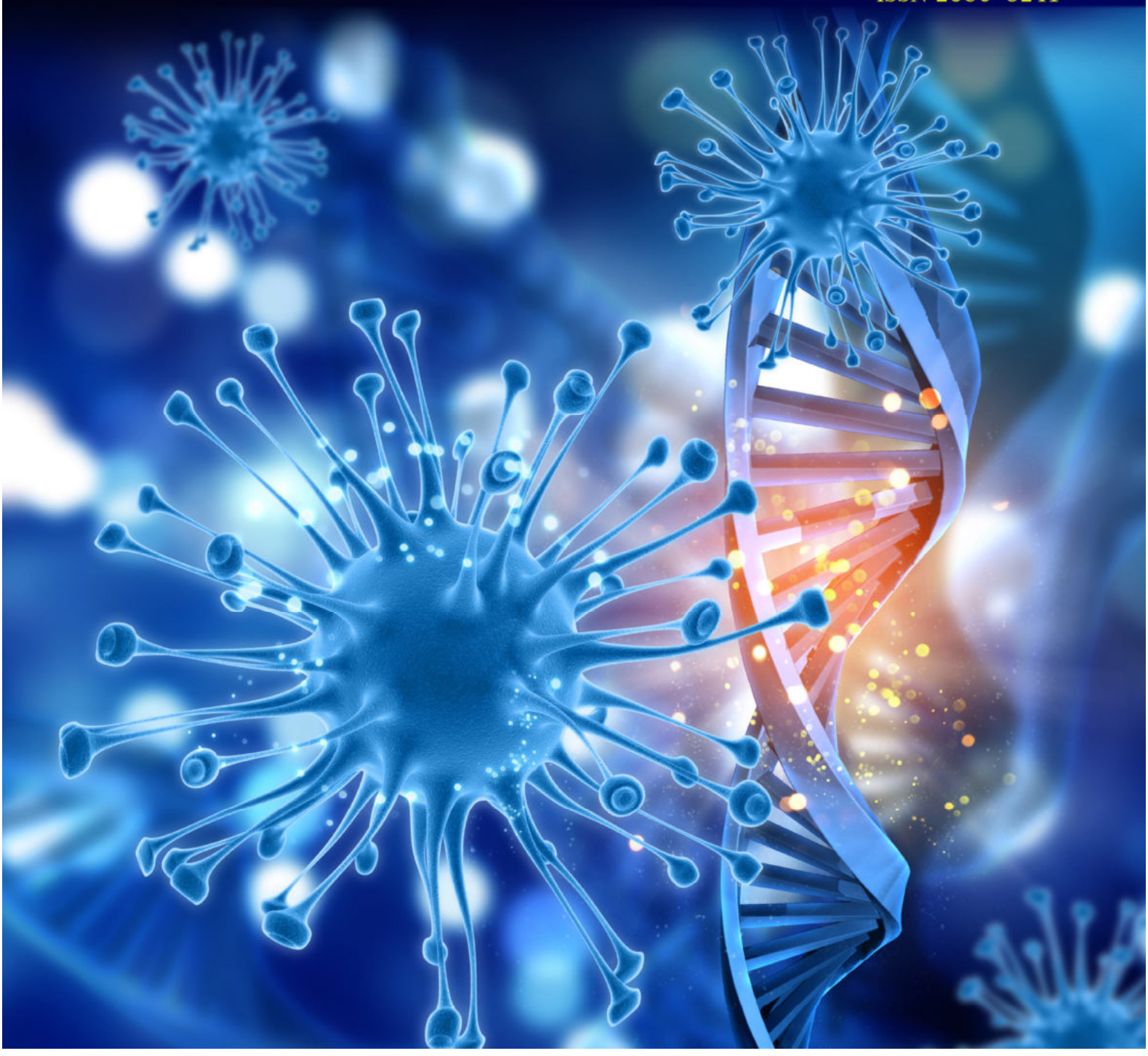
Journal of Southeast Asian Medical Research

www.jseamed.org
Vol.2 No.1 January-June 2018
ISSN 2586-8241



JOURNAL OF
SOUTHEAST ASIAN
MEDICAL RESEARCH

Introduction

The Journal of Southeast Asian Medical Research is a peer-reviewed journal with printing every 6 months. The main goal of this collaboration project is to distribute new knowledge in medical sciences to medical communities and scientists, as well as encouraging scientific collaborations within Southeast Asia and also other nations around the world. The journal publishes original research in the medical sciences: clinical and basic. We welcome original articles from across the world. The editorial board comprise of international experts in various fields of medicine, ranging from internal medicine to a variety of surgeries. The full text of the journal is available online at http://www.jseamed.org

It is our aim to publish the most up-to-date and useful research information in medical sciences. In Southeast Asia, there are some unique problems in health care and diseases, such as tropical diseases, and it is crucial that health professionals can access, share and exchange knowledge promptly. In this region, there is still a gap of knowledge in health sciences that needs to be closed by scientific research, which we are hoping to close after this collaboration project. We hope that the journal will fulfill the objectives and will provide benefit to all, both medical practitioners and researchers alike.

Editorial board

JOURNAL OF SOUTHEAST ASIAN MEDICAL RESEARCH

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A.Original Article

PREVALENCE OF FLUOROQUINOLONE - RESISTANT ENTEROBACTERIACEAE IN THE NORMAL RECTAL FLORA OF PATIENTS UNDERGOING TRANSRECTAL PROSTATE BIOPSY IN PHRAMONGKUTKLAO HOSPITAL, THAILAND

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Abstract

Background: Despite routine use of antimicrobial prophylaxis, the incidence of infections after transrectal ultrasound-guided prostate biopsy has increased over the last 2 decades. Notably, a rising incidence of postbiopsy infections from fluoroquinolone-resistant Enterobacteriaceae had been reported over the same period. Many authors have studied the rectal flora reservoir to select the most appropriate prophylaxis antibiotics.

Objectives: The study aimed to determine the prevalence of fluoroquinolone-resistant and extended spectrum β-lactamase producing isolates at Phramongkutklao Hospital, Thailand and to identify the risk factors predicting the carriage of these organisms.

Methods: Men undergoing transrectal ultrasound-guided prostate biopsy were prospectively enrolled between February and October 2015. Rectal swab culture was obtained before antimicrobial prophylaxis and prostate biopsy. Univariate and multivariate analyses were performed to identify the independent risk factors associated with antimicrobial-resistant flora.

Results: In total, 99 patients underwent biopsy, of whom 38 (38.4%) had antimicrobial-resistant rectal flora, with 26 (26.3%) presenting fluoroquinolone-resistant rectal flora and 12 (12.1%) having both fluoroquinolone-resistant rectal flora and extended spectrum β-lactamase. The incidence of postbiopsy infections was 6.1%. The use of antibiotics in the past 6 months was found in 23.7% of the resistant group vs.6.6% of the sensitive group (odds ratio = 4.86, p = 0.030), with the previous biopsy history being 31.6 and14.8% (odds ratio = 3.17, p = 0.036), respectively. Postbiopsy infections occurred in13.2 and1% (odds ratio = 10.69, p = 0.045) of patients in the resistant and sensitive groups, respectively.

Conclusion: The prevalence of fluoroquinolone-resistant rectal flora increased among patients undergoing transrectal prostate biopsy at Phramongkutklao Hospital, Thailand. A history of antibiotics in the past 6 months, previous biopsy, and postbiopsy infections were associated with antimicrobial resistance. Culture-directed prophylaxis antibiotics may reduce postbiopsy infections after transrectal prostate biopsy

Keywords : Biopsy, Fluoroquinolone, Prostate, Risk factors, Thailand

J Southeast Asian Med Res 2018; 2: 1-6.
http://www.jseamed.org

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Introduction

Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is the gold standard procedure for diagnosing prostate cancer, which is the most commonly diagnosed cancer and the second leading cause of cancer deaths among American men. In 2014, it has been estimated that 233,000 men would be diagnosed with prostate cancer and 29,480 would die of this disease.[1] Approximately 800,000 biopsies are performed in the US alone annually. [2] Although generally considered a safe procedure, complications can sometimes occur, including urinary tract infection, prostatitis, bacteremia, sepsis, hematuria, rectal bleeding, and hematospermia.[3] In a larger series, the postbiopsy infection (PBI) rate ranged from 0.1 to 7%. [4–6] Clear evidence showed that prophylactic antimicrobials reduced the rates of PBIs after TRUS-Bx.[6] Currently, the antimicrobial prophylaxis regimen, as recommended by the American Urological Association, is a single dose of fluoroquinolone(FQ) before TRUS-Bx, with cephalosporin or trimethoprim-sulphamethoxazole or aminoglycosides as alternatives.[7]

Despite routine use of antimicrobial prophylaxis, the incidence of PBI after TRUS-Bx has increased over the last two decades.[8–10] Notably, a rising incidence of PBI from FQ-resistant *Escherichia coli* has been reported over the same period, leading many to conclude that the recent rise in infectious complications is related to FQ-resistance.[10–12] Most PBIs arise from the direct inoculation of bacteria from the rectal mucosa into the urinary tract and prostatic vessels. Many authors have studied the rectal flora reservoir of patients undergoing TRUS-Bx to select the most appropriate prophylaxis antibiotics to reduce PBI.[13–18]

Based on this practice, the rates of rectal carriage have ranged from 10.6 to 22% for FQ-resistant flora in the US and Europe. [17, 19–21] In Asia, the prevalence of these organisms has ranged from 26.7 to 40.4%. [22, 23] Studies of the risk factors associated with FQ-resistant bacteria have shown a relation to diabetes, history of antibiotic use in the last three months, hospitalization, previous prostate biopsy, indwelling of urinary catheter, and use of steroids.[17,19] Our study aimed to determine the prevalence of FQ resistant rectal flora and extended spectrum β-lactamase (ESBL)-producing isolates at Phramongkutklao Hospital, Thailand, and to identify the risk factors predicting the carriage of these organisms.

Methods

We prospectively enrolled all male patients undergoing TRUS-Bx between February and October 2015 at Phramongkutklao Hospital, Thailand. The protocol for the research project was approved by the Institutional Review Board of the Royal Thai Army Medical Department. The exclusion criteria included active urinary tract or intestinal infection at the time of biopsy and coagulopathy.

Informed consent was obtained from eligible patients. Rectal swab culture was obtained before performing antimicrobial prophylaxis and prostate biopsy. For FQ-resistant testing, swabs were directly cultured on both MacConkey agar, with 1mg/L ciprofloxacin, and blood agar plates and incubated at 37°C for 18 h. Antimicrobial susceptibility testing was performed using the agar disk diffusion technique. All patients received a standard empirical prophylactic of FQ. Basic demographic and clinical data were collected from patients undergoing TRUS-Bx during the study period using questionnaires. The history of antibiotic use (less than six months), hospitalization, urethra catheter and previous prostate biopsy within six months was reviewed from medical records. The patients were followed for at least 30 days to check for infectious complications. Infections were defined as lower urinary tract symptoms with fever and positive urine culture (>104 cfu/mL).

Descriptive statistics were used for the patients' demographic and background data. Univariate analyses were performed for variables that were possible predictors of PBIs using Pearson's chi-square test and Student's t-test. Variables were considered eligible for inclusion in a multivariate logistic regression model when they had a p value of <0.05.

Results

In total, 99 patients undergoing TRUS-Bx at Phramongkutklao Hospital between February and October 2015 were enrolled in the present study. The demographic data of the patients are shown in **Table 1**. Rectal swab culture showed that 94.9% (n= 94) involved *Escherichia coli*, followed by *Klebsiella spp*. (4.1%, n= 4) and *Enterococcus faecalis* (1%, n= 1). In total, 38.4% (n= 38) of patients carried antimicrobial-resistant rectal flora, of whom 26.3% (n= 26) had FQ-resistant rectal flora and 12.1% (n= 12) had both FQ-resistant rectal flora and ESBL. The incidence of PBI was 6.1% (n= 6). The characteristics of the patients who developed PBI are shown in **Table 2.**

Table 1 Characteristics of transrectal ultrasound-guided biopsy of prostate patients

Parameters	Number	Percent
Age		
Mean ± SD		67.25 ± 8.07
Range (Min-Max)		49–84
PSA		
Mean ± SD		24.98 ± 62.62
Median		9.81
Range (Min-Max)		2.06–500
Diabetes		
Yes	17	17.2
History of ATB use (<6 months)		
Fluoroquinolone	10	10.1
Cephalosporin	3	3.0
Past admission		
Yes	4	4.0
History of urethra catheter		
Yes	5	5.1
The frequency of TRUS-Bx		
1	78	78.8
2	18	18.2
3	3	3.0
The number of biopsy cores		
12	89	89.9
>12	10	10.1

SD, standard deviation; PSA, prostate-specific antigen; ATB, antibiotic; TRUS-Bx, transrectal ultrasound-guided biopsy

Table 2 Characteristics of patients with postbiopsy infection

Characteristics	Postbiopsy patient					
	1	**2**	**3**	**4**	**5**	**6**
Age, y	55	68	67	56	68	73
PSA, ng/ml	6.6	15	6.79	53	11.5	8.07
Rectal swab culture	*E. coli*	*E. coli*	*E. coli*	*E. coli*	*E. coli*	*E. coli*
FQ-resistant	+	+	+	+	-	+
ESBL	-	-	+	+	-	-
Urine culture	*Klebsilla*	*E. coli*	*E. coli ESBL*	*E. coli ESBL*	*E. faecalis*	*E. coli*
Blood culture	-	-	-	-	-	-

PSA, prostate-specific antigen; FQ, fluoroquinolone; ESBL, extend-spectrum β-lactamase producing

FQ-resistance of a patient was not significantly associated with age, mean PSA, DM, past admission, urethra catheter and more than 12 core biopsies. FQ resistance flora significantly differed in recent antibiotic use, previous prostate biopsy and PBIs between the two groups revealed by the univariate analyses. The use of antibiotics in the past six months was found in23.7% of the resistant group vs.6.6% of the sensitive group [odds ratio (OR) = 4.86, $p = 0.030$], with a previous biopsy history being 31.6 and14.8% (OR= 3.17, $p = 0.036$), respectively. PBIs occurred in13.2 and1% (OR= 10.69, $p= 0.045$) of patients in the resistant and sensitive groups, respectively, using multivariate logistic regression analysis. **(Tables 3 and 4).**

