from the CT portion of the study. The effective dose for an adult and a child of FDG is about 0.019 mSv/MBq (0.070 rems/mCi) and 0.050 mSv/MBq (0.18 rems/mCi), respectively.[15] The organ receiving the largest radiation dose is the bladder. The radiation dose to the bladder for an adult and a child are 0.16 mGy/MBq (0.59 rads/mCi), and 0.32 mGy/MBq (1.2 rads/mCi) respectively. The CT body scan may include various portions of the body and may use

protocols aimed at reducing the radiation dose to the patient or aimed at optimizing the CT scan for diagnostic proposes. Because of the wide diversity of applications, protocols, and CT systems, the effective dose from CT could range from approximately 5 to 80 mSv (0.5 - 8.0 rems).[16]

After administration, patients are asked to rest in a quiet room during the uptake phase to avoid muscular uptake for body imaging. For brain imaging, patients rest in a quiet and dimly lit room.

Technical examination

The image acquisition for FDG-PET is undertaken approximately an hour after administration. Patients are asked to void the bladder before the acquisition to limit the radiation dose to the renal collecting system and bladder and for better image quality. Intense urinary bladder tracer activity degrades image quality and can confuse the interpretation of findings in the pelvis. Metabolic objects should be removed from the patient. For optimal imaging of the body, the arms should be elevated over the head if the patient can tolerate this position. Arms alongside may produce beam-hardening artifacts over the torso. That said, the arms should be positioned alongside for imaging of the head and neck. The PET emission image acquisition time is 5 minutes per bed position for body imaging. Typically, the PET imaging is done from skull to mid-thigh. The total acquisition time is about 20-25 minutes. The imaging time for the acquisition of a brain image is typically more prolonged.

PET images are reconstructed with and without CT-based attenuation correction. The oncologic FDG-PET/CT imaging is read by 2 different imaging experts (nuclear medicine physician and diagnostic radiologist). PET scans are interpreted by the nuclear medicine physicians with expertise in PET, and CT scans are interpreted by the diagnostic radiologists with expertise in CT. Strong opinions are summarized in a single report to avoid inconsistencies, confusion, and redundancy. Figure 1 shows a PET, CT and combined PET/CT images of a 63-year-old Thai male with esophagus cancer.

Production of radioisotopes

A summary of the physical characteristics of these PET radioisotopes and typical reactions of their production is listed below in Table 3. There are 4 most often used radioisotopes for PET imaging, namely fluorine-18 (F-18), carbon-11 (C-11), nitrogen-13 (N-13), and oxygen-15 (O-15). PET radioisotopes can be produced by either proton or deuteron reaction.

The most common PET radioisotope is typically produced by cyclotron. The first medical cyclotron was installed in 1941 at Washington University, St Louis, where radioactive isotopes of phosphorus, iron, arsenic and sulphur were produced. Nowadays, there are many commercial cyclotrons available (Table 4).[17]

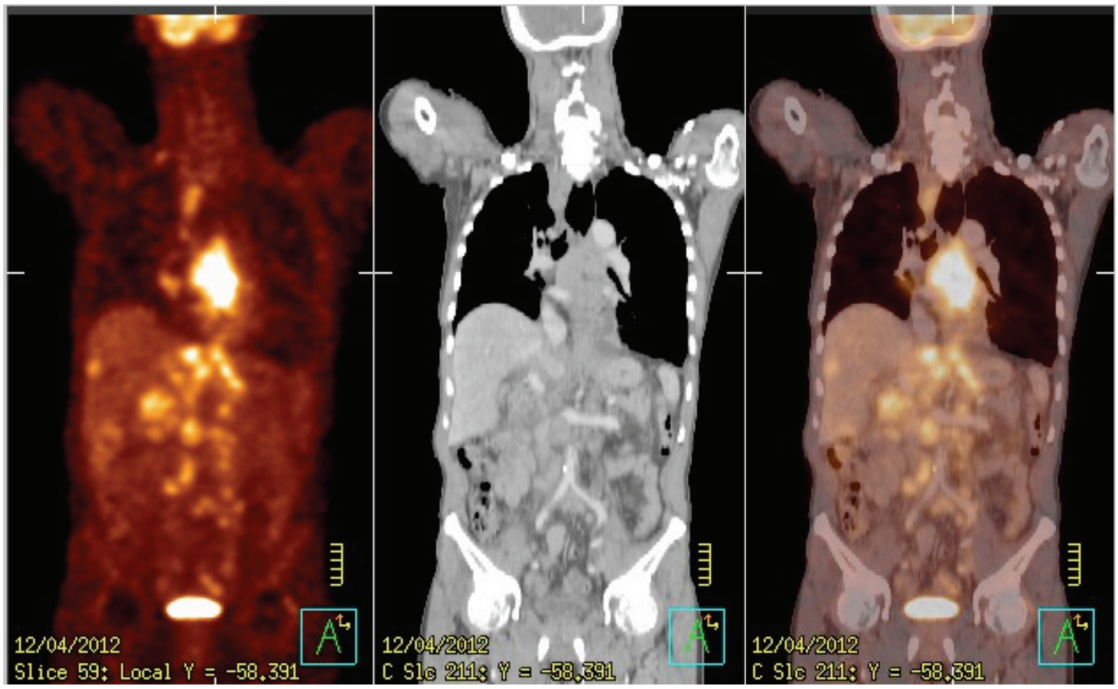


***Figure 1**: PET image, CT image and PET image fusion with CT image*

Table 3: Physical characteristic of PET radioisotopes and reaction for production

Nuclide	Half-life (min)	Decay mode	Reaction	Energy for production (MeV)	Maximum Specific activity (theoretical)
C-11	20.4	100% β	^{14}N(p, α)	11-17	9220 Ci/mole
N-13	9.98	100% β	^{16}O(p, α) ^{13}C(p, n)	19 11	18900 Ci/mole
O-15	2.03	100% β	^{15}N(p, n) ^{14}N(d, 2n) ^{16}O(p, pn)	11 6 >26	91730 Ci/mole
F-18	109.8	97% β^+ 3% EC	^{18}O(p, n) ^{nat}Ne(d, α)	11-17 8-14	1710 Ci/mole

Table 4: Characteristics of some commercial cyclotron[17]

Cyclotron model	Manufacturer	Beam	Energy (MeV)	Beam current (μA)
TR14	ACSI	proton	14.0	100
TR19/9	ACSI	proton deuteron	19.0 9.0	300 75
Minitrace	GE	proton	9.6	50
PETtrace	GE	proton deuteron	16.5 8.4	100 60
Cyclone 10/5	IBA	proton deuteron	10.0 5.0	100 50
Cyclotron 18/9	IBA	proton deuteron	18.0 9.0	160 60
Eclipse HP	Siemens	proton	11.0	120
Eclipse RD	Siemens	proton	11.0	80
HM 12	Sumitomo	proton deuteron	16.0 6.0	100 40
HM 18	Sumitomo	proton deuteron	18.0 10.0	100 40

The range of radioisotopes produced and the quantities increase with particles energy. Table 5 shows popular radioisotopes that can be produced in each proton energies range.[17] However, the increase in the number of radioisotopes that can be produced come at a cost both in equipment and in infrastructure. Moreover, as the energy increases, the number of side channel reactions increase and unwanted radioisotopes can be produced. This is especially true for beam energies greater than 30 MeV. Traditional radioisotopes used in nuclear medicine such as ^{201}Tl, ^{67}Ga, ^{123}I and ^{111}In have been produced via proton reactions for more than 25 years. Many of the most useful radioisotopes can be produced with proton energies of below 30-40 MeV. The selection of a cyclotron will depend on which radioisotopes are needed to prepare the radiopharmaceuticals used in the clinical and research programs, and on whether these radioisotopes will be distributed to other locations.

Establishing a cyclotron facility for producing radioisotopes and/or manufacturing radiopharmaceuticals is a complex process and requires careful planning in order to be successful. There are several essential considerations in development of such a facility, including design and technical aspects, feasibility studies and strategic planning, facility requirements and design, staffing, radiation protection, good manufacturing practices (GMP), and quality management. A facility for the production of radioisotopes and radiopharmaceuticals requires multi-disciplinary staff with a wide range of qualifications. Personnel required for the operation of a radioisotope facility includes cyclotron operator(s), production chemist(s), quality control (QC) chemist(s), a radiation safety officer, an electronic engineer, a mechanical engineer and a manager. In addition to the technological complexity, requiring highly skilled staff, it is also costly to build and operate. The main areas of such a facility are the

Table 5: Popular radioisotopes that can be easily produced versus the proton energies required for their reaction[17]

Proton energy (MeV)	Radioisotopes produced
0-10	F-18, O-15
11-16	C-11, F-18, N-13, O-15, Na-22, V-48
17-30	C-11, F-18, N-13, O-15, I-124, I-123, Ga-67, In-111, Na-22, V-48, Tl-201
>30	C-11, F-18, N-13, O-15, I-124, I-123, Ga-67, In-111, Na-22, V-48, Sr-82, Ge-68

***Figure 2**: TR-19 PET cyclotron*

cyclotron area, the hot laboratory areas, the dispensing areas and the QC laboratory. There are several relevant references in clinical literature describing the planning of new radiopharmaceutical production and/or PET facilities.[18,19]

In June 2005, TR-19 PET, the first PET cyclotron in Thailand, was installed at Wattanosoth Hospital (Figure 2). It produces protons up to an energy of 19 MeV. Typical F-18 production uses proton beam energy of 18.7 MeV with a beam current approximately 80-95 μA. O-18 enriched water of 2.6 mL is loaded in the F-18 target chamber. The amount of F-18 that can be produced for a 30 minute irradiation is about 3 Ci. This amount is sufficient to produce FDG to supply all of the PET centers in Bangkok. The irradiation time for each production is calculated according to the amount of FDG needed. The TR-19 PET cyclotron at Wattanosoth Hospital can produce F-18 up to 8 Ci of F-18 per irradiation period with the current set up. The TR-19 PET cyclotron at Wattanosoth Cancer Hospital is equipped with beamline which can be used for a solid target.

The radiopharmaceutical facility area at Wattanosoth Hospital includes a cyclotron vault, an equipment room, a control room, a changing room, an air lock room, a hot laboratory in a clean room environment, QC laboratory and dispensing areas. There are several potential hazards in a cyclotron facility. The normal hazards are high voltage, radiation, oxygen deficiency, high temperatures, and the movement of large pieces of equipment. All personnel receive training to understand these risks. There is an interlock protection system. Access to the accelerator or target is only allowed in a *'machine off'* condition. The shielding around the cyclotron vault is there to reduce the neutron flux during machine operation. Any shielding that will reduce the neutron flux to an acceptable level will also reduce the gamma flux. The thickness of the shielding depends on the type of cyclotron, the energy, types of particles, and the targets to be used. Final testing of the shielding is done using protons on O-18 enriched water which produces a lot of neutrons.

To minimize the downtime of the cyclotron, regular preventive maintenance as well as proactive replacement of deteriorating parts is essential. Checklists occur weekly, monthly, quarterly and yearly for preventive maintenance according to the manufacturer's recommendations. This ensures an effective maintenance regime. For production runs, a number of parameters are recorded—for example environmental and facility parameter such as temperature and pressure of cooling water, room temperature and humidity, target pressure before and during irradiation, delivery times of activity to the hot cell, and a number of cyclotron running parameters. This checklist will help to detect gradual changes over time.

Synthesis of FDG and Radiochemistry of FDG

After cyclotron produces F-18 by proton beam irradiation of O-18 enriched water via 18O(p,n)18F reaction, the irradiated O-18 enriched water is then transferred from the target site to the synthesizer in the hot laboratory to proceed for FDG production. Currently, there are many commercially available FDG synthesis modules such as FASTlab, TRACERlab MX, BIOSCAN FDG synthesis Module, EBCO FDG synthesis module, Explora FDG 4, etc. Beside the synthesis modules, there are many other types of equipment needed in the hot laboratory such as hot cells, laminar flow hot cells or manipulation hot cells. Hot cells are exhausted and a shielded enclosure provides shielding for personnel against radiation from gamma emitters. The hot cells for the production of radiopharmaceuticals need to maintain negative pressure to prevent radioactive contamination. The hot cells should be leak tight according to accepted international standards. The wall of the hot cells should be smooth, impervious and unbroken and the corner curved.