Table 3 Univariate comparision of FQ resistance by clinical finding

	FQ-sensitive (%)	**FQ-resistant (%)**	***p*-value**
Mean age	66.85	67.89	0.535
Mean PSA	23.31	27.65	0.739
Diabetes	8 (13.1)	9 (23.7)	0.650
ATB use in 6 months	4 (6.6)	9 (23.7)	0.023*
Past admission	1 (1.6)	3 (7.9)	0.187
Urethra catheter	3 (4.9)	2 (5.3)	0.311
Previous prostate biopsy	9 (14.8)	12 (31.6)	0.034*
>12 cores biopsy	7 (11.5)	3 (7.9)	0.667
Postbiopsy infection	1 (1.6)	5 (13.2)	0.019*

* $p < 0.05$, PSA, prostate-specific antigen; ATB, antibiotics; FQ, fluoroquinolone

Table 4 Multivariate analysis of FQ resistance by clinical finding

	OR (95% CI)	***p*-value**
Diabetes	1.334 (0.385–4.624)	0.649
ATB use in 6 months	4.860 (1.170–20.192)	0.030*
Past admission	5.204 (0.399–67.881)	0.208
Urethra catheter	0.285 (0.023–3.571)	0.330
Previous prostate biopsy	3.173 (1.078–9.334)	0.036*
>12 cores biopsy	0.720 (0.157–3.291)	0.720
Postbiopsy infection	10.688 (1.059–107.83)	0.045*

* $p < 0.05$, FQ, fluoroquinolone; ATB, antibiotic; OR, odd ratios;

Discussion

Currently, the antimicrobial prophylaxis regimen before TRUS-Bx is a single dose of FQ.[7] In the present study, the incidence of PBI was 6.1%; in related studies, the incidence of PBI ranged from 0.1 to 7%.[4–6] The incidence of PBI has been increasing in recent years, along with the rising prevalence of FQ-resistant flora. The prevalence of FQ-resistant rectal flora was 38.4% in the present study. Based on these findings, we suggest that the use of FQ for prophylaxis before TRUS-Bx may not be effective at Phramongkutklao Hospital, Thailand. Alternative ways included adapting the prophylaxis antibiotics to local resistant rates or identifying patients carrying FQ-resistant organisms before the procedure using culturing rectal swabs.

In the present study, we showed that a history of previous TRUS-Bx and recent use of antibiotics were risk factors of FQ-resistant rectal flora. However, these risk factors may overlap among some patients because the patients undergoing biopsy had received the prophylaxis antibiotics too.

We conclude that when patients have an appointment for TRUS-Bx, the most effective method is to perform a rectal swab culture one to two weeks before the biopsy and select a prophylaxis antibiotic using the culture result to decrease the PBI rate. When the hospital is unable to perform a rectal swab culture, the history of the previous biopsy or antibiotic (FQ or cephalosporin) used in the past six months can be used to select the most appropriate antibiotic. The alternatives for prophylaxis antibiotics are aminoglycoside, carbapenem and fosfomycin.

In the present study, we found the following limitations. The first was the limited number of patients in the study; the study had a small sample size. The second was the patient data from hospital records may have underestimated the history of antibiotic use. The prevalence of fluoroquinolone-resistant rectal flora increased among patients undergoing TRUS-Bx at Phramongkutklao Hospital, Thailand. A history of antibiotics in the past six months, previous biopsy and PBIs were associated with antimicrobial resistance. Culture-directed prophylaxis antibiotics may reduce the infectious complications after TRUS-Bx.

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INCIDENCE AND RISK FACTORS OF METABOLIC SYNDROME AND 9-YEAR FOLLOW-UP IN NA YAO COMMUNITY, SANAM CHAI KHET DISTRICT, CHACHEONGSAO, THAILAND

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Abstract

Background: Metabolic syndrome is an important risk factor for cardiovascular diseases and type 2 diabetes; it comprises a cluster of metabolic abnormalities including central obesity, insulin resistance, hypertension, dyslipidemia and endothelial dysfunction. In Thailand, the prevalence of metabolic syndrome ranges from 13.2 to 33.3% depending on differences in population and timing of each study. Therefore, due to the limitation of data related to incidence and risk factors of metabolic syndrome in Thailand, especially in rural areas, this study was established.

Objectives: To estimate the incidence and risk factors of metabolic syndrome in Na Yao Community, Tha Kradan Subdistrict a rural community, central Thailand.

Methods: From a baseline survey conducted from 2008-2009, a total of 970 metabolic syndrome-free participants were enrolled in Na Yao Community, a rural area of Thailand. However, only 511 (52.6%) cases were re-examined in December 2016 because the majority had died or migrated. The definition of metabolic syndrome was based on the NCEP-ATP III criteria to evaluate cumulative incidence and incidence density. The relative risk of possible risk factors was analyzed using Poisson regression.

Results: During the 9-year follow-up, the cumulative incidence was 14%. The incidence density was 3.47/100 person-years. In multivariate analysis using Poisson regression, being female, having serum cholesterol greater than 200 mg/dL and increased BMI every 1 kg/m^2 were considered risk factors of metabolic syndrome.

Conclusion: The study determined the incidence density of metabolic syndrome in Na Yao Community as 3.47/100 person-years. The significant risk factors of metabolic syndrome were being female, having high serum cholesterol and increased BMI. Therefore, diet control and exercise are recommended to decrease the chance of developing modifiable risk factors (serum cholesterol and BMI). In addition, strategies to detect, treat and prevent metabolic syndrome must be established.

Keywords : Metabolic syndrome, Incidence, Rural Community, Central Thailand

J Southeast Asian Med Res 2018; 2: 7-15.
http://www.jseamed.org

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Introduction

Metabolic syndrome is an important risk factor for cardiovascular diseases (CVD) and type 2 diabetes (T2DM); it comprises a cluster of metabolic abnormalities including central obesity, insulin resistance, hypertension, dyslipidemia and endothelial dysfunction.[1] People with metabolic syndrome are more likely to develop CVD and T2DM approximately two and five times than those who are not. The etiology of the syndrome originated from obesity, which is the primary cause leading to insulin resistance and other impending consequences.

Definition and diagnostic criteria of metabolic syndrome have been described by several organizations such as the World Health Organization (WHO), National Cholesterol Education Program-adult Treatment Panel 2 (NCEP-ATP III), the American Association of Clinical Endocrinologist (AACE), the International Diabetes Federation (IDF) and the American Heart Association (AHA) in coordination with the National Heart Lung and Blood Institute (NHLBI). The basic concepts of these criteria are the same but differ somewhat in details.

In the worldwide population, the IDF reported the prevalence of metabolic syndrome in 2006 ranged from 20 to 25%.[2] This strong evidence implies an important, chronic health problem in both urban and rural areas will lead to other health complications and economic problems. In Thailand, the prevalence of metabolic syndrome ranges from 13.2 to 33.3% depending on the differences in population and timing of each study.[3-7]

Therefore, due to the limitation of data related to incidence and risk factors of metabolic syndrome in Thailand, especially in rural areas, this study aimed to estimate the incidence and risk factors of metabolic syndrome in a rural community, central Thailand.

Methods

Study population

People were selected by a whole population living in Village 11, 15, 16, 18 and 19 of Na Yao Community. These people had their waist circumference and blood pressure examined and blood tested for fasting plasma glucose, triglyceride and high-density lipoprotein-cholesterol. A baseline survey was performed at Na Yao, a rural area of Thailand, from 2007-2008. At the time of baseline survey, a total of 1,362 people were recruited. Then 392 subjects were excluded for having a diagnosis of metabolic syndrome in 2008 and 2009. Therefore, our target population consisted of 970 subjects who were re-examined in December 2016. In addition, 246 did not participate in the study in 2016 because 155 died, 68 permanently migrated and 23 went missing. As a result, the actual target population totaled 724 subjects. However, only 516 were reexamined. Therefore, the follow-up rate was 53.2%. Subjects who were lost to follow-up were considered as censored cases and were not included in the statistical analysis.

Data was collected on the incidence and risk factors of metabolic syndrome using a set of questionnaires, physical examinations and biochemical measurements. The questionnaires were related to demographic data (age, sex, educational status, income, occupation, and underlying diseases), alcohol consumption (yes, no), smoking status (smoker, nonsmoker), physical activity (moderate, vigorous), eating behavior, and sedentary lifestyle. Physical examinations included height, body weight, waist circumference and blood pressure. Body weight was examined using an analog scale while all subjects dressed in light clothing and were barefoot. Waist circumference was measured in centimeters at the reference point of the anterior superior iliac spine (ASIS). Blood pressure was obtained twice by well-trained attendants in a seated position using a standard sphygmomanometer at 5-minute intervals. The first and fifth Korotkoff sounds were used to estimate systolic and diastolic blood pressure. However, when the blood pressure after the second attempt was more than 140/90 mmHg, the participants were required to rest 15 minutes before a third attempt was conducted. Blood samples were collected (7 mL) by well-trained medics from an antecubital vein after 8-hour fasting. Each tube was divided in 4 and 3 mL to determine the level of fasting blood sugar, total cholesterol, triglyceride and high-density lipoprotein cholesterol (HDL-cholesterol) using an automatic analyzer (Vitros950, Integra400 and Hitachi917). The definition of diagnosis of metabolic syndrome was based on the Third Report of the NCEP-ATP III. However, the definitions of central obesity by the IDF criteria were used due to South Asian ethnicity cut-points. Metabolic syndrome was diagnosed when participants met the criteria at least three out of five

characteristics: triglyceride ≥150 mg/dL, HDL- cholesterol <40 mg/dL in men and <50 mg/dL in women, blood pressure ≥130/85 mmHg or antihypertensive drug medications, fasting blood glucose ≥110 mg/dL or antidiabetic drug medications and waist circumference ≥90 cm in men and ≥80 cm in women.

Statistical analysis

STATA was used to perform statistical analysis. Descriptive statistics were analyzed using mean and standard deviation for continuous variables and frequency for categorical variables. Statistical analysis was analyzed by Poisson regression, both univariate and multivariate analysis, to identify risk factors of metabolic syndrome. These included sex, age group, educational status, occupation, income, BMI, smoking, alcohol consumption, serum LDL-c, serum cholesterol and family history of DM.

Subjects lost to follow-up were compared for difference with follow-up subjects using chi-square. Cumulative incidence was calculated to clarify meaning. Incidence density was calculated using the number of new cases divided by person-years of observation. In addition, incidence densities of each component of metabolic syndrome such as decreased serum HDL-c, hypertension, DM, increased waist circumferences and increased triglyceride were also calculated. Statistical significance was defined as a *p*-value of <0.05.

Ethic statements

The study protocol was approved by the IRB of the Royal Thai Army Medical Department. All participants were provided all of the information about this study by the investigators. Written informed consent was obtained from all participants.

Results

During the 9-year follow-up, 139 new diagnoses were made of metabolic syndrome implying the cumulative incidence was 14%. Therefore, the incidence density of metabolic syndrome was 3.47 per100 person-years. **Table 1** shows the comparison of baseline characteristics between responders and nonresponders in this study. Significant differences were found in age group, occupation and income. The most common age group of responders was 40-49 (31.5%) years while nonresponders were 30-39 (29.41%) years old. The most common occupation was farmer among both responders and nonresponders. However, the percentages differed (responders, 67.9%; nonresponders, 55.9%). For both responders and nonresponders, monthly income was mostly below 500 THB. However, only the percentages differed (responders, 53.8%; nonresponders, 66.1%). No difference was found in other characteristics, i.e., sex, village, educational status, alcohol consumption and smoking status.

Table 1. Comparison of baseline characteristics between responders and non-responders in the study

	Enrollment		*p*-value
	Responders	Non-responders	
Gender			0.633
Male	216 (42.27%)	201 (43.79%)	
Female	295 (57.73%)	258 (56.21%)	
Village			0.412
11	34 (6.65%)	36 (7.89%)	
15	232 (45.40%)	179 (39.25%)	
16	24 (4.70%)	26 (5.70%)	
18	62 (12.13%)	59 (12.94%)	
19	159 (31.12%)	156 (34.21%)	

	Enrollment		*p*-value
	Responders	Non-responders	
Age group (years old)*			0.000
20-29	9 (1.76%)	18 (3.92%)	
30-39	114 (22.31%)	135 (29.41%)	
40-49	161 (31.51%)	132 (28.76%)	
50-59	133 (26.03%)	75 (16.34%)	
>60	94 (18.40%)	99 (21.57%)	
Occupation*			0.008
Unemployed	23 (6.35%)	38 (13.62%)	
Farmer	246 (67.96%)	156 (55.91%)	
Contractor	66 (18.23%)	60 (21.51%)	
Shopkeeper	21 (5.80%)	22 (7.89%)	
Government officer	4 (1.10%)	2 (0.72%)	
Monk	0 (0%)	0 (0%)	
Constructor	0 (0%)	0 (0%)	
Student	0 (0%)	1 (0.36%)	
Others	2 (0.55%)	0 (0%)	
Income (Baht/ month)*			0.007
< 500	259 (53.85%)	288 (66.06%)	
500 - 1,999	33 (6.86%)	29 (6.65%)	
2,000 - 4999	137 (28.48%)	87 (19.95%)	
5,000 - 9,999	30 (6.24%)	21 (4.82%)	
10,000 - 19,999	11 (2.29%)	6 (1.38%)	
20,000 - 50,000	11 (2.29%)	5 (1.15%)	
> 50,000	0 (0%)	0 (0%)	

	Enrollment		*p*-value
	Responders	Non-responders	
Educational status			0.497
Uneducated	26 (6.28%)	15 (4.92%)	
Primary school	350 (84.54%)	260 (85.25%)	
Secondary school	19 (4.59%)	16 (5.25%)	
High school	14 (3.38%)	6 (1.97%)	
Diplomate	4 (0.97%)	5 (1.64%)	
Above bachelor degree	1 (0.24%)	3 (0.98%)	
Alcohol consumption			0.587
No	178 (50.71%)	130 (48.51%)	
Yes	173 (49.29%)	138 (51.49%)	
Smoking habit			0.145
Current smoker	107 (32.92%)	66 (26.09%)	
Ex-smoker	16 (4.92%)	18 (7.11%)	
Non-smoker	202 (62.15%)	169 (66.80%)	

In this study, using univariate by Poisson regression analysis according to each possible risk factor, revealed 4 factors (sex, BMI, serum LDL-c, serum cholesterol) showing significant association with a higher rate of metabolic syndrome as shown in **Table 2**. The incidence density of metabolic syndrome increased among females compared with males with a relative risk of 1.59 (95%CI; 1.10-2.34, p=0.009). For BMI, the incidence density increased in overweight participants (BMI 23 - 30 kg/m^2) with a relative risk of 1.66 (95%CI; 1.05-2.63, p=0.032) and obese participants (BMI > 30 kg/m^2) with a relative risk of 2.80 (95%CI; 1.89-4.14, p=0.000). Serum LDL-c greater than 130 mg/dL was associated with increased incidence density with a relative risk of 1.66 (95%CI; 1.13-2.41, p=0.007). Finally, serum cholesterol greater than 200 mg/dL was associated with increased incidence density with a relative risk of 1.62 (95%CI; 1.14-2.29, p=0.005).