***Figure 3**: Hot cells and a manipulation hot cell situated in a controlled clean room*

***Figure 4**: HFASTlab*

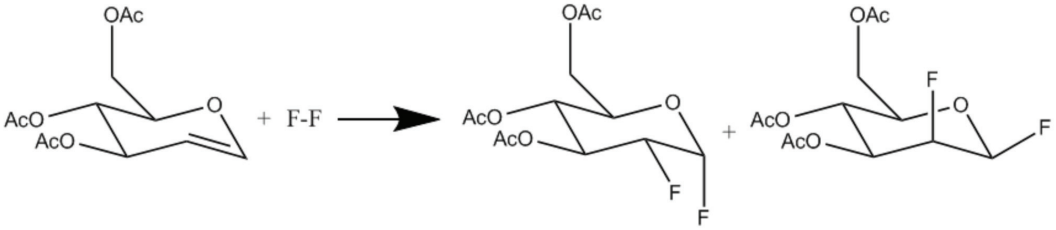


***Figure 5**: Electrophilic fluorination*

According to the recommendations for GMP, during their operation, the hot cells should be under negative pressure with a 20-fold air change per hour.[18]

The appropriate design and layout of a radiopharmaceutical production facility is an essential requirement in achieving the desired product quality and safety. The laboratory design needs to take into account GMP for radiopharmaceutical production as well as radiation protection practices. The guidelines for the design and implementation of a radionuclide and radiopharmaceutical production facility using cyclotron can be found elsewhere.[18,20-24] However, there is currently no global harmonization of FDG quality specifications, or methodologies to achieve GMP compliance. For example, WHO and European Union (EU) regulations require compliance with guidelines applicable to conventional pharmaceutical manufacturing in addition to specific requirements for radiopharmaceuticals, necessitating these production activities be performed in environmentally controlled cleanrooms.[22,23] On the other hand, in the U.S., production of FDG is governed by the GMP regulation designed specifically for PET radiopharmaceuticals.[24] In Thailand, there is no specific regulation related to FDF production at present. The FDG production facility presented by IAEA (International

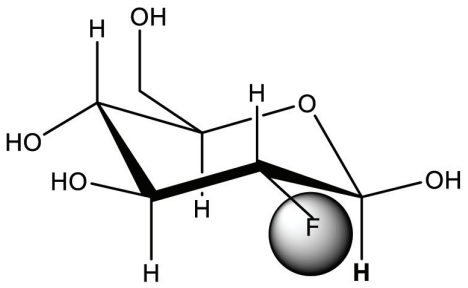


***Figure 6**: Structural formula of 2-[^{18}F]fluoro-2-deoxy-D-glucose or FDG*

Atomic Energy Agency) is based on GMP guidelines prescribed by WHO. The radiopharmaceutical production activities in Wattanosoth Hospital are performed in an environmentally-controlled clean room.

Currently, the hot laboratory in Wattanosoth Hospital is equipped with two single hot cells for FDG synthesis, one double hot cell for synthesis of C-11 radiopharmaceutical and a manipulation hot cell. Figure 3 shows the hot cells and manipulation hot cells in the hot laboratory. A hot cell with tele-manipulators and a double hot cell will be installed next year.

In 2005 and early 2006, there was only one FDG synthesis module by EBCO (currently ACSI), called Single FDG Synthesis Module. A year after its initial installation, another FDG synthesis module called Double Synthesis Module from ACSI was installed. The synthesis time for EBCO FDG synthesis modules (both Single and Double) is about 35 minutes. The uncorrected yields of FDG were approximately 40% and 50% at the end of synthesis for single synthesis module and double synthesis module respectively. Since then, the demand for FDG is growing rapidly throughout the world, and many companies keep improving the efficiency of FDG synthesis modules. In the beginning of 2012, FASTlab by GE was installed in the hot laboratory. The FDG synthesis time for FASTlab is about 25 minutes with approximately 70% yield of FDG. FASTlab is equipped with an integrated cassette pre-loaded with reagents that simply snaps into place. The system design offers consistently high reproducibility. Figure 4 shows a chemist installing a cassette into FASTlab set in hot cells.

The first synthesis of FDG was carried out in Brookhaven National Laboratory by Wolf et al[25] in 1976 by electrophilic fluorination. Electrophilic fluorination refers to the addition of fluorine atoms across a double bond, producing a difluoro derivative of the present compound as shown in Figure 5. The structure of FDG is shown in Figure 6. The synthesis took 2 hours and the yield was 8%.[25] Despite the low yield and long synthesis time, the Brookhaven team was able to collaborate with the Hospital of the University of Pennsylvania to map glucose metabolism in human brain. Several improvements to electrophilic fluorination were made thereafter. The major limitation of electrophilic fluorination was that only 50% of the radioactive fluorine atoms were incorporated into the precursors. The specific activity is low due to the presence of the non-radioactive fluorine gas since the ^{18}F-F2 was produced from a Neon gas target with 0.1% to 1% of fluorine gas via a $^{20}Ne(d,\alpha)^{18}F$ reaction. Moreover, the maintenance and operation of a Neon target is troublesome. The yield of ^{18}F- with the $^{20}Ne(d,\alpha)^{18}F$ reaction was much lower than with the $^{18}O(p,n)^{18}F$ reaction[26].

Many attempts have been made to develop a nucleophilic substitution for synthesis of FDG. But the major breakthrough was reported in 1986 by Hamacher et al. who used Kryptofix 222™ as a catalyst.[27] The reaction time is shortened to 50 minutes and the yield of FDG is over 50%. Nucleophilic substitution is a chemical reaction involving the addition of a nucleophilic molecule (highly negatively charged molecule) into a molecule with a leaving group (electron drawing group attached to the parent molecule through an unstable chemical bond). In the synthesis of FDG, ^{18}F ion is the nucleophile. The precursor for FDG is manosetriflate. In mannose triflate, the 1,3,4,6 carbon positions of a mannose molecule are protected with an acetyl group and triflate is the leaving group at the 2-carbon. In the presence of Kryptofix 222™ as catalyst and acetronitrile as solvent, ^{18}F ion approaches the mannose triflate at the 2-carbon, while the triflate group leaves the protected mannose molecule to form FDG (Figure 7). Details on FDG synthesis can be found elsewhere.[20,28] At present, commercially available computer controlled automatic synthesizers use a nucleophilic process for FDG synthesis. Purification of the final FDG can be performed with a series of anion exchange column, a C-18 reverse phase column and an alumina column.

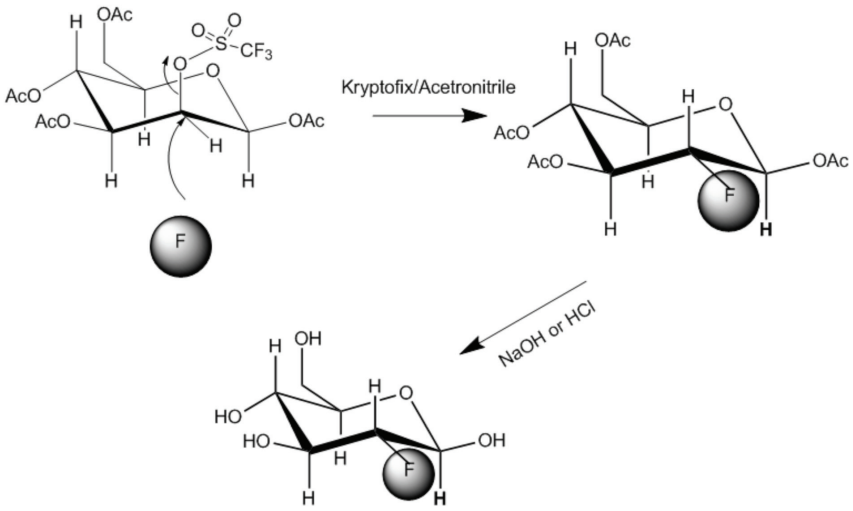


***Figure 7**: FDG synthesis by nucleophilic fluorination*

Table 6: Example of quality control criteria for FDG

Test	Acceptance criteria
Appearance	Clear
Color	Colorless or slightly yellow
Radioactivity Assay	-
Radionuclide Identity	105-115 minutes
pH	4.5-7.5
Radiochemical Identity	Rf: ±10% of Standard FDG
Radiochemical Purity	> 90% 18F-FDG
Residual Solvents:	Acetone < 5,000 µg/mL EtOH < 5,000 µg/mL MeOH < 3,000 µg/mL Acetonitrile < 410 µg/mL
Bacterial Endotoxin	≤ 175EU/V (V=Maximum Recommended total dose)
Bobble point test filter	Pressure after being filtered ≥ 3 Bar (45 psi)
Sterility	No growth after 3 days

Since it was first installed and up to November 2012, Wattanosoth Hospital has produced 1,312 batches of FDG production with total of 6,695 doses of FDG. FDG produced here was supplied not only to Wattanosoth Hospital but also many other hospitals in Bangkok namely, Bumrungrad Hospital, Chulalongkorn Hospital, Chulabhorn Hospital, Siriraj Hospital, and Ramathibodi Hospital.

Overview of quality control

FDG must conform to various quality attributes of purity, efficacy and safety prior to being considered suitable for patient use. There are some minor differences in FDG quality specifications described by three major pharmacopoeias, namely the International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph. Eur.), and the United States Pharmacopoeia (USP).[29-31] FDG specification is not currently specified in Thai Pharmacopoeia.

Since the half-life of ^{18}F is 110 minutes, it is necessary for the application of a QC test procedure to be completed in a relatively short time period. But, not all tests can be completed prior to the release of a product for patient use, namely sterility. In spite of this restriction, all tests except sterility can be performed within 30 minutes of post-production. Application of GMP, strong quality management and a validation of the entire system ensure a safe and high quality product. Table 6 shows the example of quality control test criteria for FDG used at Wattanosoth Hospital. Most of the tests are done before the release of FDG to patients.

Quality testing of FDG prior to release for patient use is a major component of manufacturing, but quality control (QC) alone does not constitute good manufacturing practice (GMP). Greater confidence in product quality can only be achieved through strict adherence to GMP guidelines during batch manufacturing. Radiopharmaceuticals are pharmaceutical products and must therefore be manufactured according to the basic principles of GMP. GMP encompasses everything that has a bearing on the quality of the pharmaceutical product including personnel, premises equipment, starting material, processes, QC/QA (quality assurance), documentation, packaging and shipping. In the past, there was no specific GMP guideline for radiopharmaceutical manufacturing. In contrast to conventional pharmaceuticals, the presence of the radioactive component in a radiopharmaceutical adds complications to the manufacturing process and controlrequirements. Specific differences include radiation hazard to the operator, and a relatively short shelf-life of several radiopharmaceutical products due to the short half-life of the radioisotope incorporated within the radiopharmaceuticals. Moreover, radiopharmaceutical products are often used in a patient prior to full assessment of quality. Therefore, quality assurance in these cases is highly dependent on the adherence to GMP protocols and procedures. Recent guidelines for radiopharmaceutical products can be found elsewhere.[32-34]

Conclusion

FDG is the most used radiopharmaceutical in PET. It is aptly named the *'Molecule of the Millennium'* due to its versatility and enormous important application in oncology, neurology and cardiology. PET continues to be the primary functional imaging technique for conduction translational research studies aimed at identifying the molecular basis of human disease. The future of PET will depend on the application of upcoming new radiopharmaceuticals and the regulatory framework for the usage and approval of new PET drug products. Establishing a PET center and radiopharmaceutical facility is a complex process. Investment and operation costs are high. Moreover, a number ofhighly qualified personnel is needed. Most PET centers and cyclotron facilities, especially where clinical research will be conducted, need collaboration among many specialties. Nuclear medicine physicians, nurses,technicians,physicists,organic/medicinal chemists, chemical engineers, mechanical engineers, analytical chemists, and radio pharmacists need to work in concert to meet the significant time constraints imposed by the short-lived radioisotopes routinely used in PET.