Table 2. Univariate analysis of incidence density and crude incidence rate ratio according to each risk factors of metabolic syndrome with 95% confidence interval by Poisson regression

	Number of Metabolic Syndrome (person) (n=139)	Person-year of Observation (Person-year)	Incidence rate (per 100 person-year)	Crude Incidence Rate ratio (95% CI)	*p*-value
Gender					
Male	43	1,678	2.57	1	
Female*	96	2,336	4.11	1.59 (1.10-2.34)	0.009
Age group (years)					
<39	24	944	2.54	1	
40-49	47	1,278	3.68	1.45 (0.88-2.36)	0.141
50-59	43	1030	4.17	1.64 (0.99-2.71)	0.052
>60	25	754	3.32	1.30 (0.74-2.28)	0.353
Educational Status					
Uneducated	7	176	3.98	1	
Primary education	124	3,542	3.50	0.88 (0.41-1.88)	0.743
Above primary education	8	288	2.78	0.70 (0.25-1.93)	0.488
Occupation					
Farmer	108	3096	3.48	1	
Others	31	910	3.40	0.98 (0.63-1.48)	0.922
Income (Baht/month)*					
<1,999	11	296	3.72	1	
200-4,999	114	3046	3.74	1.01 (0.54-1.87)	0.982
≥5,000	14	664	2.11	0.57 (0.26-1.25)	0.160

	Number of Metabolic Syndrome (person) (n=139)	Person-year of Observation (Person-year)	Incidence rate (per 100 person-year)	Crude Incidence Rate ratio (95% CI)	*p*-value
Smoking					
Non smoker	117	3,196	3.66	1	
Smoker	22	810	2.72	0.74 (0.45-1.18)	0.194
BMI					
<23 kg/m^2	40	1,919	2.08	1	
23-30 kg/m^2*	33	955	3.46	1.66 (1.05-2.63)	0.032
>30 kg/m^2*	66	1132	5.83	2.80 (1.89-4.14)	0.000
Serum LDL-c					
<130 mg/dl	96	3,156	3.04	1	
≥130 mg/dl*	43	710	5.06	1.66 (1.13-2.41)	0.007
Serum cholesterol					
<200 mg/dl	75	2,624	2.86	1	
≥200 mg/dl*	64	1,382	4.63	1.62 (1.14-2.29)	0.005
Alcohol consumption					
No	86	2,626	3.27	1	
Yes	53	1,380	3.84	1.17 (0.82-1.67)	0.362
Family history of DM					
No	108	3283	3.29	1	
Yes	31	723	4.29	1.30 (0.84-1.96)	0.199
Difference of BMI during the time of observation*	139	4006	3.47	1.04 (1.003-1.07)	0.028

Table 3 shows the incidence rate ratio of metabolic syndrome according to possible and associated risk factors using multivariate analysis. However, this analysis excluded serum LDL-c due to collinearity with serum cholesterol. Being female, having serum cholesterol greater than 200 mg/dL and increased BMI every 1 kg/m^2 were considered risk factors with relative risks of 1.52 (95%CI; 1.002-2.32, p=0.049), 1.605 (95%CI; 1.14-2.25, p=0.01) and 1.038 (95%CI; 1.005-1.07, p=0.02), respectively.

Table 3. Multivariate analysis by Poisson regression of incidence rate ratio of metabolic syndrome according to possible and associated risk factors in univariate analysis

	Incidence Rate Ratio	Standard Error	p-value	95% Confidential interval
Gender	1.525	0.33	0.049	(1.00-2.32)
Age	1.009	0.007	0.24	(0.99-1.02)
Serum Cholesterol	1.605	0.28	0.01	(1.14-2.25)
Smoking	0.947	0.26	0.84	(0.56-1.61)
BMI change	1.038	0.02	0.02	(1.01-1.07)

Discussion

In this study, the incidence density of metabolic syndrome at Na Yao Community, a rural community, central Thailand (3.47/100 person-years) resembling the study results in Dalseong-gun, a rural area of Korea (men, 30.0/1,000 person-years; women, 46.4/1,000 person-years). In addition, the cumulative incidence of our study (14%) also resembled the study results in Korea (men, 13.9%; women, 20.8%).[8] This could be explained by the similar race and lifestyle, such as food and type of occupation. However, the incidence density in this study was lower than that of a study among Portuguese (47.2/1000 person-years), [9] which could be explained by the differences in ethnicity and living habits. In Portugal, the major population is Caucasian but in Thailand, Asian. Apart from that, Portuguese usually consume meat and dairy products instead of vegetables unlike in Thailand.

After univariate analysis by Poisson regression, four significant risk factors were identified, i.e., being female, increased BMI, serum LDL and serum cholesterol. These risk factors were all the same factors found in a USA survey from 1988-1994 by the Third National Health and Nutrition Examination.[10] The reason why metabolic syndrome is found among females more than males can be explained by a higher prevalence of dysglycemia and difference of hormones regulating body weight and lipid distribution between males and females. Moreover, decreased estrogen occurring only among females, is also associated with decreased metabolism that can cause both obesity and metabolic syndrome as consequences. [11] Increased BMI is caused by increased body weight, which is also associated with lipid accumulation in the body. Metabolic syndrome then occurs as a result. Serum LDL and serum cholesterol, which are collinearity to each other, can lead to dyslipidemia that also can aggravate metabolic syndrome.

The strength of this study is being a retrospective cohort with long follow-up period. Furthermore, this is the first study of metabolic syndrome incidence in a rural community, central Thailand. On the other hand, the limitation of this study was a high lost to follow-up rate of 47.4% that may have resulted in bias. Nevertheless, the comparison between subjects who were responders and nonresponders showed no significant differences among

other factors except age group, occupation and income. Using multivariate analysis, these factors were not potential risk factors of metabolic syndrome in this study.

We recommend diet control and exercise to lower the chance of developing high cholesterol levels and increased BMI. These findings indicate the urgent need to establish and strengthen strategies to detect, treat and prevent metabolic syndrome.

The study determined the incidence density of metabolic syndrome in Na Yao community, a rural area of Thailand, as 3.47/100 person-years. The significant risk factors from multivariate analysis using Poisson regression were being female, serum cholesterol greater than 200 mg/dL and increased BMI every 1 kg/m^2. Therefore, diet control and exercise are recommended to decrease the chance of developing modifiable risk factors (serum cholesterol and BMI). In addition, the primary healthcare unit should provide early detection and prevention of metabolic syndrome including health literacy, supporting physical activities and dietary controlled. Moreover, the people with metabolic syndrome should be received medical treatment at a community hospital.

Acknowledgements

This research was supported by the Department of Military and Community Medicine and Department of Parasitology, Phramongkutklao College of Medicine. We thank all of our colleagues from group 9 who provided insights and expertise that greatly assisted the research. We wish to thank Sanam Chaiyaket District Chief, the Na Yao Temple Abbot and public health volunteers for their hospitality and well-provided location. We are also immensely grateful to all Na Yao Community Members for their voluntary enrollment.

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SAFETY AND EFFICACY OF PIOGLITAZONE AMONG TYPE 2 DIABETES MELLITUS PATIENTS RECEIVING LONG TERM HEMODIALYSIS

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Abstract

Background: Type 2 diabetes mellitus (T2DM) frequently causes end stage renal disease (ESRD). Glucose-lowering treatment options for patients with T2DM with ESRD are limited. Thiazolidinedione is an oral glucose lowering agent used to treat patients with ESRD. We evaluated the potential for pioglitazone in combination with other hypoglycemic medications among patients with T2DM receiving long term hemodialysis.

Objectives: To evaluate the safety and efficiency of pioglitazone among patients with ESRD receiving hemodialysis.

Methods: The retrospective study was conducted in the outpatient clinic of Phramongkutklao Hospital during 2006 and 2015. HemoglobinA1C (HbA1c), fasting plasma glucose (FPG), body weight, hematocrit and history of diagnosed chronic heart failure were evaluated after starting medication and 1 year of follow-up.

Results: Data for hemodialysis patients on pioglitazone were analyzed (n=50). Mean FPG changes from baseline were -28.8±80.0 mg/dL after 12 weeks (p =0.018) and -59.2±80.0 mg/dL after 12 months of treatment (p <0.001). Mean HbA1cchanges from baseline were also -0.25±1.62 % after 12 weeks (p =0.318) and -1.52±1.77 % after 12 months of treatment (p <0.001). The differences in mean body weight (63.2±13.0 kg vs. 64.6±13.0 kg; p = 0.139) and hematocrit (33.4±5.5 vs. 33.6±5.3; p = 0.929) at baseline and 12 months were not significant, while episodes of congestive heart failure were low (4%). No serious adverse effects such as hypoglycemia with hospitalization or liver failure were observed in any of the patients.

Conclusion: These data suggest that adding pioglitazone to standard hypoglycemic agents among patients with T2DM undergoing hemodialysis improved glucose control and was well tolerated.

Keywords : End stage renal disease, Hemodialysis, Diabetes Mellitus, Thiazolidinedione, Pioglitazone

J Southeast Asian Med Res 2018; 2: 16-21.
http://www.jseamed.org

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Introduction

Patients with Type 2 diabetes mellitus (T2DM) and impaired renal function have become an important public health problem[1,2] and diabetic nephropathy is the most prevalent cause of end stage renal disease (ESRD) worldwide.[3,4] Patients with T2DM receiving dialysis have an increased mortality risk and especially a higher risk of cardiovascular death, compared with other diabetic patients without dialysis.[5] Moreover, hemodialysis patients with T2DM are known to be at a higher risk for cardiovascular disease and muscle wasting than nondiabetic hemodialysis patients.[6]

Altered pharmacokinetics of hypoglycemic medications complicate the treatment of patients with T2DM undergoing dialysis and can present inadequate glycemic control and adverse events. In addition, advanced chronic kidney disease (CKD) and hemodialysis with reduced intake, previous hypoglycemic episodes and longer duration of diabetes are recognized risk factors for prolonged hypoglycemia.[7] Thiazolidinediones (TZD) are oral hypoglycemic agents used for hemodialysis patients. In addition, patients with T2DM and CKD and/or receiving dialysis or treatment with pioglitazone are associated with a lower all-cause mortality rate.[8-10] TZD is an insulin sensitizer that reduces insulin resistance, increases glucose uptake in muscle and adipose tissue and decreases hepatic glucose production. It selectively enhances or partially mimics certain actions of insulin, causing a slowly generated hypoglycemic effect among patients with T2DM. The effect is often accompanied by reduced insulin in plasma, triglycerides and fatty acids.[11] Several clinical studies have shown that TZD specifically binds to a family of nuclear receptors, and peroxisome proliferation activator receptors (PPAR gramma) can improve indices of glucose control. Reduced fasting plasma glucose between 16 and 70 mg/dL and hemoglobinA1C between 0.4% and 2% has been reported.[12, 13] A few trials have compared the efficacy of TZD among hemodialysis patients.[14, 15] Here we report the results after assessing efficacy and safety of pioglitazone among patients receiving long term hemodialysis.

Methods

Study Design and population

This retrospective cohort study evaluated the efficacy and safety of pioglitazone treatment among hemodialysis patients during January 2005 and January 2015. The study was approved by the Ethics Review Committee for Research in Human Subjects, Pharmongkutklao Hospital, Thailand. The primary objective was to determine the efficacy of glycemic control and safety after pioglitazone treatment for 12 months. The primary efficacy evaluation was based on the percent change in hemoglobin A1C (HbA1c) levels from baseline to weeks 12 and 54.

All patients aged 18 years or older, with a previous diagnosis of T2DM according to the criteria of the American Diabetes Association, received hemodialysis treatment at least 12 weeks and were initially treated with pioglitazone for glycemic control. The primary renal diagnosis of all patients was diabetic nephropathy due to T2DM. Exclusion criteria included acute kidney injury episode, pregnancy, unspecified type of DM and patient life expectancy <1 year. Patients with T2DM and receiving medical care for at least 12 months were included in the present study. T2DM was reviewed using retrieved medical and personal data, including baseline demographic characteristics, hypertension, use of glycemic lowering medications and comorbidities. The patients continued regular medications such as blood pressure lowering agents, lipid lowering agents, recombinant human erythropoietin and phosphate binders during the study period. Safety was assessed by physical examinations, clinical laboratory tests and the incidence and severity of adverse events recorded from treatment. Fasting blood samples were drawn and processed following standardized protocols. Fasting plasma glucose (FPG), HbA1c and hematocrit levels were measured.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Continuous variables were assessed using the Paired-*t test*. For all tests, a *p*-value less than 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS, Version 16.0 (SPSS Inc., Chicago, IL, USA). All results were considered significant when *p*- value was <0.05.

Results

A total of 50 subjects (100% Thai ethnicity) with a mean age of 63.3±11.7 years were included.The average duration

of diabetes was 16.3±3.7years. The mean HbA1C was 7.9±1.9%, and 25% of patients had an HbA1C <7%. The mean systolic and diastolic BP were 133.5±10.2 and 76.0±9.8 mmHg, respectively, In the entire population, 98% had hypertension, 96%, dyslipidemia, 24%,cardiovascular disease, 6%, malignancy and 6% had autoimmune disease as comorbid diseases. The dosage of pioglitazone was 15-30 mg/day among all subjects. The characteristics and baseline measurements of the patients who entered the study are listed in **Table 1**.

Table 1. Baseline characteristics of the enrolled patients

Characteristics	**Total (N=50)**
Age (year)	63.3±11.7
Male (N, %)	24 (48%)
Duration of diabetes (years)	16.3±3.7
Body weight (kg)	63.2±13.0
Systolic blood pressure (mmHg)	133.5±10.2
Diastolic blood pressure (mmHg)	76.0±9.8
Co-morbid diseases (N, %)	
Hypertension	49 (98%)
Dyslipidemia	48 (96%)
Cardiovascular disease	12 (24%)
Malignancy	3 (6%)
Autoimmune disease	3 (6%)
Fasting plasma glucose (mg/dL)	176.6±74.9
HemoglobinA1C (%)	7.9±1.9
Hematocrit (%)	33.4±5.6
Insulin monotherapy	25 (50.0)
Insulin + other oral hypoglycemic agents	13 (26.0)
Other oral hypoglycemic agents	12 (24.0)

Data are expressed as mean ±SD or as number (percentage) of patients

Efficacy of treatment

As shown in **Table 2**, significant decreases were observed in FPG levels at 12 weeks after the start of pioglitazone therapy, and the levels continued to decrease throughout the 54-week treatment. Table 2 shows similar results for HA1c: the levels decreased at 12 weeks after the start of pioglitazone therapy and continued to significantly decrease for 54 weeks. Mean FPG changes from baseline were -28.8±80.0 mg/dL after 12 weeks (p =0.018) and -59.2±80.0 mg/dL after 12 months of treatment (p <0.001). Mean HbA1c changes from baseline were also -0.25±1.62 % after 12 weeks (p = 0.318) and -1.52±1.77 % after 12 months of treatment (p <0.001) **(Fig 1).**

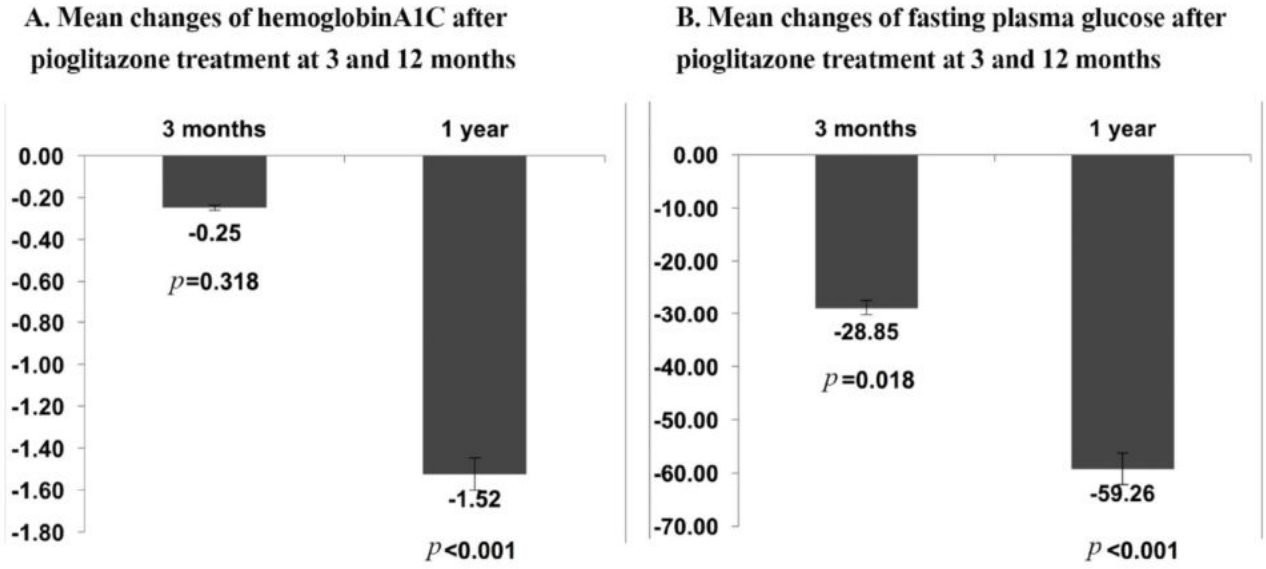
Safety of treatment

The safety analysis included all patients who entered the study. Two patients with congestive heart failure (4%) were eliminated due to adverse events. No significant changes in body weight were observed after treatment **(Table 2)**. No significant differences were found in hematocrit or the erythropoietin dose throughout the 54-week treatment. No serious adverse effects such as hypoglycemia with hospitalization or liver failure were observed among any of the patients.

Table 2. Changes of fasting plasma glucose, hemoglobinA1C, body weight and hematocrit after pioglitazone treatment

	Body weight (kg)	Fasting plasma glucose (mg/dL)	HemoglobinA1C (%)	Hematocrit (%)
Baseline	63.2±13.0	176.6±74.9	7.9±1.9	33.4±5.6
At 3 month of treatment	63.8±13.2	152.4±62.2	7.8±1.6	33.5±5.0
p- value (at 3 month vs. baseline)	0.463	0.018	0.318	0.858
At 12 month of treatment	64.6±1.3.0	128.2±37.7	6.8±0.9	33.7±5.3
p- value (at 12 month vs. baseline)	0.139	<0.001	<0.001	0.929

Figure 1. Changes of glycemic control after pioglitazone treatment among hemodialysis patients
Data are expressed as mean±SD. Comparisons between treatment groups using the Independent *t*-test (continuous variables)



Discussion

This study evaluated the efficacy and safety of pioglitazone among patients with T2DM on hemodialysis. Overall, the study demonstrated that pioglitazone was effective to treat Thai patients with T2DM receiving hemodialysis. HbA1c levels among patients with T2DM decreased from 7.9% at baseline to 6.8% after 54 weeks of treatment. The results of this study showed that pioglitazone treatment exhibited high efficacy as previously reported in the general [16] and ESRD populations. [14, 15] In a Japanese population of diabetics on hemodialysis, pioglitazone was effective in reducing plasma glucose and HbA1c from baseline levels from week 4 after the commencement of treatment and no serious adverse effects were observed among any of the patients.[15] Moreover, TZD produced a number of pleiotropic actions concerning cardiovascular risk factors and TZD treatment could improve survival among CKD with and without hemodialysis.[8-10]

The serious side effects of TZD treatment included congestive heart failure, fluid retention, weight gain and anemia. [17,18]

The meta-analysis of four randomized, controlled trials comparing rosiglitazone with other oral hypoglycemic agents demonstrated a two-fold significantly increased risk for congestive heart failure in the general population[19] and significant associations of rosiglitazone use with higher cardiovascular and all-cause mortality rate among hemodialysis patients with T2DM.[20] The incidence of serious heart failure also increased with pioglitazone vs. placebo among 5,238 patients with T2DM with pre-existing cardiovascular disease.[21] However, some studies did not detect these adverse events with pioglitazone among patients with normal renal function [21], CKD[8]and those receiving hemodialysis. [9,10] This finding was similar to our findings, in which patients demonstrated a low frequency of treatment limiting weight gain and heart failure among hemodialysis patients receiving pioglitazone treatment. No changes were found in hematocrit values, erythropoietin dose requirements or weight gain in the present study. These results might have been due to the success of the low dose pioglitazone treatment in minimizing the expansion of the intravascular volume.

There remains the possibility of residual confounding regarding the efficacy of TZD treatment. One must consider whether TZD-treated patients received better care and exhibited good compliance. Second, assessment of glycemic control among hemodialysis patients is difficult. Among hemodialysis patients, the use of HbA1c is limited due to the shortened half-life of erythrocytes and recombinant human erythropoietin treatment.[22] Finally, all patients received other hypoglycemic agents and an adjusted dose of anti-diabetic therapy according to standard of care.

This study had some limitations. First, because of the retrospective cohort design, we could not evaluate long term patient outcomes, and could not assess the mechanisms of pioglitazone associated with heart failure. Second, the outcomes of this study were based on primarily Asian patients with long term dialysis and may not be generalizable to a special population, e.g., peritoneal dialysis, advanced renal disease without dialysis and high comorbid illnesses. This cohort consisted of patients with T2DM incident to hemodialysis. Generalization to prevalent hemodialysis patients should be undertaken cautiously; further, generalization to nondiabetic hemodialysis patients is unadvisable. In addition, assessment of outcomes in this study was limited to one year of follow-up and no control group; further study is needed to clarify longer term effects.

Conclusion

Pioglitazone therapy is safe and effective for patients with T2DM receiving hemodialysis. The long term safety of pioglitazone treatment will require further evaluation in longer duration studies and high risk groups regarding heart failure.

Acknowledgements

The authors wish to acknowledge the contributions of the following individuals to this study and staff in the Biomedical Clinical Research Center, Phramongkutklao Hospital. This work was supported by Phramongkutklao Hospital and Phramongkutklao College of Medicine Research Fund.

Competing interests

The authors declare that they have no competing interests.

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EFFECT OF DELAYED CORD CLAMPING VERSUS CORD MILKING AMONG PRETERM INFANTS: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Delayed cord clamping (DCC) is currently recommended for preterm infants to improve blood volume and decrease the rate of blood transfusion. Umbilical cord milking (CM) has similar advantages without interrupting neonatal resuscitation. However, the differences in neonatal outcomes between DCC and CM have not been well elucidated.

Objective: To compare neonatal outcomes between DCC and CM among preterm infants

Methods: Infants born at 25-34 weeks of gestation were randomly allocated to 1 of 2 groups; group 1 received DCC for 60 seconds whereas group 2 received CM. Initial hemoglobin value was measured, while blood pressure and urine output were monitored. Neonatal complications and the rate of blood transfusion were recorded.

Results: Twenty-two infants were enrolled in each group. No differences were observed regarding sex, gestational age, birth weight, mode of delivery, Apgar scores and rate of resuscitation between groups. The initial hemoglobin level of the DCC group [median 17.1 (13.1, 21.3) g/dL] did not differ from that of the CM group [median 17.1 (14.0, 22.5) g/dL], p=0.963. During the first 24 hours, no significant differences were observed regarding blood pressure and urine output between groups. No differences were found in the rates of hypothermia, hyperbilirubinemia, intraventricular hemorrhage, necrotizing enterocolitis and rate of blood transfusion.

Conclusion: We demonstrated no different effects on neonatal outcomes between DCC and CM among preterm infants. CM can be applied as an alternative to DCC especially in emergency situations. However, larger studies are warranted to determine the effects and safety of CM among preterm infants.

Keywords : Delayed cord clamping, Umbilical cord milking

J Southeast Asian Med Res 2018; 2: 22-27.
http://www.jseamed.org

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Introduction

Currently, strong evidence supports delayed cord clamping (DCC) over immediate cord clamping (ICC) among preterm infants.[1] Many studies have confirmed that DCC increased initial hematocrit levels [2-4], improved transitional hemodynamic status [5-7], decreased blood transfusion due to anemia[8, 9] and reduced rates of intraventricular hemorrhage.[9-11] Since 2006, many professional societies and committees have recommended DCC for at least 30 seconds at preterm births.[12, 13] Umbilical cord milking (UM) was proposed as an alternative to DCC without delayed neonatal resuscitation and was proved to have similar benefits compared with ICC. [14-21] However, UM has not been recommended especially among infants born at less than 29 weeks of gestation due to the issue of rapid changes of blood volume. To date, only a few studies have been conducted comparing neonatal outcomes between DCC and CM among preterm infants.[23, 24] Therefore, we conducted a randomized controlled trial to compare initial hemoglobin and hematocrit levels and short term outcomes between DCC and CM among preterm infants.

Methods

This study was conducted in a single tertiary care center, Phramongkutklao Hospital, Bangkok, Thailand. Preterm infants delivered between 25 and 34 completed weeks of gestation were included when parental informed consent was obtained before delivery. Exclusion criteria included multiple pregnancies, hydrops fetalis, known major congenital anomalies, maternal bleeding from the placental previa or abruption, intention to withhold care, obstetrician's disagreement or parental refusal to participate in the study. Infants were allocated immediately before delivery to one of two groups using random permuted blocks of 4 sequentially numbered opaque sealed envelopes. Randomization was stratified by gestational age, <30 weeks and >30 weeks. For the DCC group, umbilical cord clamping was delayed for 60 seconds after delivering the infant's whole body. For the CM group, about 30 cm of umbilical cord was milked towards the umbilicus four times before clamping the cord. During the procedures, the infant was held at the introitus level for vaginal delivery or placed between the mother's thighs for cesarean section. A digital stopwatch was used to indicate timing of cord clamping in each delivery. Interruption of the procedure for cardiopulmonary resuscitation depended on the infant's condition and physician's decision. Subsequent management was at the consideration of the attending neonatologist. The primary outcomes were venous hematocrit and hemoglobin levels obtained within 2 hours after birth. The secondary outcomes were blood pressure, urine output, volume replacement or inotropic support for hypotension during the first 24 hours of life and blood transfusion for anemia within 28 days of age. The variables measured included hypothermia, polycythemia, peak serum bilirubin level, duration of phototherapy, duration of oxygen supplementation and morbidities including respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis stage, late onset sepsis, chronic lung disease and retinopathy of prematurity. The sample size was calculated based on the difference in hematocrit level at 8% with type I error of 0.05 and power of 0.80. The number of infants needed in each group totaled 23. Comparisons between the two groups were analyzed using the Mann-Whitney U test for continuous data and Chi-square or Fisher's Exact test for categorical data. Data were analyzed on an intention-to-treat basis.

Results

Forty-four of 93 eligible infants were recruited in the study. Twenty-two were randomly allocated to each group **(Fig 1)**. The median time of cord clamping in the CM group was 11.5 (4-43) seconds. No significant differences were observed regarding sex, gestational age, birth weight, mode of delivery, Apgar scores, requirement for resuscitation and rectal temperature between the two groups **(Table 1)**. The initial hemoglobin and hemoglobin levels, mean blood pressure, heart rate, urine output and hypotension requiring fluid or inotropic therapy were comparable between both groups **(Table 2)**. Peak serum bilirubin, duration of phototherapy, rate of blood transfusion due to anemia, incidence of intraventricular hemorrhage, necrotizing enterocolitis and other morbidities did not differ between the two groups **(Table 3)**. The results did not change when performing subgroup analysis based on gestational age (<30, >30 weeks). One infant in the DCC group presented asymptomatic polycythemia with a hematocrit of 66.7%. One infant in the DCC group died on the 9th day of life due to severe pneumoniaand acute kidney injury.