However, the number of PET scans for each scanner is still small. There are only 6 PET centers in Thailand at present and the number of PET scanners per million people in Thailand is far fewer than many other countries. The limited indication for reimbursement is

one of the important factors for the underutilization of PET scanners in Thailand. Besides this, the knowledge of medical personnel to use PET is also a factor. Governmental support to maximize the use of existing facilities is crucial for improving the healthcare of the Thai population.

Acknowledgements

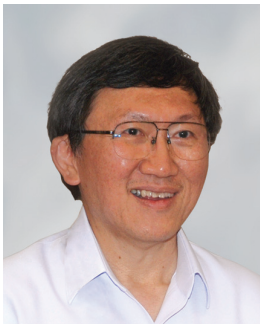
The author thanks the PET center and Cyclotron facility team at Wattanosoth Cancer Center including doctors, nurses, physicists, technologists, chemists, engineers and pharmacists. During the past 7 years, they have put a lot of effort into continued improvements in quality and range of services. Also, the author is very grateful for the support from the executive of the Bangkok Hospital Medical Center and Wattanosoth Cancer Center.

References

1. Ido T, Wan CN, Casella V, et al. Labeled 2-deoxy-D-glucose analogs: 18F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy -2-fluoro-D-mannose and 14C-2-deoxy-2-fluoro-D-glucose. *J Labeled Compounds Radiopharm* 1978; 24:174-83.
2. Reivich M, Kuhl D, Wolf A, et al. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 1979;44:127-37.
3. Kostakoglu L, Agress H, Goldsmith SJ. Clinical role of FDG PET in evaluation of cancer patients. *RadioGraphics* 2003;23:315-40.
4. Gallagher BM, Fowler JS, Gutterson NI, et al. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978;19:1154-61.
5. Hoh K, Howkins RA, Glaspy JA, et al. Cancer detection with whole-body PET using [F-18]fluoro-2-deoxy-D-glucose. *J Comput Assist Tomogr* 1993;17:582-9.
6. Delbeke D. Oncological Applications of FDG PET imaging. *J Nucl Med* 1999;40:1706-15.
7. Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the Use of 18F-FDG PET in Oncology. *J Nucl Med* 2008;49:480-508.
8. Von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: current applications and future directions. *Radiology* 2006;238:405-22.
9. Medicare National Coverage Determinations Manual. Chapter 1, Part 4 (Sections 200-310.1)(Rev. 146, 08-03-12)Available at http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/ncd103c1_Part4.pdf[Access December 16, 2012.]
10. Buck AK, Herrmann K, Stargardt T, et al. Economic Evaluation of PET and PET/CT in Oncology: Evidence and Methodologic Approaches. *J Nucl Med Tech* 2010;38:6-17.
11. Review of PET services in Hong Kong hospital authority. Part 2—Programming and service rationalization. Release Date June 2012. Available at http://www.ha.org.hk/haho/ho/adm/210576e.pdf[Access December 17, 2012].
12. The Royal College of Radiologists. PET-CT in the UK, A strategy for development and integration of a leading edge technology within routine practice. 2005; Available at http://www.rcr.ac.uk/docs/general/pdf/PETCT_final.pdf[Access December 17, 2012].
13. Martinuk SD. The Use of Positron Emission Tomography (PET) for Cancer Care Across Canada Time for a National Strategy. 2011; AAPS, Inc. and TRIUMF.
14. Funding arrangements for diagnostic imaging services, an international literature review. 2009 Available at https://www.health.gov.au/internet/main/publishing.nsf/Content/DA4840C15CF15F0CCA2576D300019741/$File/ACIL%20TASMAN%20Final%20Report%20-%20International%20Funding%20Models%20for%20Diagnostic%20Imaging.pdf[Access December 18, 2012].
15. International Commission on Radiological Protection. Radiation Dose to Patients from Radiopharmaceuticals. St.Louis, MO:2000;49. ICRP publication 80.
16. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure Guidline for Tumor Imaging with 18F-FDG PET/CT 1.0. *J Nucl Med* 2006;47:885-95.
17. International Atomic Energy Agency (IAEA), Cyclotron Produced Radionuclides: Principles and practice, Technical Reports Series No. 465, IAEA, Vienna, 2008.
18. International Atomic Energy Agency (IAEA), Cyclotron Produced Radionuclides: Guidelines for setting up a facility, Technical Reports Series No. 471, International Atomic Energy Agency (IAEA), Vienna, 2009.
19. Jacobson MS, Hung JC, Mays TL, Mullan BP. The planning and design of a new PET radiochemistry facility. *Mol Imaging Biol* 2002;4:119-27.
20. IAEA, Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of [^{18}F]Fluorodeoxyglucose (FDG), IAEA radioisotopes and radiopharmaceuticals series No.3, IAEA, Vienna, 2012.
21. Stafford RG. Code of Practice for the Design of Laboratories using Radioactive Substances for Medical Purposes, Commonwealth of Australia, Australian Government Publishing Service, Canberra 1981; Appendix XVIII.
22. World Health Organization, Annex 3: Guidelines on Good Manufacturing Practices for Radiopharmaceutical Products, WHO Technical Report Series, No. 908, WHO, Geneva, 2003.
23. European Union, EudraLex: The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 3: Manufacture of Radiopharmaceuticals, Brussels, September, 2008.

24. US Food and Drug Administration, Department of Health and Human Services, 21 CFR Part 212 Current Good Manufacturing Practice for Positron Emission Tomography Drugs.
25. Fowler JS, Ido T. Initial and subsequent approach for the synthesis of 18FDG. *Semin Nucl Med* 2002;32:6-12.
26. Levy S, Elmaleh DR, Livni E. A new method using anhydrous [18F]fluoride to radiolabel 2-[18F]fluoro-2-deoxy-D-glucose. *J Nucl Med* 1982;23:918-22.
27. Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 1986;27:235-8.
28. Yu S. Review of ^{18}F-FDG synthesis and quality control. *Biomed Imaging Interv J* 2006;2:e57.
29. International Pharmacopoeia, Monograph: Fludeoxyglucose (^{18}F) Injection, International Pharmacopoeia, 2008.
30. European Pharmacopoeia, Monograph: Fludeoxyglucose (^{18}F) Injection, European Pharmacopoeia Ed. 6, 2009.
31. US Pharmacopoeia, Monograph: Fludeoxyglucose^{18}F Injection, US pharmacopoeia, 2009.
32. International Atomic Energy Agency (IAEA), Guidelines for Good Manufacturing Practices of Radiopharmaceuticals, IAEA, Vienna, 2001.
33. The European Pharmacopoeia (Ph.EUR): The European GMP Guidelines for Medicinal Products for Human Use. Annex 1: Manufacture of Sterile Products and Annex 3. Manufacture of Radiopharmaceuticals.
34. Canadian Health Products and Food Branch Inspectorate, Positron Emitting Radiopharmaceuticals (PER), Annex to the Good Manufacturing Practices (GMP) Guidelines, Guide-0071, February 15, 2006.

Road Traffic Accident Management System



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Keywords:
road traffic accidents, traffic injury, strategy, Haddon Matrix, decade of action

Road traffic injuries in Thailand are becoming more critical and are the 2nd leading cause of death, second only to heart disease. In many provinces, traffic accidents rank as the leading cause of death. Furthermore, traffic injuries are the 1st leading cause of death among people aged below 40. This age group is the most economically productive and their loss has a great impact on their families and on national productivity.[1]

Traffic injuries are responsible for more morbidities and disabilities, than any other cause. Moreover, they result in damage to goods and property and can cause a significant post-crash impact on the victim's family, public health, society, and the economy.[2-5]

Each year, more than 600,000 trauma patients are hospitalized, and more than 1,000,000 receive minor injuries from traffic accidents. Traffic injuries alone account for more than 10,000 deaths a year, whilst about 40,000 people become disabled a year, causing a heavy economic burden to family, society, and the country as a whole.[1,6,7]

The Faculty of Engineering of Prince of Songkla University, with the support of the Department of Highways at the Ministry of Transportation conducted a study to assess the losses from road traffic injuries. They found that losses were a staggering THB168,000 million in 2006.[8]

Road traffic accidents in Thailand are still at a critical point

No matter whether young or old, male or female, students, workers or officers, almost everyone has to use the road to get to their destination and back home at least twice a day.

At present, there are many drivers who do not obey the rule of the road and are at risk of being in or causing a serious traffic accident. Road users increase their chance of being involved in an accident if:

- Driving while drunk
- Acting carelessly or acting aggressively
- Suffering from personality disorders
- Inexperienced, underage or badly trained
- Not paying attention

These everyday factors mean that nobody is safe on our roads. A traffic accident can happen in a second.

It is not hard to list the different possible causes of road traffic accidents. It is much harder to implement successful and effective preventive measures that involve multiple government agencies and individuals. The Thai public health sector is well aware of the grave losses from injuries and fatalities, but lacks the requisite experience and technical expertise to overcome multiple obstacles. The reduction of traffic accidents is not just a matter for the public health service, it also involves multiple agencies. A great number of individuals just do not realize the importance of taking responsible steps to avoid traffic accidents. Furthermore, there needs to be coordination and effective cooperation between agencies to synchronize activities to maximize their effectiveness. The failure of government agencies and individuals to deal with this issue has resulted in an increasing number of injuries recorded.

Moreover, there is a false belief that road traffic safety measures exist in Thailand. Furthermore there are falsely held beliefs about the reason for so many accidents:

- It is widely believed that a traffic accident is down to fate or the will of God despite being preventable.
- Many organizations campaign for the prevention of road traffic injuries. But this is only done with poster campaigns, to affect behaviour change with too little focus on the strategy of policy development and law enforcement. Furthermore, most campaigns are reserved for New Year and Songkran festivals only. Campaigns should be ongoing, year round.
- There are many people who still believe that the best way to solve the number of traffic accident injuries is to raise awareness through campaigns and education programs aimed at school goers and the general public.
- Many people agree to being driven by a drunk driver.
- Many people are too frightened to ask a driver to slow down, or even to get out of the vehicle if the driver persists in speeding.

Principles of Injury Prevention and Road Safety Control Measures[2]

Injury prevention and road safety control measures can be developed systematically.

In 1937, Godfrey adopted an epidemiological model in his analytical study of traumatism and achieved a systematic planning of injury control.

In 1949, Gordon proved that a detailed epidemiological classification was viable for injury as well as for other sudden or chronic diseases.

In 1978, the very famous epidemiologist William Haddon Jr. (1926-1985) from the Insurance Institute for Highway Safety of the United States, promoted injury control measures (Table 1). The proposed approach was a matrix in which the human, vehicle and environmental factors of a crash are shown interacting with the three phases of a crash – pre crash, during the crash, and post crash – to form a nine-cell matrix, which became known as the Haddon matrix. This was then used as a planning tool for road traffic injury prevention worldwide. Each cell in this matrix offers opportunities for intervention or countermeasures to reduce fatalities caused by motor vehicle accidents.

Based on Haddon's Matrix, we can develop a systematic program of injury prevention and control and cover all phases by implementing the required interventions placed in each cell of the matrix.

Table 1: Injury Control Measures Classified According to Three Factors and Three Phases

Phases	Education	Environment	Enforcement
Pre crash	1	2	3
Crash	4	5	6
Post crash	7	8	9

From "To Prevent Harm" Washington, D.C.: Insurance Institute for Highway Safety, 1978

The following are examples of preventive measures based on Haddon's Matrix.

Phase 1: Primary Prevention - Pre Crash Prevention Refers to Preventing the Crash from Happening

	Cell number 1: Education	Cell number 2: Engineering	Cell number 3: Enforcement
Principle	- Launch an educational campaign to prevent injuries caused by road traffic accidents targeted at the general public and school-going children.	- The manufacturing of vehicles, regular vehicle servicing, road maintenance and construction all play an important role in the prevention of road traffic injuries.	- Strict enforcement of rules of the road is a key factor to enhancing the efficiency and effectiveness of injury prevention and control.
Method	- Educate the public on injury prevention through the mass media. - Incorporate road safety rules into school health education curriculums. - Carry out specific road safety awareness campaigns during major festivals.	*Road* - Safety must be a major component in the design of any new road. - Improvements and proper maintenance of road surfaces, street lighting as well as traffic lighting are essential. *Vehicle&Transportation system* - The effective management of a mass transportation system has been shown to have a big impact in reducing injuries from road traffic accidents. - Safety should be a major component in the design of motor vehicles and vehicle standards should be agreed on and enforced.	- Enforce the law comprehensively, continuously, covering all areas.
Example	- Knowledge should be transferred to the target group and should include: *Pedestrian* - Children under 9 should never cross a road alone, and should be accompanied by an adult. - Cross at a marked crosswalk, zebra crossing or overpass. - Stop, look and listen, and look both ways, before crossing. - Walk towards oncoming traffic when there are no sidewalks (i.e. walk on the right-hand side of the road if traffic is on the left-hand side). - Wear bright or light-colored clothing (red, yellow, white colors) when walking in dusk or darkness and wear reflective bands when cycling. - Goods should not be sold on the pavement, obstructing the way for pedestrians. *Bicycle* - Bicycles should be bright colors such as yellow or white. - Reflectors should be attached to the wheel rim, front and rear mudguard.	- All road construction and vehicle manufacturing should take safety measures into account *Road* - Traffic islands can prevent head-on collisions. - Bridges over intersections can prevent collision at intersections - Freeways should have an acceleration lane. - Slopes at sharp bends can lessen the centrifugal force. - A bicycle lane and sidewalk can protect cyclists and pedestrians. - A wide parking lane. - Adequate street lighting. - Accurate traffic signals and signs. - Humps and roundabouts to reduce speeds and rumble strip to warn of hazards on the road. *Vehicle* - ABS brakes. - Radial tire for preventing explosions. - Headlights with a high and low beam.	- In 1997, policemen in Victoria, Australia, operated an alcohol breath test up to 2.8 million times. 1.3 million drivers were given random breath testing. - A high level of enforcement in 3 areas : speed limits of 100 km/h, enforcing the use of seat belts and identifying illegal blood alcohol concentration levels (0.05 mg%) in drivers. As a result of these measures, Australia, witnessed 3 times fewer traffic related deaths over a period of 20 years.

	Cell number 1: Education	Cell number 2: Engineering	Cell number 3: Enforcement
Example	*Motorcycle* - Ride motorcycles in accordance to traffic regulations. - Wear good quality appropriate helmets, with visors, chin guards and straps. - Never drink and ride - Obey the speed limit. - Always turn on the indicator when turning right or left. - Slow down at intersections. - Ensure the motorcycle goes for regular servicing. - Have the headlight and rear light on at night. *Motor Car* - Don't drink and drive. - Don't take drugs or medication that can impair performance before driving. - Stop and take a rest when feeling drowsy or very fatigued.	- Speeding warning light. - Sensors for alcohol detection in the car. - etc.	

Phase 2: Secondary Prevention - Injury Prevention Refers to Preventing an Injury when The Crash Occurs.

	Cell number 4: Education	Cell number 5: Engineering	Cell number 6 : Enforcement
Principle	- Educate the target group to practise preventing injury when traffic accidents take place.	- Road and vehicle design can prevent injury of passengers in a car when a road accident takes place.	- The strict enforcement of the law is a key factor in enhancing the efficiency and effectiveness of injury prevention during road traffic accidents.
Method	- Educate the public on injury prevention when accidents take place through mass media campaigns. - Incorporate road safety rules into the health education curriculums of schools. - Carry out campaigns during major festivals.	- Safety equipment or components should be incorporated in road and vehicle design to prevent injuries when traffic accidents take place.	- Enforce the law comprehensively, continuously, covering all areas.
Example	The target group should be aware of the following: - Wear a helmet while riding a motorcycle (rider or passenger). - Wear a seat belt while driving a car (or travelling as a passenger in the back). - Place children in protective car seats (avoid car seats in seats with airbags) - Practise guidelines in emergency situations such as; • Car slipping and falling into a ditch. • Burst tyres. • Driving in adverse weather conditions such as heavy rain or through environmental hazards such as steep roads.	*Road* - Shoulder with a gentle slope. - Trees not too close to the road. - Hollow lampposts. - Curves with guard-rail. - etc. *Vehicle* - Strong Global Outstanding Assessment (GOA) body. - ABS brakes. - Windshields made of safety glass. - Seatbelts and air bags. - Helmets and leg guards for motorcycles.	

Phase 3: Tertiary Prevention – Post Crash Prevention Refers to Preventing Fatalities when an Injury Occurs.

	Cell number 7: Education	Cell number 8: Engineering	Cell number 9: Enforcement
Principle	- Educate students, and the general public, first on the scene volunteers and policeman about first aid, primary assessment and the safe transportation of injured people.	- Manufacture good quality resuscitation equipment and well equipped ambulances ready for use.	- Strict enforcement of penalties for offenders who cause road traffic accidents.
Method	- Educate the public on how to prevent injuries through mass media campaigns. - Incorporate road safety knowledge into health education curriculums in schools.	- Conduct research to develop better quality medical devices to help road traffic accident victims. - Improve and maintain these devices and keep ready for use at all times.	- Enforce the law comprehensively, continuously, and cover all areas aspects of road safety.

The above systematic concept enables all agencies involved to apply these measures of injury prevention and control to cover all phases of road traffic accidents. After the strategies are determined, the next step is to consider how to implement them.

The International Association of Traffic and Safety Science has stipulated four major principles in injury prevention:[1]

1. Multi-sectorial approach
2. Multidisciplinary approach
3. Internationality
4. Practicality

The most significant principle is the multi-sectorial approach due the complexity of the problem and the need to involve several government and civic agencies. Therefore, all agencies involved have to work together to reach sensible solutions.

The World Health Organization (WHO) Collaborating Center on Safe Community, Karolinska Institute, Sweden proposed the following principles for a safer community:[1]

1. The project implementation must be multidisciplinary.
2. There must be good information systems for project monitoring and evaluation.
3. Communities should participate and support the activities.
4. The selection of activities is a decision-making process which must be based on the problem and possible solutions to the problem.
5. Implementation must be based on all a range of actions which are acceptable to the community.

Based on the above concept and principles, the United Nations announced the Decade of Action for Road Safety 2011-2020. Its strategies for preventing road traffic injuries are as follow:[9]

1. Build road safety management capacity.
2. Influence safety road design and network management.
3. Influence safety vehicle design.
4. Influence road user behavior.
5. Improve post road traffic accident care.

Thailand needs to implement a wide range of programmes and initiatives before we can expect to travel safely on our roads. Only by working together will we be able to prevent road traffic injuries from increasing year on year.

References

1. Chadbunchachai W, Suphanchaimai W, Srimahawong S. Traffic Accident Prevention, Khon Kaen Province 1997. Khon Kaen Press, Khon Kaen:1997.
2. Mohan's D. Basic Principles of Injury Control. Proceeding of an international Course Organized by the John Hopkins University School of Hygiene and Public Health and the World Health Organization Baltimore: 1983.
3. Mock C. Injury Control Overview : Policy Issues to address in Strengthening Surveillance, Injury Prevention and Trauma Treatment. International Conference on Road Traffic Injuries and Health Equity. Massachusetts: 2002.
4. Peden M et al., eds. World report on road traffic injury prevention. Geneva, WHO, 2004. Downloaded from www.who.int/violence_injuty_prevention/publication/road_traffic/world_report/en/index.html.
5. World Health Organization, Global status report on road safety: time for action. Geneva, World Health Organization, 2009. Downloaded from www.who.int/violence_injury_prevention/road_safety_status/2009.
6. Trauma and Critical Care Center, Khon Kaen Regional Hospital, 13 Years Anniversary Trauma Registry, 1997-2008.
7. Thai Road Foundation. Thailand road traffic injury statistics 200: 2009.
8. Faculty of Engineering, Prince of Songkla University supported by Department of Highways, Ministry of Transportation, The study of Traffic Accident Costs in Thailand, 2006.
9. Department of Disaster Prevention and Mitigation, Directing Center for Road Safety, Strategic map: Strategic map for decade of action 2011-2020, 2011.

The Experience of Blood Purification in Sepsis by Coupled Plasma Filtration Adsorption in Thailand

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Keywords:
sepsis, coupled plasma filtration adsorption, CPFA , blood purification

Sepsis is an inflammation syndrome which is caused by severe infection. This severe inflammation is characterized by vasodilatation, leukocyte accumulation and increased microvascular permeability. The pathophysiology of sepsis is believed to be due to the dysregulation of the inflammatory response. The human body generates and releases a massive uncontrolled amount of proinflammatory mediators into the blood stream which causes cellular and tissue injury. This injury leads to the development of multiple organ dysfunction syndromes (MODS), and causes life-threatening conditions.

The normal host response to infection involves the activation of circulating and fixed phagocytic cells, the generation of proinflammatory and anti-inflammatory mediators. When the body releases massive cytokines beyond the infection site, sepsis occurs. These mediators cause fever, hypotension, acute phase protein response, induction of interleukin 6, coagulation activation, increased endothelial permeability and so on. These large quantities of proinflammatory mediators will cause cellular damage and lead to multiple organ failure.

In conventional therapy for sepsis, the priority is to eradicate infection by using appropriate antibiotics and surgical interventions, and to initiate supportive care in order to correct physiologic abnormalities such as hypoxemia and hypotension.[1-4] Despite optimal treatment and close monitoring in intensive care units, the mortality rate due to severe sepsis and septic shock is approximately 40% and can exceed 50% in the sickest patient.[5-8]

A study from Nakada TA, et al.[9] in 2008 showed a decrease of interleukin 6 and procalcitonin correlated with survival during sepsis. The innovative idea to reduce proinflammatory cytokines led to the development of the extracorporeal blood purification technique. Extracorporeal blood purification can be performed in different ways. The treatment restores the normal balance of the targeted substances within the patient's body.

Coupled plasma filtration adsorption (CPFA) is a therapeutic extracorporeal blood purification tool combining 3 techniques namely plasma filtration, adsorption and hemofiltration. CPFA is suitable for illnesses involving renal failure together with large molecules, especially if these have a molecular weight close to that of albumin such as inflammatory substances found in sepsis and in liver failure. The CPFA technique has been performed in animal experimentation and in clinical settings worldwide since 1998. Some CPFA studies have been reviewed (Table 1).

Table 1: Coupled plasma filtration adsorption (CPFA) studies review.