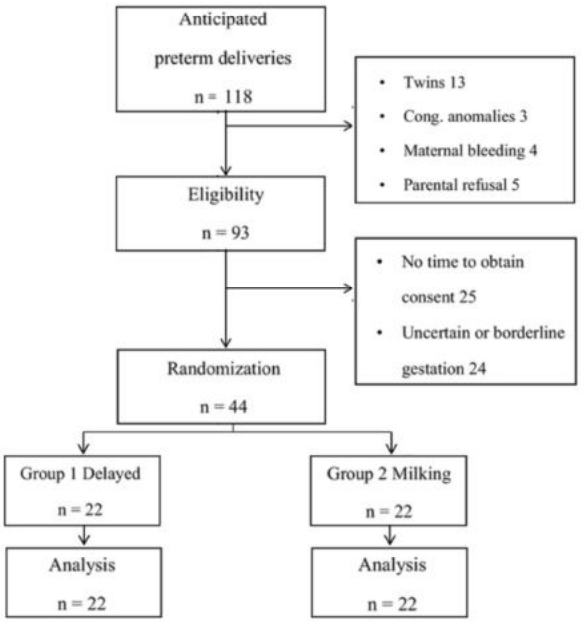

Fig 1. Flow chart of subject recruitment and analysis in the trial

Table 1. Demographic data and delivery room outcome

	Delayed n=22	Milking n=22	*p*-value
Maternal preeclampsia or chronic hypertension (%)	11 (50.0)	11 (50.0)	1.000
Maternal diabetes (%)	1 (4.50)	4 (18.2)	0.345
Male gender (%)	12 (54.5)	12 (54.5)	1.000
Gestational age (week)	32 (27-34)	33 (26-34)	0.410
≤ 30 weeks	5 (22.7)	6 (27.3)	
> 30 weeks	17 (72.3)	16 (72.7)	
Birth weight (gram)	1724 (922, 2210)	1766 (682, 2280)	0.925
Small for gestational age	0 (0.0)	1 (4.5)	1.000
Large for gestational age	1 (4.5)	0 (0.0)	1.000
Cesarean delivery (%)	15 (68.2)	15 (68.2)	1.000
Apgar score at 1 minute	7.5 (2, 9)	6 (0, 9)	0.106
Apgar score at 5 minutes	8 (5, 9)	8 (1, 9)	0.323
Apgar score < 5 at 5 minutes (%)	0 (0.0)	2 (9.1)	0.488
Chest compression or adrenaline (%)	1 (4.5)	2 (9.1)	1.000
Delivery room temperature (°C)	36.5 (35.3, 37.0)	36.4 (35.1, 37.2)	0.828
Hypothermia (%)	11 (50.5)	12 (54.5)	0.763

Table 2. Hematocrit and hemoglobin levels and hemodynamic status within 24 hours of life

Variables	Delayed n=22	Milking n=22	*p*-value
Hematocrit within 2 hours (%)	49.8 (36.9, 66.7)	50.8 (38.8, 64.8)	0.760
Hemoglobin within 2 hours (g/dL)	17.1 (13.1, 21.3)	17.1 (14.0, 22.5)	0.963
Mean blood pressure (mmHg)	45.7 (40.0, 54.3)	46.0 (39.7, 57.3)	0.817
Heart rate (beats /min)	141.7 (120.7, 157.3)	137.7 (115.0, 170.3)	0.337
Urine output (mL/kg)	70.2 (7.1, 143.5)	82.7 (30.6, 151.8)	0.253
Fluid replacement (%)	3 (13.6)	4 (18.2)	1.000
Inotropic drug (%)	2 (9.1)	2 (9.1)	1.000

Table 3. Neonatal outcomes

Variables	Delayed n=22	Milking n=22	*p*-value
Maximum bilirubin (mg/dL)	8.8 (6.4, 12.5)	8.8 (3.0, 15.0)	0.991
Duration of phototherapy (day)	3.5 (0, 9)	2 (0, 6)	0.081
Polycythemia (%)	1 (4.5)	0 (0.0)	1.000
Blood transfusion within 28 days (%)	3 (13.6)	4 (18.2)	1.000
Respiratory distress syndrome (%)	6 (27.3)	5 (22.7)	0.728
Patent ductus arteriosus (%)	5 (22.7)	3 (13.6)	0.698
Intraventricular hemorrhage (%)	1 (4.5)	2 (9.1)	1.000
Necrotizing enterocolitis (%)	0 (0.0)	2 (9.1)	0.488
Late-sepsis (%)	2/21 (9.5)	3/22 (13.6)	1.000
Chronic lung disease (%)	4/21 (19.0)	4/22 (18.2)	1.000
Retinopathy of prematurity requiring laser therapy (%)	0/21 (0.0)	1/22 (4.5)	1.000

Discussion

Our study demonstrated that CM was comparable to DCC regarding the effect on initial hematologic values and hemodynamic status among preterm infants. Recently, only a few studies have compared DCC and CM among preterm infants with equivocal results. Rabe et al [23] did not find differences in initial hematocrit, maximum serum bilirubin and morbidities between the groups. In contrast, Katheria, et al. [24] exhibited higher delivery room temperature, initial hemoglobin, urine output and blood pressure among infants delivered by cesarean section that underwent CM.No such differences were observed in vaginally delivered infants. The disparity between these two studies was probably due to the higher rate of cesarean section among infants undergoing CM in Rabe et al.[23] It has been speculated that anesthesia and surgical intervention may interfere with uterinecontraction which subsequently resulted in decreased blood flow from the placenta to the infant. Our study revealed a high rate of cesarean delivery but the rate was comparable in both groups. The method of our study differed slightly from others, e.g., length of milked cord and infant position during the procedures. The median time of cord clamping in our CM group (11.5 seconds) was almost one half of Katheria et al. (20 seconds).[24] The shorter and varied time of CM in our study may have affected blood volume transferred from the placenta to the infant. One infant in the DCC group had polycythemia. She was a 32-week-gestation, 1,848 gm infant born to a mother who had chronic hypertension with superimposed pre-eclasia. Though intra-uterine growth restriction, large for gestational age and infants of diabetic mothers are important risks factors for neonatal polycythemia, we did not observe polycythemia among other infants at risk. We propose that the risks should not be contraindications for DCC or CM among preterm infants. However, further studies are warranted to determine the optimal timing for DCC and technique of CM in this group of infants.Our study had limitation from the inadequate power to compare complications of the procedures and neonatal morbidities between the two groups. Despite being an alternative to DCC, one concern is that CM may provide rapid bolus of blood to the infant. Moreover, the effec- tiveness of CM may depend on the milking technique and time of cord clamping which may vary from case to case.

Conclusion

We conclude that performing DCC or CM during vaginal or cesarean deliveries is feasible. Both procedures provided comparable effects on short term outcomes among preterm infants. We suggest that larger studies be undertaken to answer unclear questions. In addition, further studies on long term neuro-developmental outcomes in both DCC and CM groups are warranted.

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LACK OF SIGNIFICANT ASSOCIATIONS BETWEEN COMPONENT ALIGNMENT AND FUNCTIONAL OUTCOMES IN TOTAL HIP ARTHROPLASTY

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Abstract

Objective: To evaluate the functional outcome and hip range of motion (ROM) post total hip replacement (THR) associated with prosthesis orientation angle.

Methods: This cross sectional analytical study was conducted at the RSUPN Cipto Mangunkusumo Hospital, Jakarta, Indonesia from July to September 2014, selecting 38 subjects among 83 primary THR-treated through January 2008-May 2014. Patients were divided in two groups of safe and non-safe zones with at least six months postsurgery follow-up. Prosthesis orientation angle (acetabular abduction, acetabular anteversion, femoral anteversion and their combinations) were measured using AP and lateral radiographs. Functional outcomes were obtained from Harris Hip Score (HHS) and hip ROM, including Attahiyat praying position and squatting position.

Results: No significant differences were noted between prosthesis orientation angles in safe zone and non-safe zone groups compared with the HHS (p>0.05). No significant differences were observed between component orientation angles with the ROM, except on internal rotation at the safe zone (p=0.015). As many as 22.6% of hips had the ability to perform Attahiyat and squatting with more in the non-safe zone acetabular abduction group (p=0.035).

Conclusion: THR with prosthesis fixed in non-safe and safe zones of orientation gave similarly good functional outcomes. The non-safe zone of the acetabular abduction angle group showed more internal rotation range of motion. Patient's fears, habits and obesity status in performing such tasks were unable to be ruled out as confounders.

Keywords : Total hip replacement, Prosthesis component orientation, Functional outcome, Attahiyat position, Squatting position

J Southeast Asian Med Res 2018; 2: 28-36.
http://www.jseamed.org

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Introduction

Total hip replacement (THR) is one of the mainstays of therapy in the treatment of osteoarthritis or inflammatory pelvic disease that has been proven to relieve pain and increase both mobility and physical function of patients.[1-5] THR is exceedingly common and arguably one the most successful surgical procedures of modern time.[6-7] However, incorrect placement of THR implants and misalignments between the acetabulum components and femoral stem have been attributed to various complications, from ambulatory discomfort to hip osteolysis and secondary revisions.[8-17]

Many studies have been conducted to prove the effect of the THR prosthesis component orientation on various outcomes and complications represented by acetabular abduction and the anteversion and femoral anteversion angles or combinations. However, no studies have evaluated such parameters regarding patient's functional outcomes. We divided the patients according to Lewinnek [10] and Komeno[18] in safe and non-safe zones with the safe zone believed to present the least number of complications. Prosthetic component orientation, when tested with hip models, was proven to affect the hip's range of motion. We employed functional scoring using the Harris Hip Score (HHS) as an objective measure of THR outcomes. We also added the Attahiyat salat praying position and the squatting position as outcomes due to their specificity to the Indonesian population. This paper aimed to determine the effect of THR prosthesis component orientation on patient's functional outcomes.

Methods

This cross sectional analytical study was conducted at the Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia from July to September 2014 and involved patients treated from January 2008 to May 2014. We obtained ethical approval from the Institutional Research Ethics Committee FKUI/RSCM (422/H2.F1/ETIK/2014).

Sample size was derived from two independent proportion difference test formula. Of 83 primary THR, 38 subjects were consecutively selected and divided in two groups of safe and non-safe zones with at least six months postsurgery follow-up. The prostheses implanted in this cementless THR included the pinnacle acetabular shell and corail femoral stem (Depuy Johnson-Johnson). We excluded complicated primary THR such as additional acetabuloplasty or femoral part reconstruction. Patients with prior hip arthroplasties (bilateral THR) or comorbidities were also excluded from the sampling.

Patients that matched our inclusion criteria were given thorough informed consent. Anteroposterior and cross table lateral radiographs were performed. We measured the acetabular abduction (safe zone = 40 ± 10^0) and anteversion (15 ± 10^0) angles. Femoral anteversion (10^0) was obtained from the lateral view. The anteversion combination angles, the sum of the femoral and acetabular components angles ($25\text{-}45^0$), and combination of abduction and anteversion of the acetabulum were also obtained (**Fig 1**).

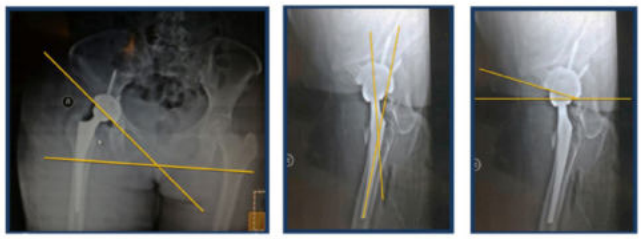


Fig. 1 The measurement of (A) acetabular abduction angle, (B) femoral anteversion angle and (C) acetabular anteversion angle

Functional scoring using Harris Hip Score along with squatting and Attahiyat positions (**Fig 2**) were obtained during office or home visits with scores ranging from 90-100: excellent, 80-89: good, 70-79: fair, 60-69: poor and <60: failed. The results were then collected and analyzed using SPSS, Version 20 (IBM).

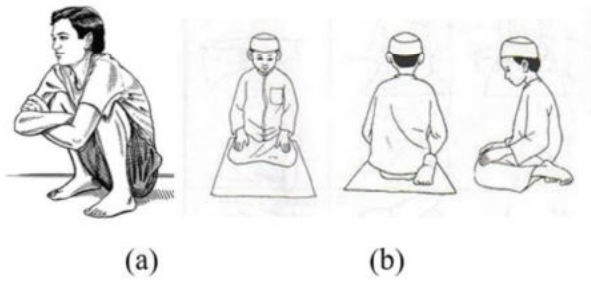


Fig. 2 (a) An oblique view of the squatting position, (b) Attahiyat praying position scheme, anterior, posterior and lateral view (From: Isbit J. 2008(18) and MN al-Alabani. 2005(19))

Results

The mean follow-up of this study was 21 months. The mean patient age was 16-79 (±15.90) consisting of 40% males and 60% females. **Table 1** shows postoperative outcomes such as functional outcomes and the ROM of the hip compared with pre-operative status. A significant difference was noted between before and after outcomes, covering Leg Length Discrepancy THR (LLD), HHS and ROM pre-THR. Other postoperative outcomes assessed included the incidence of dislocation, the ability to perform the squatting and the Attahiyat positions as shown in **Table 2**. For the outcomes of post-THR regarding dislocation level, we found two patients had dislocations and for the Attahiyat and squatting positions, we found 12 patients could perform these positions (**Fig 3**).

Table 1. Comparison of outcomes between pre- and post-THR. Outcomes of post-THR showed better results compared with pre-THR including LLD, HHS and Hip ROM.