Author	Year	Type of study	Total (n = 302)
Tetta C.[10]	1998	Experiment in vitro	↓TNF-α, ↓IL-1β, ↓IL-1Ra, ↓IL-8
Tetta C.[11]	2000	Experiment Rabbit sepsis	↓ 72 hours mortality
Ronco C.[12]	2002	ARF + sepsis	↑ MAP, ↑leukocytes response ↓ norepinephine, no side effects
Bellomo R.[13]	2003	Septic shock	↑leukocytes response, no side effects
Formica M.[14]	2003	Septic shock + MODS ± ARF	↑ MAP, ↑CI, ↑SVRI, no side effects ↓ CRP, ↓ norepinephine, ↓ mortality
Cesano G.[15]	2003	Septic shock + MODS	↑ MAP, ↑CI, ↑SVRI, ↑PaO2, ↑survival ↓ norepinephine
Mariano F.[16]	2004	Septic shock + ARF	↓ Clot with citrate
Page M.[17]	2007	Clinical cases	Simple to use, no side effects
Turani F.[18]	2009	Sepsis	↑ MAP, ↑PaO2 ↓ norepinephine, ↓ IL-6, ↓procalcitonine

CI = cardiac index CRP = C-reaction protein MAP = mean interval pressure RAP = right atrial pressure SVRI = 80 x (MAP-RAP)/CI
TNF = tumor necrosis factor

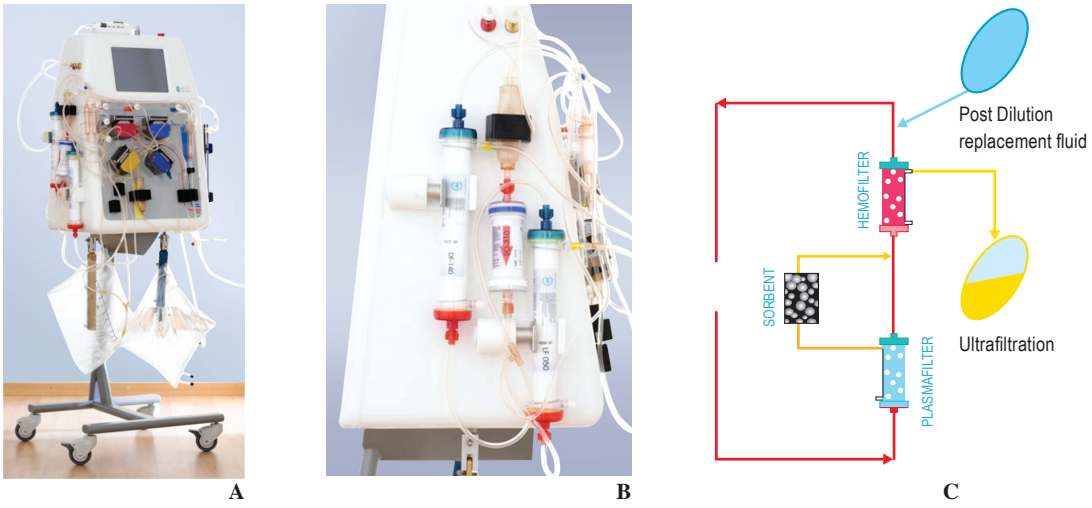

Figure 1: *Shows CPFA Machine (A-B) and the third filter (Hemofilter) (C)*

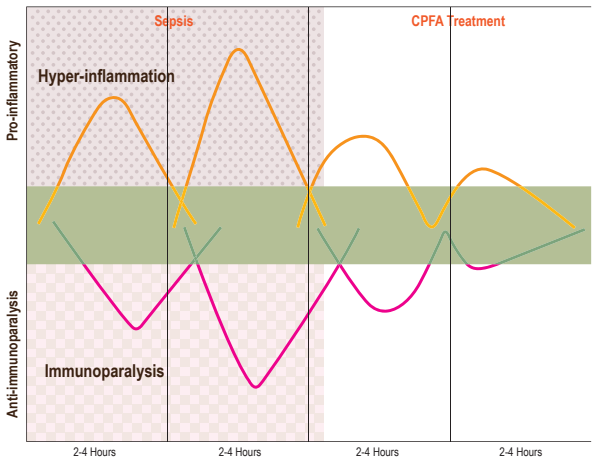

Figure 2: *The innovative idea to reduce inflammatory substances in sepsis by CPFA treatment.*

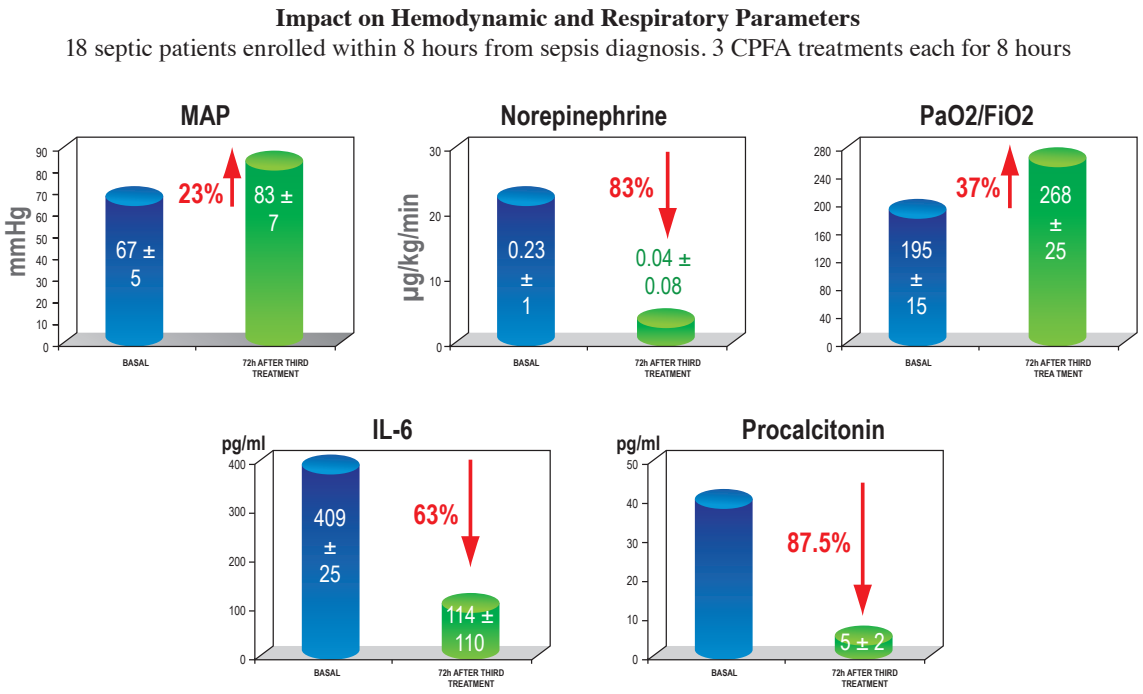

Figure 3: *This Turani F. study showed the improvement of mean interval pressure (MAP). The decrease of norepinephrine dosage use, the increase in oxygenation, and the reduction of interleukin 6 and prolactin in 72 hrs after the 3rd CPFA treatment*

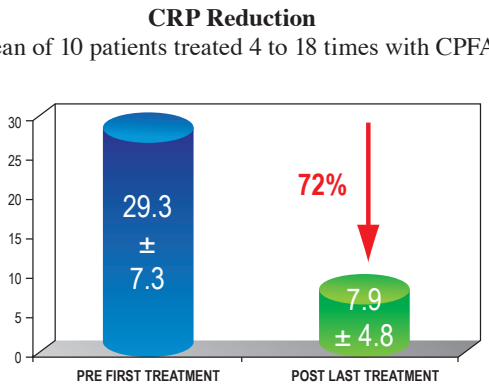

Figure 4: *Laboratory data shows a sharp decline of C-reaction protein (CRP) throughout the treatment time (from before the first treatment to after the last treatment).*[19]

The principles of a mechanized CPFA technique

CPFA is designed to remove some specific large substances by plasma perfusion in-line with continuous veno-venous hemofiltration (CVVH) which replaces kidney failure. The CPFA machine (blood purification HF 440, Infomed, Switzerland) contains 5 blood pumps and 3 filters (Figure 1A-B).

There are 3 steps to the technique. First, blood is passed through a plasma filter. The plasma is filtered and sent to a second filter (a sorbent cartridge). This sorbent cartridge is important because it absorbs large molecules, in particular interleukin 1β, interleukin 6, interleukin 8, interleukin 10, macrophage inflammatory proteins (MIP-α, MIP-β), tumor necrosis factor (TNF-α), endotoxin, peptidoglycan, bradykinin, angiotensin, leptin, retinol binding protein, prostanoids, complement factors, coagulation components, nitric acid, oxygen radicals, and bilirubin. The obtained plasma returns to the blood, and together passes through the third filter (hemofilter). The hemofilter placed on the blood flow allows hemofiltration to be performed which compensates for the kidney failure often associated with the main disease (Figure 1C).

In late 2012, at the Bangkok Hospital Medical Center (BMC), a 60-year-old man with a past medical history of diabetes and end stage renal disease on hemodialysis was admitted due to an infected diabetic foot. During hospitalization, he had an ischemic bowel requiring surgery. Later on, he developed sepsis and multiple organ dysfunction syndromes, including acute respiratory distress, hemodynamic instability, liver injury with high bilirubin levels, and bleeding disorders. His proinflammatory cytokines were very high especially interleukin 6, procalcitonin, and C-reactive protein.

A BMC medical team decided to perform blood purification by CPFA technique in order to reduce proinflammatory cytokines and bilirubin levels. However, he had abnormal coagulopathy so the team decided to use a citrate substrate for anticoagulation instead of heparin.

After 3 sessions of 10 hours CPFA with 0.22l/kg/d of plasma purification, the level of interleukin 6, procalcitonin, C-reactive protein, and bilirubin had declined drastically (Table 2).

Table 2: Coupled plasma filtration adsorption (CPFA) studies review.

Serum	T0	T1	T2
IL-6 (pg/ml)	996.5	464.5	617.4
Procalcitonin (pg/ml)	18.3	9.6	12.5
CRP (mg/l)	203	184	150
Total Bilirubin (mg/dl)	45.7	35.8	26.9

T0 : Before starting CPFA T1 : After 1st session of CPFA
T3 : After 3rd session of CPFA

In Thailand, this was the first case time a coupled plasma filtration adsorption treatment was used to reduce cytokines in sepsis. The cooperation between the Bangkok Hospital Medical Center and Infomed gave the team the required knowledge, learning experience, and the necessary additional tools to fight this life-threatening disease.

Acknowledgements

The author thanks doctors and staff at Bangkok Hospital, Bangkok, Thailand: Dr. Paithoon Boonma (Infectious Disease Clinic), Dr. Chanwit Wuttichaipradit, Dr. Somsit Tancharoen (Colorectal Clinic), Dialysis Nurses, Intensive Care Unit (ICU 1) Nurses. Thanks also to Econtech Supply of Thailand and Infomed of Switzerland.

References

1. Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet* 2005;365:63-78.
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock:2008. *Crit Care Med* 2008; 36:296-327.
3. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004;32:1928-48.
4. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Task Force of the American College of Critical Care Medicine. *Crit Care Med* 1999; 27:639-60.
5. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997;336:912-8.
6. McCloskey RV, Straube RC, Sanders C, et al. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group. *Ann Intern Med* 1994;121:1-5.
7. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock; a reassessment. *Crit Care Med* 1997;25:1095-100.
8. Sasse KC, Nauenberg E, Long A, et al. Long-term survival after intensive care unit admission with sepsis. *Crit Care Med* 1995;23:1040-7.
9. Nakada TA, Oda S, Matsuda K, et al. Continuous hemodiafiltration with PMMA Hemofilter in the treatment of patients with septic shock. *Mol Med* 2008;14:257-63.
10. Tetta C, Cavaillon JM, Camussi G, et al. Continuous plasma filtration coupled with sorbents. *Kidney Int Suppl* 1998;66:186-9.
11. Tetta C, Gianotti L, Cavaillon JM, et al. Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock. *Crit Care Med* 2000;28:1526-33.
12. Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med* 2002;30:1250-5.
13. Bellomo R, Tetta C, Ronco C. Coupled plasma filtration adsorption. *Intensive Care Med* 2003;29:1222-8.
14. Formica M, Olivieri C, Livigni S, et al. Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock. *Intensive Care Med* 2003;29:703-8.
15. Cesano G, Livigni S, Vallero A, et al. [Treatment of septic shock with the use of CPFA (associated plasma filtration and adsorption): impact on hemodynamics monitored with PiCCO. *G Ital Nefrol* 2003;20:258-63.
16. Mariano F, Tetta C, Stella M, et al. Regional citrate anticoagulation in critically ill patients treated with plasma filtration and adsorption. *Blood Purif* 2004;22:313-9.
17. Page M, Hayi-Slayman D, Ber CE, et al. [Use of coupled plasma filtration adsorption for septic shock treatment]. *Ann Fr Anesth Reanim* 2007;26:990-3.
18. Turani F, Lanini G, Alessandrini C, et al. Improvement of haemodynamic and respiratory parameters during coupled plasma filtration and adsorption correlates with the clearance of inflammatory mediators. *Critical Care* 2009;13:284.
19. Formica M, Olivieri C, Livigni S et al. Hemodynamic response to coupled plasmafiltration adsorption in human septic shock. *Intensive Care Med* 2003;29:703-8.