Outcome variable	Pre-operation	Post-operation	*p*
Leg length discrepancy (LLD)			
0	11 (24.4)	27 (60.0)	
1	13 (28.9)	13 (28.9)	
2	13 (28.9)	3 (6.7)	
>2	8 (17.8)	2 (4.4)	
Harris hip score (HHS)	26 (13.0-36.0)	85,0 (73.0-95.0)	0.001
Range of movement (ROM)			
Flexion	70.0 (30.0-90.0)	105.0 (90.0-115)	0.001
Extension	0.0 (0.0-2.5)	5.0 (5.0-10.0)	0.001
Abduction	20.0 (10.0-30.0)	35.0 (30.0-40.0)	0.001
Adduction	10.0 (5.0-20.0)	27.0 (25.0-35.0)	0.001
Internal rotation	10.0 (5.0-15.0)	30.0 (24.5-35.0)	0.001
External rotation	15.0 (10.0-21.0)	32.0 (26.0-35.0)	0.001

The results are displayed in the median (inter-quartile range) for numerical data or frequency (percentage) for the proportion of data.

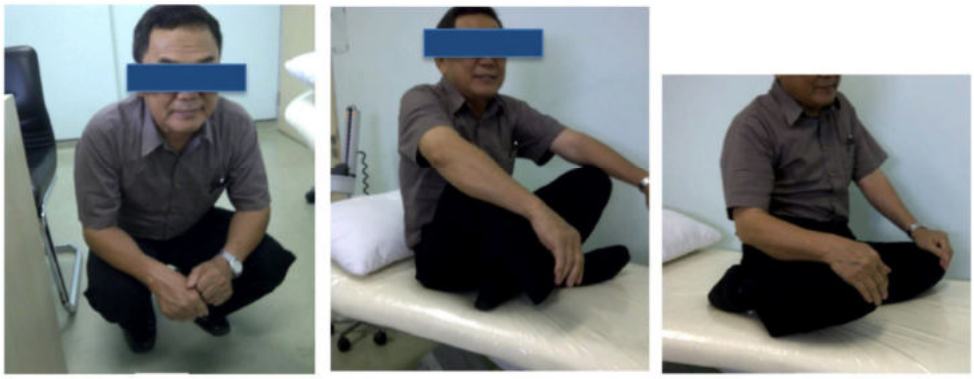
* *p*-values were calculated using the Pearson chi-square test or Fischer's exact proportion to the data, and the Wilcoxon signed rank test for paired numerical data.

Table 2. Relationship between acetabulum abduction angle, acetabulum anteversion angle and combination anteversion angle in the safe zone and non-safe zone groups with HHS post-THR regarding the ability to perform Attahiyat and squatting positions. Patients unable to perform Attahiyat and squatting positions post-THR were significantly more common among safe zone patients regarding the abduction angle of the acetabulum.

Component orientation angle	HHS		*p*	Attahiyat-squatting position		*p*
	≤80	>80		Yes	No	
Abduction acetabulum						
Safe zone	18 (46.2)	21 (53.8)	0.105	6 (15.4)	33 (84.6)	0.035
Non-safe zone	3 (21.4)	11 (78.6)		6 (42.9)	8 (57.1)	
Anteversion acetabulum						
Safe zone	12 (38.7)	19 (61.3)	0.872	5 (16.1)	26 (83.9)	0.179
Non-safe zone	9 (40.9)	13(59.1)		7 (31.8)	15 (68.2)	
Anteversion combination						
Safe zone	14 (46.7)	16 (53.3)	0.231	7 (23.3)	23 (76.7)	0.891
Non-safe zone	7 (30.4)	16 (69.6)		5 (21.7)	18 (78.3)	

The results are displayed in the median (inter-quartile range) for numerical data or frequency (percentage) for the proportion of data.

* *p*-values were calculated using the Pearson chi-square test, linear-by-linear association, or Fischer's exact proportion to the data, and the student T independent test or Mann-Whitney for numerical data.



(a) (b) (c)

Fig. 3 (a) Squatting position in patient after THA procedures, (b) cross-legged sitting position, (c) Attahiyat praying position

We processed the data using bivariate analysis. The results did not differ in HHS functional outcomes in the safe zone group of patients with orientation angle of prosthesis components from the non-safe zone group both at the acetabulum abduction angle, acetabulum anteversion angle as well as combined anteversion angle (**Table 3**).

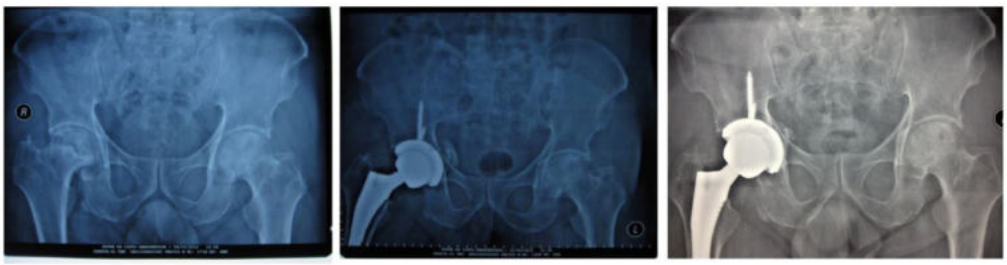
The angle of the femur anteversion and combined abduction- anteversion acetabulum angles (non-safe zone ranges appear in the literature) did not show a mean difference when comparing HHS score between groups with "Good to Excellent" (>80) and "Nongood to Excellent" (<80) (**Fig 5**). The same results were observed when the orientation angles were compared between groups with the ability to perform Attahiyat-squatting position and without. Likewise, almost all the prosthesis component orientation angles compared with the Attahiyat and squatting positions yielded no significant relationship. However, regarding the abduction angle of the acetabulum, more significant outcomes were found among patients who were unable to perform Attahiyat and squatting positions in the safe zone group (**Table 3**). Almost all the interaction analyses of the prosthesis component orientation angle with ROM post-THR operation showed no difference in ROM post-operative outcomes of both groups, with the exception of increased internal rotation in the abduction angle of the acetabulum in the non-safe zone group (**Table 3**).

Table 3. Interaction of prosthesis component angle with ROM post-THR. Significant results obtained regarding the internal rotation increase in the abduction acetabulum angle non-safe zone group.

ROM post-operation	Abduction acetabulum angle			Anteversion acetabulum angle			Femur anteversion combination angle		
	Safe zone	Nonsafe-zone	*p*	Safe zone	Nonsafe-zone	*p*	Safe zone	Nonsafe-zone	*p*
Flexion	100.0 (90.0-110.0)	110.0 (93.8-130.0)	0.462	100.0 (90.0-115.0)	107.5 (98.8-117.5)	0.763	105 (90.0-116.3)	100 (95.0-115.0)	0.962
Extension	5.0 (5.0-5.0)	5.0 (5.0-10.0)	0.163	5.0 (5.0-10.0)	5.0 (5.0-10.0)	0.866	5.0 (5.0-10.0)	5.0 (5.0-10.0)	0.995
Abduction	35.0 (30.0-40.0)	35.0 (29.3-40.0)	0.788	35.0 (30.0-40.0)	35.0 (30.0-40.0)	0.835	35.0 (30.0-40.0)	40.0 (30.0-40.0)	0.097
Adduction	27.0 (25.0-35.0)	27.5 (23.8-35.8)	0.675	27.0 (25.0-30.0)	30.0 (21.5-35.0)	0.389	27.0 (25.0-35.0)	26.0 (22.0-35.0)	0.962
Internal rotation	26.0 (23.0-35.0)	33.5 (29.3-36.3)	0.015	30.0 (24.0-35.0)	30.0 (24.5-35.0)	0.822	28.5 (23.0-33.5)	30.0 (25.0-35.0)	0.468
External rotation	30.0 (25.0-35.0)	35.0 (30.0-40.0)	0.127	30.0 (25.0-35.0)	35.0 (26.5-36.3)	0.341	30.0 (25.0-36.3)	35.0 (27.0-350)	0.219

The results are displayed in the median (inter-quartile range).

* *p*-values were calculated using test or Mann-Whitney U test



(a) (b) (c)

Fig.4 (a) Before operation pelvis x-ray (b) postoperative x-ray and (c) 6-month postoperative x-ray

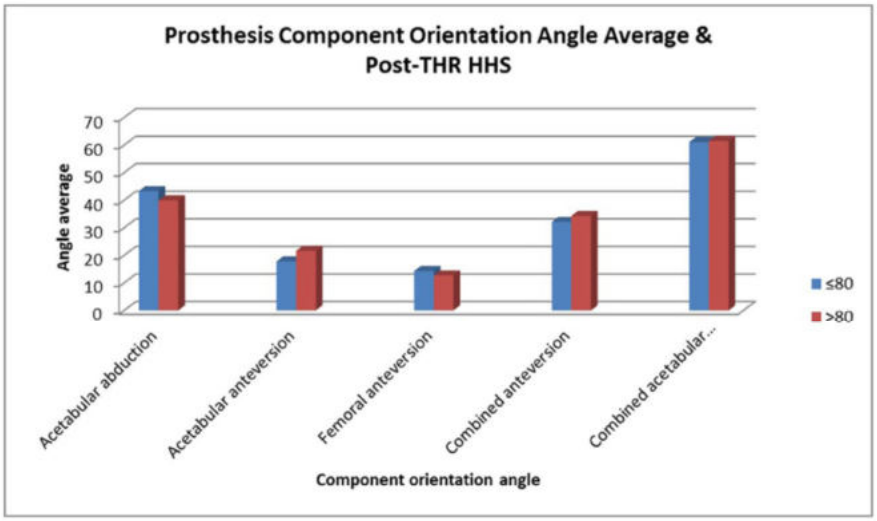


Figure 5. Relationship between THR component orientation angle with HHS post-THR and the ability to perform Attahiyat and squatting positions

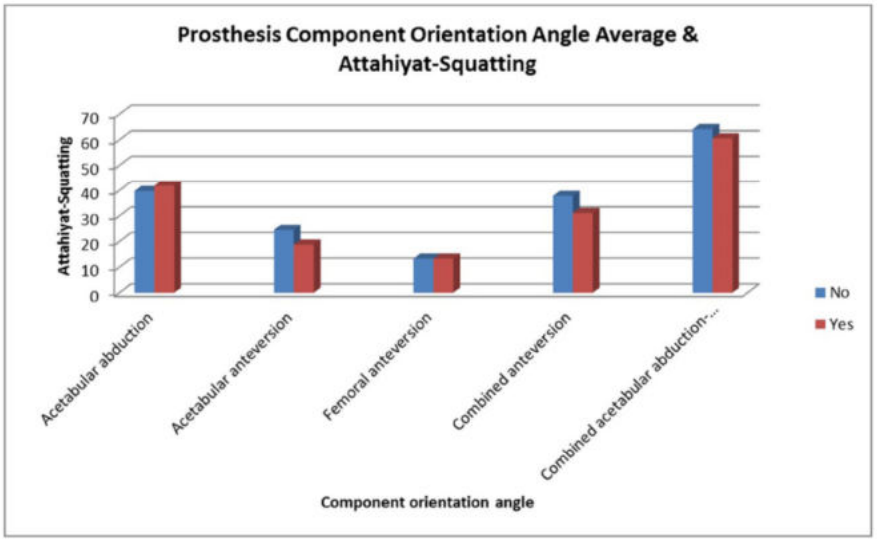


Figure 6. Relationship between THR component orientation angle and the ability of to perform Attahiyat and squatting positions

Discussion

Many studies have been conducted to assess functional outcomes of THR. Walker et al. stated that THA among patients less than 30 years yielded good functional THA outcomes.[26] However, Clement stated that THA among older patients developed poor outcomes due to more complications and higher mortality rates.[27] Ethgen et al. [20] conducted a systematic review in 2004 concerning the quality of life of patients with post-THR assessed using the Short Form-36 (SF-36) and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The results showed significant improvements in their quality of life. However, Laupacis et al.[5] showed a significant increase in the mean HHS of 44 to 98. We used two types of approaches, i.e., anterolateral or posterior. Graves et al. stated that different types of approaches yielded similar results regarding short term outcomes; thus, the selection of approach posed no bias.[28]

In this study alone, HHS post-THR significantly improved from a median of 26 to 85.

The score of "Good" HHS showed that patients improved pain management, improved mobilization function and improved social function in the patient community.

Concerning Hip ROM outcomes, this study showed significant improvement in each component of the Hip ROM. ROM was limited among patients undergoing primary THR caused by pelvic pain due to arthritis. THR removes a source of pain and replaces the hips with a prosthesis that serves to simulate the previous pelvic functions. Thus, a significant increase in ROM can occur.

In a study conducted by Le Duff et al. [21], the ROM postprimary THR increased flexion to 123° (90-140), abduction to 43° (25-50), adduction to 28° (20-40), external rotation to 35° (15-60) and internal rotation to 40° (10-70). In our study of post-THR, we discovered that the ROM was slightly lower, with a flexion of 105° (90-115), abduction of 35° (30-40), adduction of 27° (25-35), external rotation of 32° (26-35) and internal rotation of 30° (24, 5-35). This significant increase in ROM has become a component of HHS as a measure of the patient's improved quality of life.

Attahiyat and squatting positions could be performed by 12 patients with postprimary THR at a proportion of 22.6%. Both of these positions are the expectations, often a necessity, among Indonesian patients undergoing THR procedures with respect to beliefs and culture. The majority of Indonesia's population is Muslim and required to use the Attahiyat position to pray. In addition, some Indonesians frequently use the squatting position everyday life. We believed that our study evaluated this outcome for the first time. Our study showed no difference in functional outcomes for HHS with a good prosthesis component orientation angle whether with a safe area zone or not. However some literature has indicated otherwise such as that conducted by Fujishiro et al.[24] This is may be because the HHS itself has many aspects of assessment including pain, walking difficulties, walking aids, walking distance, interference in sitting, the ability to use public transportation, the ability to climb stairs, the ability to wear shoes, the existing deformity and Hip ROM. Prosthesis component orientation angles have the greatest influence on aspects of Hip ROM with the maximum value at only 5 for HHS (HHS maximum value of 100). HHS score >80 was categorized as the "Good to Excellent" group. Thus indirectly, the influence of the orientation angle of the prosthesis component to HHS is not great.