The Green Fluorescent Protein (GFP)

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Keywords:
green fluorescent protein (GFP), biomarkers, cellular expression, bioluminescence

Molecular biology is one of the most significant fields of biological science. The main aim of molecular biology is to explore and understand biological functions including all living beings. The knowledge gained could be extended to practical use in cell biology, pharmacy or medicine. Cellular biology is a key to visualise a blueprint of life; development of drugs, the use of biomarkers and the study of gene expression rely on molecular biology methodology.[1-4]

Back in the 20th century, limitations in experiments were common due to the complexity of cellular structures. Real-time monitoring of cellular processes was very difficult in the past with the tools available at the time.[5-9] The scientific community was waiting for a better and well-defined monitoring tool for further cellular exploration.[1]

A revolutionary technique was developed in the early 21st century which made a vast contribution to biological sciences.[2] The discovery of Green Fluorescent Protein (GFP) and its application enabled real-time monitoring of cellular functions in living organisms. This novel tool was a ground-breaking discovery. In the present day, many forms of cellular expression are described and clarified using GFP-based methodology.[1,3,4,10-16]

It had been observed for decades that some living organisms such as jelly fish or other sea creatures, lit up when photographed with a flash light. At first it was described in the 1950s that a green fluorescent substance within a jellyfish was responsible for a light emission effect. In the 1960s, after a dedicated hard working mission to extract more than 10,000 jellyfish to find a fluorescent substance, Osamu Shimomura finally isolated an associated protein from the crystal jelly fish Aequorea Victoria and visually described its bioluminescent effect.[5] Basically, GFP absorbs light between the blue to ultraviolet band and emits a bright green fluorescence after binding with Ca^{2+}. The term *'Green Fluorescent Protein'* or GFP was coined later in the 1970s by Morin and Hastings.[3] During the time from the 1970-1990s, GFP structures were broadly studied to gain a better understanding of its scientific merit.[1,3,6-13] Douglas Prasher realised its potential illumination effect and proposed that GFP could be inserted into cellular structures to observe their function. In the 1990s, he successfully cloned and mapped its genetic sequence. Unfortunately, his funding ran out and he was unable to carry out further experiments to merge the GFP gene into a living organism. The samples and data were sent to several institutions to carry on the study.[6,11]

In 1994, Martin Chalfie successfully incorporated the GFP gene, a native GFP extracted from Aequorea Victoria (also called wild-type GFP), into *E.coli* and *C.elegans* and induced bacteria to exhibit a green fluorescence after exposure to blue light.[12] Previous studies expanded the use of GFP by developing GFP derivatives

and produced various colors with quicker illumination. This development extended GFP applications to diverse laboratory techniques for studying biological science.[2,17,18]

A wild-type GFP (wtGFP) contains 238 amino acids. The GFP crystal structures were fully described in 1996. Its shape looks like a soda can, a typical barrel structure composed of one β-sheet with alpha helixes. It contains a chromophore within the centre of the barrel shape.[8] The chromophore is responsible for the bioluminescence.[5,10,11] Lukyanov described GFP's natural function as a light activated electron donor similar to the process that chlorophyll donates electrons in photosynthesis. The peak excitation spectrum is in a wavelength at 395nm and a smaller maximum at about 470nm. The fluorescent emission spectrum is at 505nm which is approximately a green colour band of visible light spectrum.[19]

GFP is non-toxic and provides low host specificity, which is why it can be used in various species of organisms from single cell organisms to multi-cellular living beings. When merging GFP into the organism's gene, it will mutually express a bioluminescent effect along with its normal cellular function without compromising the general physiology. Cellular activities can be observed in real-time with instant visualisation. The most common use of GFP is to monitor protein activities within a cell; the location, movement and protein cycle, or it is tagged to display gene expressions.[2,11,13,15] The flow of dynamicity can be imaged as a successful temporal study. GFP can be used as a biosensor to monitor intracellular parameters such as pH or metabolic activity. In medicine, GFP is widely used for functional tissue imaging for example when studying neuron activity. GFP is also valuable for studying cancer from its basic molecular properties to developing new treatments.[2]

Given its huge impact on biological sciences, including subsequent benefits from GFP and the dedicated work of high academic merit, the GFP and its applications was awarded the Noble Prize in 2008 for chemistry. Osamu Shimomura, Marty Chalfie and Roger Tsien were acknowledged *"for the discovery and development of the green fluorescent protein, GFP."* Also, Douglas Prasher was highly praised as a co-contributor of GFP development.

References

1. Heim R, Cubitt AB, Tsien RY. Improved green fluorescence. *Nature* 1995;373:663-4.
2. Shaner NC, Patterson GH, Davidson MW. Advances in fluorescent protein technology. *J Cell Sci* 2007;120: 4247-60.
3. Morin JG, Hastings JW. Energy transfer in a bioluminescent system. *J Cell Physiol* 1971;77:313-8.
4. Merzlyak EM, Goedhart J, Shcherbo D, et al. Bright monomeric red fluorescent protein with an extended fluorescence lifetime. *Nat Methods* 2007;4:555-7.
5. Shimomura O, Johnson FH, Saiga Y. Extraction, purification and properties of aequorin, a bioluminescent protein from the luminous hydromedusan, Aequorea. *J Cell Comp Physiol* 1962;59:223-39.
6. Prasher DC, Eckenrode VK, Ward WW, et al. Primary structure of the Aequorea victoria green-fluorescent protein. *Gene* 1992;111:229-33.
7. Cody CW, Prasher DC, Westler WM, et al. Chemical structure of the hexapeptide chromophore of the Aequorea green-fluorescent protein. *Biochemistry* 1993;32:1212-8.
8. Ormö M, Cubitt AB, Kallio K, et al. Crystal structure of the Aequorea victoria green fluorescent protein. *Science* 1996;273:1392-5.
9. Brejc K, Sixma TK, Kitts PA, et al. Structural basis for dual excitation and photoisomerization of the Aequorea victoria green fluorescent protein. *Proc Natl Acad Sci U S A* 1997;94:2306-11.
10. Morise H, Shimomura O, Johnson FH, et al. Intermolecular energy transfer in the bioluminescent system of Aequorea. *Biochemistry* 1974;13:2656-62.
11. Prasher D, McCann RO, Cormier MJ. Cloning and expression of the cDNA coding for aequorin, a bioluminescent calcium-binding protein. *Biochem Biophys Res Commun* 1985;126:1259-68.
12. Chalfie M, Tu Y, Euskirchen G, et al. Green fluorescent protein as a marker for gene expression. *Science* 1994; 263:802-5.
13. Heim R, Prasher DC, Tsien RY. Wavelength mutations and posttranslational autoxidation of green fluorescent protein. *Proc Natl Acad Sci U S A* 1994;91:12501-4.
14. Campbell RE, Tour O, Palmer AE, et al. A monomeric red fluorescent protein. *Proc Natl Acad Sci U S A* 2002;99: 7877-82.
15. Patterson GH, Lippincott-Schwartz J. A photoactivatable GFP for selective photolabeling of proteins and cells. *Science* 2002;297:1873-7.
16. Chudakov DM, Belousov VV, Zaraisky AG, et al. Kindling fluorescent proteins for precise in vivo photolabeling. *Nat Biotechnol* 2003;21:191-4.
17. Mishin AS, Subach FV, Yampolsky IV, et al. The first mutant of the Aequorea victoria green fluorescent protein thatforms a red chromophore. *Biochemistry* 2008;47: 4666-73.
18. Rizzuto R, Brini M, De Giorgi F, et al. Double labelling of subcellular structures with organelle-targeted GFP mutants in vivo. *Curr Biol* 1996;6:183-8.
19. Lukyanov KA, Chudakov DM, Fradkov AF, et al. Discovery and properties of GFP-like proteins from nonbioluminescent anthozoa. *Methods Biochem Anal* 2006;47:121-38.

Chronic Plaque on the Ear

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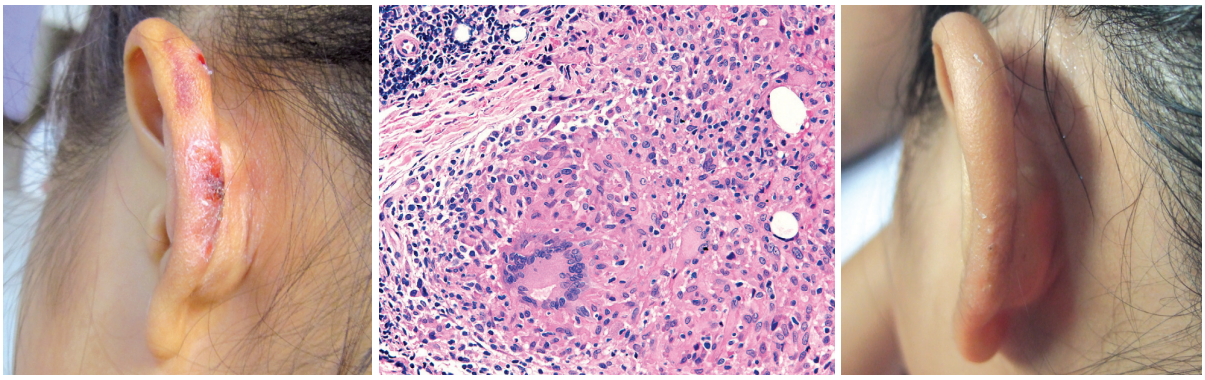

A B C

A 9-year-old Thai girl presented with pink plaques on the left ear for 6 months without any symptoms. She received topical steroids and antibiotic without clinical improvement. Physical examination revealed well demarcated, irregularly bordered, pink infiltrated plaques on the left ear (Figure A). Apple-jelly color was seen when examined by diascopy. No regional lymphadenopathy was detected. Other systemic examinations were unremarkable. The histopathological examination revealed tuberculoid granuloma with Langerhans giant cells in the papillary dermis (Figure B) which was a hallmark of cutaneous tuberculosis. The tissue was negative for acid-fast bacilli, polymerase chain reaction and mycobacterium culture. The purified protein derivative (PPD) Mantoux test was positive with 20mm induration. Chest x-ray was unremarkable. She received anti-tuberculous treatment as standard regimen (2 HRZE/4HR). She was able to tolerate the medications well and showed marked clinical improvement after treatment (Figure C).

Lupus vulgaris is the most common form of cutaneous tuberculosis. Chronic progressive plaque is a typical characteristic. Lupus vulgaris can be acquired as result of direct extension through lymphatic or hematogenous spread or rarely by cutaneous inoculation of *M*. tuberculosis. It most often develops, following cervical lymphadenitis or pulmonary tuberculosis and the most common sites are nose and cheek.[1]

Lupus vulgaris can be diagnosed mainly by clinical and histopathological features. Standard anti-tuberculous medications are very effective and well tolerated.[1-2]

References

1. Kumar B, Muralidhar S. Cutaneous tuberculosis: A twenty-year prospective study. *Int J Tuberc Lung Dis* 1999;3:494-500.
2. Morelli JG. Tuberculosis of the skin. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE, eds. Nelson textbook of Pediatrics. Philadelphia: Elsevier Saunders Inc. 2011, 2307-8.

Special Feature

The Risk of Head Injuries in Motorcycle Traffic Accidents from Not Wearing a Helmet: A Case Study of Motorcycle Riders and Passengers in Bangkok

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Keywords:
motorcycle accident, helmet, head injuries

It is well documented that wearing a helmet can reduce motorcycle crash fatalities. In 2007[1] it was reported that there were 37% fewer fatalities for riders wearing a helmet and 41% fewer motorcycle passenger fatalities.[2] Furthermore, motorcyclists not wearing helmets were three times more likely to suffer brain injury.[3] In Thailand, there are no statistics available on motorcycle accidents and the use of helmets.

This report is a collaboration between the ABAC Poll Research Center and the Bangkok Health Research Center (BHR center) to survey and ask respondents about wearing a helmet (both the rider and passenger) on both personal and taxi service motorcycles.

The survey aimed to determine current level of risk of suffering head injuries from motorcycle accidents when helmets were not worn. The poll was conducted from December 12-20, 2012 and 836 motorcycle passengers in Bangkok were interviewed, aged 15 years and above. The majority of taxi-service motorcycles (57.9%) and more than half of all personal motorcycle riders (52.6%) had been in an accident before.

The most concerning issue is that, when asking the respondents about the helmet wearing habits of both riders and passengers, it was found that 72.1% of riders and 94.3% of passengers did not wear helmets or wore them only occasionally. Only 27.9% of riders and 5.7% of passengers always used helmets when travelling by motorcycle.

When respondents were asked about their experience of witnessing motorcycle riders and passengers being arrested for not wearing a helmet (in the past 3 months), the majority of motorcycle passengers (62.8%) and over half of the taxi-service motorcycle passengers (51.7%) had never seen an arrest take place. Likewise, the riders of both personal motorcycles (45.6%) and taxi-service motorcycles had never seen the police arrest someone because they were not wearing a helmet.

The majority of riders and passengers on personal motorcycles, (54.1% and 74.4%, respectively), had never been arrested by the police when they were not wearing a helmet. Similarly 43.0% of taxi-service motorcycle riders and 76.4% of motorcycle taxi passengers had not been arrested either.

The study discovered that 64.8% of passengers who travel by taxi-service motorcycles and 49.9% of personal motorcycles had children travelling with them. These two groups of motorcycle passengers, taxi-service motorcycle riders and personal motorcycle passengers, never put helmets on children riders or only occasionally put helmets on children riders about 83.5% and 93.3% of the time, respectively.

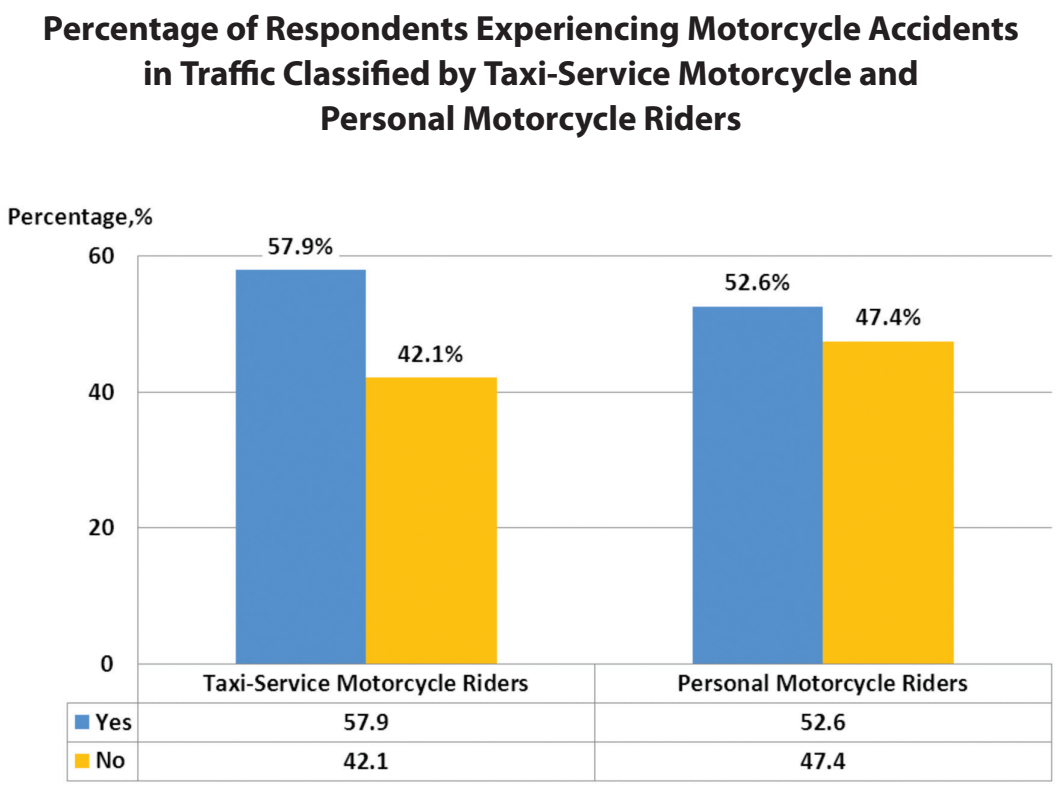

***Figure 1**: Shows the percentage of respondents who have been in a motorcycle traffic accident classified by taxi-service motorcycle and personal motorcycle riders.*

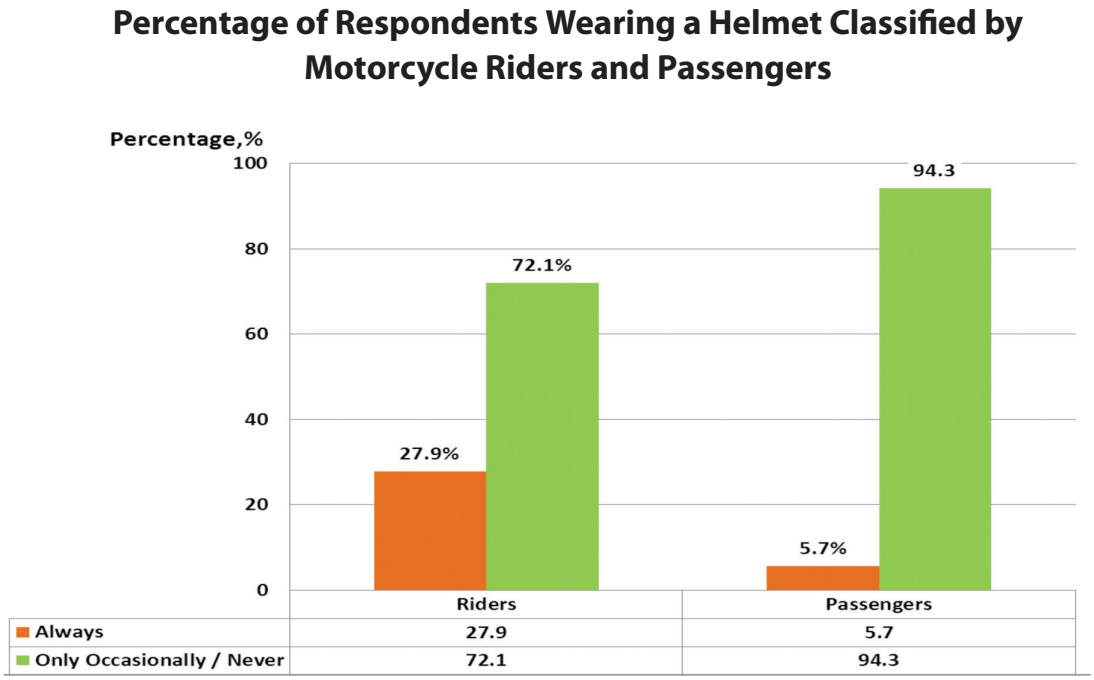

***Figure 2**: Shows the percentage of respondents wearing a helmet classified by motorcycle riders and passengers.*

The reasons for not wearing or using a helmet were because:

- People were travelling a short distance and thought it would not be harmful (69.3%).
- There were no police on the particular street or road (39.3%).
- They were in a hurry or there was no time to put on a helmet (25.7%).
- Putting on a helmet is uncomfortable when riding and impairs their vision (21.8%).

Other reasons given by respondents include: helmets have a bad smell and are dirty; helmets mess up your hair; helmets might be stolen when hung up on the motorcycle; no storage room; the respondent does not have a helmet; and the police do not enforce the law.

The majority of passengers of both taxi-service and personal motorcycles who did not buckle the chin strap (or only buckled it occasionally) accounted for 70.9% and 54.5% of passengers, respectively. Likewise, a great number of riders of taxi-service and personal motorcycles did not buckle their chin strap (or only put it on occasionally) which accounted for 40.1% and 40.8% of riders, accordingly.

The findings about the relative risk statistical analysis by using Odds Ratio for the risk of head injuries from motorcycle accidents, found that the group of riders or passengers who did not buckle their chin strap were six times greater at risk of head injuries than the group that used their chin strap.

To reduce the number of motorcycle rider and passenger accidents, we recommend the following measures:

First, the police should strictly and constantly warn or impose a fine to motorcycle riders and passengers who do not wear a helmet.

Second, the government should formulate a policy to promote the use of helmets, "The Public Supports Helmets" (Muak Kan Nog Eur Arthorn). It could provide a piece of head covering cloth for one time use only or a cloth that is reusable after washing. This would encourage the habit of wearing a helmet and encourage low-income people to use a helmet when travelling by motorcycle.

Third, the government should consider a policy to make personal cars more affordable because the decrease in the use of motorcycles would reduce the risk of being injured in a motorcycle accident.

Fourth, the helmet manufacturing sector should be supported by the government to produce more helmets for children. Adults must pay more attention to children in terms of safety.

Fifth, personal cars and motorcycle riders and passengers should not assume that others will see their vehicles while riding or driving on the road. Drivers and riders should always turn on their headlights when they use their car or motorcycle in order to reduce accidents that may occur to themselves and others.

Sixth, both motorcycle and car passengers should be more conscious of observing the rule of the road and should respect other road users and pedestrians while riding or driving.

Lastly, drivers and riders must never consume any kind of alcohol while on the road because drink-driving can be a contributory cause of accidents that result in injury and death.

General data of the respondents

Of the respondents of this study, 68.3% were male and 31.7% were female. When classifying the sample by age, 32.9% were 20-29 years old, 29.9% were 30-39 years old, 22.9% were 40-49 years old, 8.7% were 50-59 years old, 4.4% were 15-19 years old, and 1.2% were 60 years old or above. Regarding personal monthly income, 48.9% earned 5,001-10,000 Baht, 31.1% earned 10,001-15,000 Baht, 9.5% earned 15,001-20,000 Baht, 5.9% earned not more than 5,000 Baht, 3.8% earned 25,001 Baht or above and only 0.8% earned 20,001-25,000 Baht. When classified by education completed, 33.2% graduated high school, 31.7% graduated middle secondary school or lower, and 15.8% graduated with a bachelor's degree. When classifying the sample by their current occupation, 40.2% were taxi-service motorcycle riders, 16.3% were employees of a private company, 11.8% were students/university students, 10.3% work for wages, and 9.7% were retailers/peddlers.

This research illustrates that motorcycle passengers who wear helmets correctly could reduce the risk of head injuries. It is frightening to discover that people are not aware of this issue because they think that accidents could never happen to them. Moreover, respondents believed that travelling or riding on a motorcycle for a short distance is not dangerous or would not be harmful. In fact, accidents can happen at any moment. Children are a high-risk group and are of the greatest concern when it comes to motorcycle accidents. Many children never wear a helmet because they are not provided with a helmet of an appropriate size. Furthermore, children are likely to sustain more severe and serious injuries, when compared to adults. For this reason, it is necessary that our hospitals should have a team of specialized doctors for such accidents. The findings supported that people are still not aware of the dangers of head injuries. Riding a motorcycle without wearing a helmet on a daily basis is high risk behavior, yet respondents were not aware of this.