Another case investigated the influence by the prosthesis component orientation angle of the post-THR ROM. Studies conducted by Seki et al. [23], and D'lima et al.[24], in a three-dimensional computer model, showed that the abduction angle of the acetabulum and the anteversion combination angles at the safe zone area produced optimal THR prosthesis. This has yet to be proven in an actual patient's pelvis and the results of research on the computer model remain unproven in this study. The only significant association found was increased internal rotation in the abduction angle of the acetabulum in the non-safe zone group. However, the internal rotation of the pelvis was not a major focus because relevant literature revealed internal rotation is not an issue in the impingement prosthesis.[23] ROM pelvic post-THR is not only influenced by the prosthesis component orientation angle, but also by the head-to-neck ratio prosthesis, soft tissue tension and post-THR rehabilitation. These factors were not present in studies using computer models.

The interaction between the prosthesis component orientation angles with one component of the ROM in this study was also non-significant. For example, one study of computer models reported that the increase in abduction angle of the acetabulum would increase flexion, extension and abduction of the pelvis and lower adduction range of motion and axial rotation. However, the correlations of the test results obtained were without meaning. This indicated that studies using computer models could not simulate the real pelvis. The prosthesis component orientation angle also did not have a meaningful relationship with the patient's ability to perform Attahiyat and squatting positions, except in the safe zone group regarding abduction angle of the acetabulum where more patients were unable to perform Attahiyat or squatting positions. Basically, both positions involve a combination of various ROM, with flexion as the dominant ROM. In addition, the relationship between the prosthesis component orientation angles with Hip ROM post-THR has been known to have no meaningful relationship. Moreover, some factors remain unable to be ruled out as confounders, e.g., patients' fears, habits and obesity status.

A significant difference was found between functional outcomes and hip ROM in pre- and post-THR, with a mean score of "Good". Patients in the safe zone group regarding the acetabular abduction angle were more frequently unable to perform "Attahiyat" and squatting positions.

Conclusion

The application of the THR prosthesis component orientation angle in the non-safe or safe zone areas produced comparable results (within certain ranges) based on HHS score. The non-safe zone group showed greater internal rotation range of motion regarding the acetabular abduction angle.

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PREDICTED MALIGNANCY OF PULMONARY LESIONS USING THE TUMOR INSPECTOR PROGRAM, VERSION 1, PHRAMONGKUTKLAO HOSPITAL

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Abstract

Background: Pulmonary nodules can originate from any cause, ranging from benign to malignant. Surgical lung resectioning at the early stage of lung cancer provides the best chance for cure. As a result, establishing the etiology of pulmonary nodules accurately is critically important. Rapid identification can also avoid unnecessary surgery among patients with benign diseases. Currently, endobronchial ultrasound (EBUS) is a standard procedure used to investigate pulmonary nodules. The characteristics of pulmonary nodules from EBUS can differentiate benign from malignant. However, the interpretation of EBUS findings depends on the pulmonologists' experience. Thus, we developed and analyzed the performance of software, called "Tumor Inspector Program, Ver. 1" to help interpreting characteristics of pulmonary nodules from EBUS.

Objective: To evaluate accuracy in interpreting EBUS findings using the Tumor Inspector Program, Ver.1 compared with three pulmonology interventionists' agreements.

Methods: We conducted a cross-sectional study of patients undergoing radial-probe EBUS-guided bronchoscopy to investigate pulmonary nodules between May 2015 and December 2016, Phramongkutklao Hospital. For diagnosis, we obtained pathological tissue from bronchial brushing and transbronchial biopsy. The characteristic findings from EBUS were analyzed and diagnosed using the Tumor Inspector Program, Ver.1 and three pulmonary interventionists.

Results: Two hundred and eight patients with a mean age of 61 ± 1 years were included in the study. The pathological reports comprised 80 (38.46%) benign and 128 (61.54%) malignant cases The sensitivity, specificity, negative predictive value and diagnostic accuracy by pulmonary interventionists were 90.%, 22.5%, 60%, and 64.4%, respectively. On the other hand, the diagnosis using the Tumor Inspector Program, Ver.1 showed a sensitivity of 90.0% and specificity of 81.2%, negative predictive value of 84.4% and an accuracy of 87%.

Conclusion: Among patients with pulmonary nodules, the Tumor Inspector Program, Ver.1 had significantly higher specificity and accuracy to predict malignancy possibility than three pulmonology interventionist agreements.

Keywords : Endobronchial ultrasound, Malignancy, Pulmonary nodule

J Southeast Asian Med Res 2018; 2: 37-44.
http://www.jseamed.org

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Introduction

Bronchoscopy has been applied for decades in evaluating pulmonary nodules. Among patients with peripheral lung nodules, bronchoscopy has been reported to give variable diagnostic yields in the range of 16.7 to 65.6% through BAL, bronchial brushing cytology, or transbronchial biopsy.[1–4]

Various procedures have been developed to diagnose peripheral pulmonary lesions (PPLs). The transbronchial biopsy (TBB) procedure, using a bronchoscope under fluoroscopic guidance, has been performed since the 1970s, with 36 to 86% diagnostic accuracy.[5-9] Diagnostic accuracy is influenced by lesion size; Schreiber and Mc Crory [5] reported a systematic review revealing that the diagnostic accuracy of lesions <20 mm in mean diameter was 33%. Other studies[6-9] have reported that the diagnostic accuracy of benign lesions was 35 to 50%, lower than that of malignant lesions. So far, small-caliber, radial-type ultrasound probes can be used for clinical applications of ultrasonography to tracheal-bronchial lesions and PPLs. Endobronchial ultrasonography (EBUS) has been used for imaging guidance in the TBB of PPLs.[10-11]

In 2002, Kurimoto et al.[12] found that endobronchial ultrasonography (EBUS) images of peripheral pulmonary lesions could be visually classified in three types and six subtypes and concluded that the images helped differentiate benign and malignant lesions.

In 2007, Kuo CH et al.[13] showed that characteristics of EBUS pictures could distinguish benign and malignant tumors. The characteristic of EBUS pictures which favor malignancy include: 1) heterogeneity 2) continuous margin and 3) linear-discrete air bronchogram. When the results are positive in two of the three characteristics, that pulmonary lesion has a chance of 89.2% to be malignant. In contrast, when the results are negative for all of the three characteristics, the chance to be benign is about 93.7%. Thus, interpreted outcome depends on the pulmonologists' experience as well as pathological diagnosis. In this study, we developed a Tumor Inspector Program, Ver.1 to aid in interpreting characteristics of EBUS pictures to increase consistency, reduce time to interpret and use for treatment planning. However, the accuracy of this new program has not yet been validated. Using the pathological diagnosis as a gold standard, we aimed to evaluate the accuracy in interpreting characteristics of EBUS pictures of the Ver.1 Tumor Inspector Program compared with agreements of three pulmonary interventionists.

Methods

Study design and inclusion criteria

A cross-sectional study was conducted among patients undergoing EBUS for tissue diagnosis at Phramongkutklao Hospital. Consecutive adult patients with a clinical indication for EBUS-GS, i.e., age ≥18 years, presenting pulmonary lesions, having computed tomography (CT) scan of chest 1-1.5 mm in thickness, undergoing EBUS for the first time and having a pathological diagnosis. Exclusion criteria comprised incomplete radiological examination, undergoing previous EBUS, poor quality of video files, and other standard exclusions for EBUS (coagulopathy, uncontrolled underlying diseases, e.g., unstable cardiovascular system and hypertension). A total of 272 patients were recruited in the study from May 2015 to December 2016. Of these, 208 patients met the criteria and were enrolled in the study. All patients or their relatives provided written informed consent to participate. This study was approved by the Institutional Review Board of the Royal Thai Army Medical Department.

Study design

This trial analyzed the accuracy of predicted malignancy of pulmonary lesions between interpretation using the Tumor Inspector Program, Ver.1 and agreements of three pulmonology interventionists. For enrolled patients who met the criteria and underwent EBUS, we recorded video files while performing EBUS at a range of 4 cm. Then we assigned these video files to three pulmonology interventionists to interpret the outcomes. All three pulmonology interventionists were blinded for each interpretation as well as patients' medical records. Simultaneously, these video files were assigned to interpreted outcomes using the Tumor Inspector Program, Ver.1.

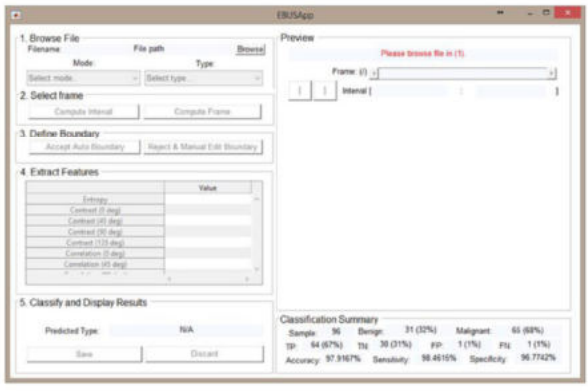
Data interpretation using three pulmonology interventionists

Before interpreting all video files, we provided standardized EBUS pictures of 20 cases for the three pulmonology interventionists to practice to achieve consensus for each characteristic. In addition, we assigned video files to three pulmonology interventionists. Each video file was interpreted

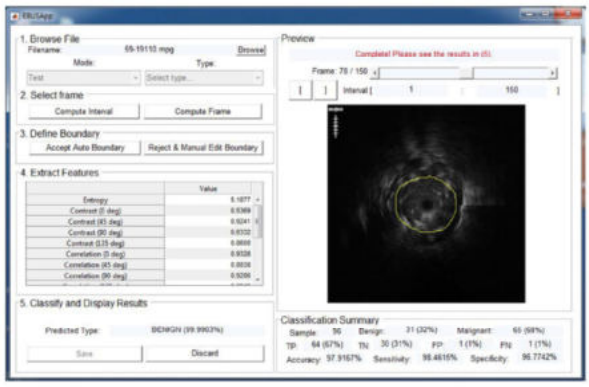
simultaneously and based on characteristics of EBUS pictures, i.e., heterogeneity, continuous margin, linear discrete air bronchogram, arcs, dots, anechoic and provisional diagnosis (benign or malignant). Their independently interpreted outcomes without knowing patients' medical record were compared. The agreement diagnoses of two of three pulmonary interventionists were compared with the pathological diagnosis to evaluate the sensitivity, specificity and accuracy.

Data interpretation using the Tumor Inspector Program, Ver.1

After patients underwent EBUS, videos were recorded at 4 cm in range. We selected file videos simultaneously and assigned three pulmonologists to interpret the outcomes. **Picture 1** shows the screen of the Tumor Inspector Program, Ver.1. The boundary was the next step that was chosen for an auto or manual boundary. In this study, we used a manual boundary and a region of interest, which was 2 cm in radius (or 4 cm in diameter) from the center. Using an auto boundary, a lesion that was larger than 4 cm in range could not be used. After completing the manual boundary, the Tumor Inspector Program, Ver.1 was used to analyze the outcome as shown in **Picture 2**. A circle was drawn five times for data analysis and the outcomes were chosen, which were predominant as a provisional diagnosis. Finally, we compared these outcomes with the pathological report to evaluate the sensitivity, specificity, negative predictive value and diagnostic accuracy.



Picture 1. Window of tumor inspector program, Version 1



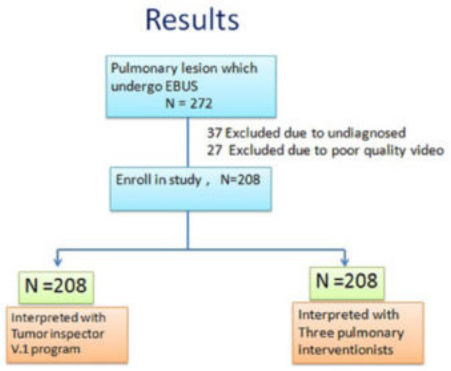
Picture 2. Window of tumor inspector program, Version 1

Data analysis

Categorical data were compared using Chi-square or Fisher's exact test. To determine the accuracy, sensitivity and specificity and differences between both groups, Pearson's Chi-squared test analysis was performed. Fisher's exact test was used for baseline characteristics, presented as mean, median (IQR; interquartile range) and proportion (%). For inter-observer correlation, 208 patients were analyzed using three different pulmonology interventionists. Inter-observer correlation was assessed by measuring outcomes which were interpreted by three pulmonology interventionists simultaneously. Inter-observer correlation coefficients were used at the following cut-off points; <0.5 = fair agreement, 0.51-0.75 = moderate agreement and >0.75 = substantial agreement. Statistical significance was set at p-value <0.05. Data analyses were performed using the SPSS, Version 23 and Stata, Version 14.

Results

Two hundred and seventy-two patients were screened for the inclusion criteria. Of these, 208 patients were enrolled in the study. Sixty-four patients were excluded because 37 had no pathological diagnosis and 27 had poor quality video files. Subject enrollment, exclusion and analyses are summarized in a flowchart **(Fig 1)**.



Baseline characteristics of patients are shown in **Table 1**. Most patients had age more than 60 years (58.65%), and mean age was 61.9 years. More than one half were male (60.58%), nonsmokers (40.87%), had no history of airway or structural lung diseases (87.02%) and no history of any cancers (83.65%).

Baseline characteristics of EBUS pictures are shown in **Table2**. Tumor sizes more than 3 cm totaled 55.7%. Most characteristics of EBUS pictures were heterogeneity (89.9%), incomplete margin (75.50%), present dots (54.3%), absent arcs (55.8%), absent air bronchogram (94.2%) and absent anechoic (63.8%). Statistically significant differences of the specificity, accuracy, positive predictive value and negative predictive value were observed between both methods. The specificity was higher using the interpretation by the program showing 22.5% by pulmonology interventionists' consensus and 81.25% using the Tumor Inspector Program, Ver.1 (p <0.001). The accuracy was higher using the program, i.e., 64.42% by pulmonology interventionists' consensus and 87.02% using the Tumor Inspector Program, Ver.1 (p <0.001). The positive predictive value (PPV) and negative predictive value (NPV) were higher using the program. In pulmonology interventionists' consensus, PPV and NPV were 65.2% and 60%, respectively while using the Tumor Inspector Program, Ver.1, PPV and NPV were 88.54% and 84.41%, respectively (p = <0.001 and 0.007, respectively). However, no significant difference in sensitivity was observed between the two methods. The sensitivity was 90.6%, performed by pulmonology interventionists and 90.62% using the Tumor Inspector Program, Ver.1 (p = 1.00) **(Table 3)**.