Conclusion

The risk of sustaining a head injury if involved in a motorcycle traffic accident while not wearing a helmet is statistically high. Wearing a helmet can save lives.

A public awareness campaign is needed in Thailand to protect children, who are at greater risk than adults of sustaining life-threatening head injuries. Children have the right to wear properly fitted helmets, yet these are too seldom provided. The traffic police have a duty to enforce the law of the road and to take appropriate measures when they intercept riders and passengers who are not wearing a helmet.

References

1. Preventing an Auto Accident: U.S. Department of Transportation's (DOT), 2007 (Accessed January 2013 at http://www.dot.gov/).
2. Motorcycle Accident Statistics, 2009 (Accessed January 2013 at http://www.edgarsnyder.com/motorcycle-accidents/motorcycle-accident-statistics.html)
3. Motorcycle Helmet Use Laws (accessed January 2013 at http://www.nhtsa.gov/staticfiles/DOT/NHTSA/Communication%20&%20Consumer%20Information/Articles/Associated%20Files/810887.pdf)

How to perform a study - some practical tips based on our experience

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Keywords:
AO Foundation, AOCID, study design, clinical research, PICOT

This article does not specifically deal with the situation for clinical research in Thailand. Instead, just as we conduct multicenter studies to ensure that the results are generalizable, the following points are some practical tips derived from the AO Foundation's long experience in the conduct of multicenter clinical trials around the world and as such, have general applicability. If you require more targeted information, a simple Internet search will reveal many useful addresses with country-specific information (such as the Thai FDA: www.fda.moph.go.th).

While many researchers are interested in publishing studies, the publication that results from a study is just the tip of the iceberg. It is the visible end-product of many phases which have contributed to a study's success. The planning and study design stage is absolutely critical which is why it is the only section highlighted and presented as a step-by-step process here.

Planning and Study Design

1. Do preliminary research

Find out more about the topic that interests you (e.g. search on PubMed, the Cochrane Library, hold discussions with your colleagues, consult professional forums etc.). Ensure your idea has not already been tried.

2. Consider the purpose of your study

What is the rationale for conducting your study? Why was the new implant developed and what's its added value? What makes the new technique more beneficial for your patient compared to the standard approach? Can you find a way to compare A to show it is better than B? If you think of your idea as being simply *"interesting to look at"* then you should seriously reconsider trying to conduct a trial on it. Another possible question to ponder is what possible results from the trial are likely to change clinical practice / improve patients' lives?

3. Plan your clinical question carefully

Your clinical question will determine how good your study is, so define it very precisely. It is the bedrock upon which your study's success will be built. The PICOT acronym (Patient, Intervention, Control, Outcomes, and Timing) is a very helpful scaffold upon which to start building your research. For example, if you have a diagnostic question you might consider the following PICOT factors:

Patient	-	Which patient group? Consider patient characteristics that may affect outcomes.
Intervention	-	Define the diagnostic procedure of interest (e.g. a new technology).
Control	-	Is there a gold standard? If necessary, you have to define the *'control'* group to which the intervention group will be compared.
Outcomes	-	Be specific and aim for the most important outcomes (e.g. nonunion, major complications, death, etc.).
Timing	-	How long will the study last? How many follow-up visits and when?

4. Find an acceptable study design

Decide on this very carefully once all the necessary information is to hand. Let your clinical question and resources guide your choice of study design.

5. Sample size and feasibility

A sample size of 500 patients in an indication where you see 20 patients yearly is not going to work. Be aware of Lasagna's Law which states that the number of patients available to join a trial drops by approximately 90% the day a trial begins, only to reappear as soon as the study is over. Remember that some fracture types are rare. Be prepared for such studies to only recruit small amounts of patients and for their recruitment to be painfully slow.

Two to five years follow-up is a very difficult task. Once healed, injured patients often do not return to their doctor so in most cases you will have to chase them up.

6. Implement a study design freeze at an early stage

Don't have the design questioned at every meeting. Good Clinical Practice dictates that you cannot change a study design once the first patient has been recruited.

7. Clearly define everything in the study protocol

This is an essential document which allows you to ensure uniformity for all the investigators and sites involved in the study.

8. Don't make your inclusion criteria too restrictive

Obviously you need to exclude certain types of patients but be careful that you do not shut out those who may still be acceptable for the study's purposes. Broad exclusion categories such as *'active systemic infection'* should be more exactly defined to help widen the net of eligible study participants.

Some General Points to Remember

Have clear communication with stakeholders throughout the study process

At AO Clinical Investigation and Documentation (AOCID), in addition to the regular updates through meetings and personal contact, we send out a newsletter for each study approximately 3 times a year to ensure that all the stakeholders are aware of how things are progressing. Provide information on the number of patients included and the follow-up rates for each site.

Define roles, and trust in the other's expertise

The Principal Clinical Investigator (PCI) is the expert in the operating room but the Clinical (or Contract) Research Organization (CRO) is the expert in the planning and conduct of the study. A mutual respect for one another's competencies helps the process along.

Regulatory problems with the medical device approval process

The approval process can vary from country to country and lead to bottlenecks in the study. Do not assume your planned national timeline will hold true for international studies.

Do not forget to get informed consent

There are intrinsic elements to trauma studies which make obtaining informed consent difficult. You may be faced with unconscious patients, or find it difficult to explain the study as the patients are in pain. Similarly, it may be hard to obtain consent as patients could be whisked into the operating room within a short time after admission. Prepare for this and make allowances in the study protocol, e.g., by allowing proxy consent if appropriate.

Comorbidities

Consider your patient cohort carefully as comorbidities can play a negative role in follow-up rates. For example, mortality rates of approximately 30% in elderly patients with hip fractures will naturally lead to low follow-up rates.

Rehabilitation protocol

Be aware of the effect that this can have on outcomes. Ensure that the same standardized procedures are in place in all participating centers.

A study project manager liaising with a study coordinator in the clinic

Initiation visits are very important to a study's success

Outcome

Respect cultural differences if you perform a study in different countries

Use only patient-assessed scores that have been cross-culturally adapted and validated. Do not translate scores yourself for clinical use.

Avoid selection bias

Consider the population you would like to make inferences about and whether your sample size is truly representative of it. Not all conclusions may be transferable to other population groups. If there is a possible selection bias it is essential that this is also reported (e.g. conducting a study in the military among young healthy males).

Do not be shy about reporting complications

Knowledge of complications is very important to the improvement of patient care. So try to shake off the feeling that comprehensive and complete reporting of complications will handicap your chances of publication, reflect badly on your surgical skills etc. In the end, it will assist many more patients and help to avoid future adverse events.

Regulatory

Find out and follow the legal framework in place

Remember that there is no clinical study without ethics committee approval and the patient's informed consent.

Ensure your clinical study has been entered into a registry

It's a prerequisite for publication in many journals these days. The best-known is probably www.clinicaltrials.gov but there are other registries such as www.anzctr.org.au which are also acceptable.

Get agreement from all parties before proceeding with ethics committee submission

It should be borne in mind that there is a cost to submitting and resubmitting to ethics committees. For example, the cost of submitting to a German ethics committee is generally around €1,500. You may have to apply to several such committees and their processes can vary – even within the same country. This is an element which is often underestimated in planning international multicenter trials.

At the Clinic

Make sure your study center personnel are adequately trained

The initiation of a study is crucial. Ensure that all material is available and that enough time is given to train all the relevant personnel. Get them to *"buy into"* the study from the very start so that they are actively screening patients for recruitment in their daily clinical practice.

Early monitoring may save you future headaches

A first monitoring visit / check after only a few patients have been recruited can help to identify and correct

systematic mistakes at an early stage, thereby saving a lot of time later on.

Try to anticipate issues and to head them off

For example, be aware that less experienced staff members at your center will probably require closer support and more training and supervision than others.

Keep your database constantly clean

This means ensuring that there is ongoing monitoring, ongoing data checks, and so on.

Data management

Have adequate procedures in place to ensure data quality. Do not wait until tomorrow to reply to a request if you can do so today.

Don't be afraid to delegate

You're most likely working full-time and are in the operating room most of the time. If your center can afford it, consider hiring a study nurse to manage your study documentation and data for you. AOCID has had very good experience with this arrangement.

Final Report

Define clear timelines

Remember that with so many actors involved the review and approval process can take a long time – which can be frustrating when you are so near your goal.

Finally, share your work with the world!

Do not forget to celebrate your achievements. Submit your manuscript to a journal, be prepared that rejection and resubmission happen to almost everyone, go to conferences and share your new knowledge with the scientific community.

For more information on conducting clinical studies and information about AOCID's services, please visit www.aofoundation.org/cid or write to us: aocid@aofoundation.org.

Book Review

Skeletal Development of the Hand & Wrist

A radiographic Atlas & Digital Bone Age Companion

Cree M. Gaskin, S. Lowel Kahn, J. Christopher Bertozzi, and Paul M. Bunch : Oxford University Press, Inc.
Publisher: Oxford University Press, Inc.

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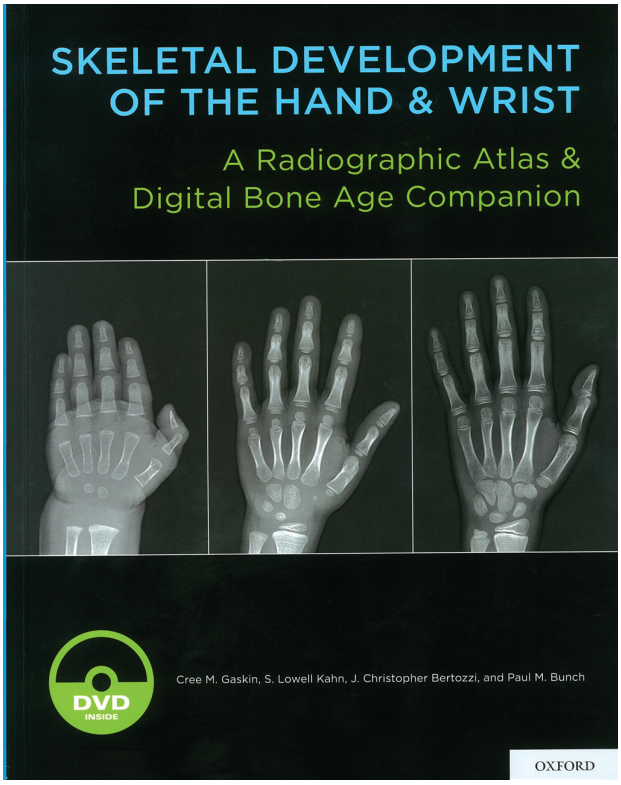

The Radiographic Atlas of Skeletal Development of the Hand and Wrist by Drs. Greulich and Pyles has long been the reference text for medical practitioners to determine bone age maturity. It has seen widespread use for more than fifty years. The atlas includes a detailed description of the subtle changes of a human hand as it matures. Each image is accompanied by reference charts of the appropriate standard variation values. Comparing the subtle changes of the hand and wrist against reference standards can be very time consuming.

The objective of this modified printed atlas is to modernize the Greulich and Pyle method for pediatric bone age interpretation for contemporary and timely medical practice. It contains updated high-quality skeletal radiographic images and reference standards of the left hand up to the age of 18 for females and 19 for males from many thousands of candidate images from PACS (Picture Archiving and Communication System), University of Virginia. It also contains annotated images, opposite the bare images, that highlight important and subtle features. This layout is designed to make it easy to access data which makes interpretation faster, more accurate and educational.

This printed atlas is bundled with the Digital Bone Age Companion (DBAC), which is also available for individual or institutional purchase. The DBAC is a freestanding™ application, which means the user can easily zoom in on subtle radiographic features, set the image level and width to their preference, and compare two or three reference standards side by side for difficult cases.

We highly recommended this modified bone age atlas: it is easy to use, practical and user-friendly.