Table 1. Baseline characteristics of the enrolled patients

Characteristics		N	%	Mean
Age group	<30	7	3.37	
	31-60	79	37.98	
	>60	122	58.65	
Age				61.90
Sex	Male	126	60.58	
	Female	82	39.42	
Previous pulmonary disease	Old lung disease	11	5.29	
	Airway disease	16	7.69	
	No both	181	87.02	
Pulmonary disease	Asthma	2	0.96	
	Bronchiectasis	3	1.44	
	COPD	16	7.69	
	NTM or Pulmonary tuberculosis	2	0.96	
	Old pulmonary tuberculosis	4	1.92	
Smoking	Yes	34	16.35	
	No	85	40.87	
	Not record	29	13.94	
	Ex-smoker	60	28.85	
Previous Cancer	Present	34	16.35	
	Absent	174	83.65	

Table 2. Baseline characteristics of EBUS pictures

		N	%
Tumor size	<3 cm	92	44.23
	>=3	116	55.77
Echogenicity	Homogenous	21	10.10
	Heteogenous	187	89.90
Margin	Complete	51	24.50
	Incomplete	157	75.50
Dots	Yes	113	54.30
	No	95	45.70
Arcs	Yes	92	44.20
	No	116	55.80
Air bronchogram	Yes	12	5.80
	No	196	94.20
Anechoic	Yes	75	36.20
	No	132	63.80

Table 3. Sensitivity, specificity, accuracy, PPV and NPV between tumor inspector program and agreement of three pulmonology interventionists

	Pulmonology interventionists	Tumor inspector program	*p*-value
Sensitivity	90.60%	90.62%	1.00
Specificity	22.50%	81.25%	<0.001
Accuracy	64.42%	87.02%	<0.001
PPV	65.20%	88.54%	<0.001
NPV	60%	84.41%	0.007

In addition, we also analyzed the correlation among three pulmonology interventionists and predominant characteristics of EBUS pictures. For the inter-observer correlation, we found that each characteristic of EBUS pictures included echogenicity, dots and anechoic exhibiting fair agreement (ICC = 0.30, 0.43, and 0.46; $p = 0.001$, <0.001 and <0.001, respectively) and continuous margin, arcs and air bronchogram showed moderate agreement (ICC = 0.73, 0.60 and 0.52; all had p <0.001, respectively). Whereas, outcomes from each of three pulmonology interventionists revealed fair agreement (ICC= 0.14; $p = 0.098$), as shown in **Table 4**.

We also observed the predominant characteristic of EBUS pictures favoring malignancy from the interpretation using three pulmonology interventionists. No significant difference favoring malignancy was found among all characteristics of EBUS pictures . Heterogeneity was 90.63% in malignant cases and 88.75% in benign cases (p = 0.66; 95% CI = 0.49-3.05). Complete margin was 74.22% in malignant cases and 77.50% in benign cases which did not differ significantly (p = 0.88; 95% CI = 0.62-2.31). Linear discrete air bronchogram was 7.03% in malignant cases and 3.75% in benign cases (p = 0.28; 95% CI= 0.51-7.40), as shown in **Table 5**.

Table 4. Inter-observer correlation coefficient model among three pulmonology interventionists.

	ICC	**95%CI**		***p*-value**
Echogenicity	0.30	0.12	0.45	0.001
Margin	0.73	0.66	0.79	<0.001
Dots	0.43	0.28	0.55	<0.001
Arcs	0.60	0.50	0.69	<0.001
Air bronchogram	0.52	0.39	0.62	<0.001
Anechoic	0.49	0.35	0.60	<0.001
Outcome	0.14	-0.08	0.33	0.098

Table 5. Predominant characteristic patterns which favor benign or malignancy

		Pathology							
		Malignancy		Benign					
Human agreement		N	%	N	%	OR	95%CI		*p*-value
Echo	Heterogenous	116	90.63	71	88.75	1.26	0.49	3.05	0.660
	Homogenous	12	9.38	9	11.25				
Margin	Complete	33	74.22	62	77.50	1.20	0.62	2.31	0.880
	Incomplete	95	25.78	18	22.50				
Dot	Yes	70	54.69	43	53.75	1.04	0.59	1.82	0.900
	No	58	45.31	37	46.25				
Arcs	Yes	53	41.41	39	48.75	0.74	0.42	1.30	0.300
	No	75	58.59	41	51.25				
Air bronchogram	Yes	9	7.03	3	3.75	1.94	0.51	7.40	0.280
	No	119	92.97	77	96.25				
Anechoic	Yes	50	39.37	25	31.25	1.43	0.79	2.58	0.240
	No	77	60.63	55	68.75				

Discussion

This cross-sectional study investigated the accuracy of the first developed program (Tumor Inspector Program, Ver.1) which interpreted characteristics of EBUS pictures compared with agreements among three pulmonology interventionists. All enrolled patients underwent EBUS for the first time at Phramongkutklao Hospital from May 2015 to December 2016. In this study, we found that the interpretation between the Tumor Inspector Program, Ver.1 and the three pulmonology interventionists showed no significant difference for the sensitivity, but significantly differed in specificity, accuracy, positive predictive value and negative predictive value. These could be explained by the difference of experiences among the three pulmonology interventionists. Before reading all video files, case practices were preliminary provided for the three pulmonology interventionists. Using the Tumor Inspector Program, Ver.1 by one operator was more feasible and easy to perform because it did not depend on human experience. This program could be used as diagnostic test for pulmonary lesions among patients undergoing EBUS. In this study, fewer benign cases were enrolled; thus, we suggest using clinical characteristics, history of risk factors and tumor doubling time to follow up those cases presenting benign results. In addition, we also observed characteristics of EBUS pictures of malignant cases, reported by Kurimoto et al.[12] and Kuo et al.[13] In this study, the characteristics of EBUS pictures didn't reveal the predominant pattern favoring malignant or benign cases. These can be explained by the different experiences of the three pulmonology interventionists to read the video files because mild to moderate agreement was recorded.

In this study, an under diagnosis of benign pulmonary lesions could have occurred due to the fewer cases of benign lesions. In addition, cases presenting pulmonary lesions larger than 4 cm using the ultrasound range or cases having the ultrasound probe adjacent to the lesion could cause a problem when analyzing video files. Notably, the region of interest chosen was about 2 cm in diameter from the center. The Tumor Inspector Program Ver.2 was used to correct these weak points and gain more accuracy to detect benign pulmonary lesions. Thus, a further study is needed, which should be based on clinical manifestations, other risk factors, e.g., smoking behavior, history of contact tuberculosis, history of cancer, characteristics of CT lesion etc. However, limitations were observed in this study, that is, variable quality of video records as well as unequal experiences of the three pulmonology interventionists.

Conclusion

Among patients with pulmonary lesions, the Tumor Inspector Program, Ver.1 showed significantly higher accuracy to predict malignancy possibility than that of the three pulmonology interventionists.

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A REAL WORLD MANAGEMENT OF PATENTS WITH OSTEOARTHRITIS KNEE UNDERGOING TOTAL KNEE REPLACEMENT – A RETROSPECTIVE STUDY IN THAILAND (ARMOR STUDY)

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Abstract

Background: In Thailand, total knee replacement (TKA) is a common clinical intervention to manage patients with OA (osteoarthritis). Public and private hospitals tend to exhibit different patterns of TKA use. Hence, knowledge with regard to TKA practice patterns, use and treatment outcomes in different hospitals in Thailand will improve the understanding of clinical management of OA and patient care.

Objectives: The primary objective of the study was to examine the patterns of pain management during pre-operative, hospital admission for TKA, and postoperative periods (surgery to 3 months after discharge) for patients receiving TKA in public and private hospitals. The data were collected from various hospitals and subjected to analysis.

Methods: This retrospective observational multi-center chart review study was conducted in public (n=2) and private (n=2) hospitals in Thailand. A total of 220 patients diagnosed with knee OA (ICD-10 code, M17.0 and 17.1) who had undergone TKA were included in the study. The estimated ratio of patients from public and private hospitals was 1:1. Patient medical charts were accessed with the Ethics Committee's approval. De-identified patient data were extracted from the chart and entered into a paper Case Report Form (CRF). Patients with history of major cardiovascular events and bilateral total knee replacement were excluded from the study.

Results: At clinical baseline, cyclooxygenase-II (COX-II) inhibitors followed by traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) were the preferred drug classes for pain management irrespective of hospital type or age group. At operation, use of pain control drugs was comparable between public and private hospitals. The use of concomitant drugs such as antithrombotic agents was observed to be frequent in both the hospital types and different age groups. After surgery, use of opioids was the highest among other drug classes followed by COX-II inhibitors and tNSAIDs; however, the use of opioids decreased faster daily compared with COX-II inhibitors which remained constant until 4 days after surgery. Among discharge pain control medications, analgesics and opioids were used extensively followed by COX-II inhibitors; however, the use of NSAIDs was very limited because of associated complications. During the follow-up period, opioids were the most commonly prescribed drug class in both hospital types; use of COX-II inhibitors was significantly higher in private hospitals The same trend of drug use was observed by age group (both >70 and <70 years of age). The proportion of patients with complications was observed more in public hospitals as compared with private settings. In the present study, patients receiving COX-II-inhibitors combined with other pain control medications reported lower pain scores than average after surgery. The clinical outcome distribution among patients receiving multiple pain control drugs during discharge was observed to be better compared with other combined regimens or analgesics alone.

Conclusion: Pain management is one of the most important and challenging aspects of TKA. The patterns of pain management during pre-operative, during operation and postoperative stages differed. The use of COX-II inhibitors followed by NSAIDs was observed to be higher in the pre-operative stage, while use of opioids was higher after surgery and follow-up period compared with COX-II inhibitors.

Keywords : Total knee arthroplasty, Total knee replacement, Knee osteoarthritis, Pain management

J Southeast Asian Med Res 2018; 2: 45-57.
http://www.jseamed.org

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Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal disorders that impact patients' quality of life. It causes permanent disability, especially among the elderly. [1] Research on defining optimal outcomes in pain management is still in its infancy and more understanding is needed. Generally, the main treatment goals for management of pain, both acute and chronic, are to relieve pain, facilitate function and improve quality of life. Achieving a pain-free state is challenging and unrealistic as a treatment goal. For optimal results, the treatment plan should be tailored to the needs, desires and circumstances of individual patients.

Nonoperative therapies, namely, pharmacological and nonpharmacological treatment modalities, [2-5] have been found to be effective and convenient in helping OA patients achieve pain relief. In Thailand, traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) and selective cyclooxygenase (COX)-II inhibitors are usually prescribed to patients with OA to control pain. Due to the low cost, tNSAIDs are one of the most common drugs used for pain relief among patients with OA. Although tNSAIDs are effective in controlling pain in mild to moderate OA, they were also found to cause peptic ulceration and life threatening complications such as hemorrhage and perforation due to its nonselective action on COX-I. The risk of these side effects increases with long term use. Recently, COX-II selective inhibitors have been recommended for pain management among patients with high risk of adverse drug events from tNSAIDs.[6-9] This is because COX-II inhibitor drugs only inhibit the COX-II isoenzyme, which is released during inflammation. Therefore, COX-II inhibitor drugs are able to control pain without increasing the risk of bleeding and gastrointestinal complications. However, in Thailand, patients with OA pain have limited access to COX-II inhibitors due to the lack of reimbursement. The COX-II inhibitor drugs are currently in a controlled list of government drug use evaluation (DUE). The study by Philip G and colleagues indicated that approximately 54% patients had moderate to severe pain while on the currently prescribed pain treatments (most commonly NSAIDs, followed by paracetamol and opioids); and therefore, presents a high unmet need in the pain management in patients with knee OA[10]. Therefore, when more serious joint deformity occurs and pain is uncontrolled, operative options like total knee arthroplasty (TKA) or total knee replacement are considered.

TKA is an elective surgery, indicated for disability, pain and limited function from OA, rheumatoid arthritis, or any type of arthritic knee deformity. This surgery has to be considered in light of the patient's symptoms, current health status and radiographic evidence of primary or inflammatory degenerative joint disease. The latter is shown as narrowed joint space, osteophytes (spurring) and bone cysts, squaring of condyles and bone sclerosis. [11] As TKA is an elective surgery, the decision to pursue TKA could be subjective, depending upon the physician's opinion /practice and patients' conditions, as well as patients' response to other treatment options.[12] No age or weight limit exists for a patient to undergo TKA. Operations have been successfully performed among young patients with juvenile arthritis and among elderly patients with degenerative arthritis.[12] Postoperative pain management is also important, as related research has demonstrated that poor acute pain control after TKA could

lead to long term chronic pain.[13] Therefore, effective acute pain control with analgesia or anesthesia techniques should be provided.

Methods

This study was a retrospective, observational multi-center chart review study conducted in public and private hospitals in Thailand. Patient data were identified and extracted using ICD-10 and/or procedural codes that were used at each institution.

Study population

A total of approximately 220 male and female patients with OA were included in this study. The study was conducted in four medical centers in Bangkok – two public hospitals (Phramongkutklao Hospital and Ramathibodi Hospital) and two private hospitals (Bangkok Hospital and Bumrungrad Hospital). A hundred and ten patients were selected from public and private sectors. Eligible patients comprised patients with OA who had undergone TKA between January 2014 and December 2015, and were randomly selected for chart review. All related data were extracted from the chart and entered into an approved paper Case Report Form (CRF). The Ethics Committee's approval was obtained from each institute before accessing patient medical charts.

Inclusion Criteria

Patients' inclusion criteria included aged >35 years, with a diagnosis of OA of the knee (ICD-10 code, M17.0 and 17.1) and who had undergone unilateral total knee replacement. Patients had a regular clinical record at the study site.

Exclusion Criteria

Patients' exclusion criteria included having a history of major cardiovascular events, i.e., acute MI, unstable angina, congestive heart failure, history of total knee replacement (same side) or bilateral total knee replacement. Patients with incomplete/insufficient data required for the primary objective were also excluded.

Data collection

Investigators and designees extracted data from medical charts of eligible patients. Paper CRFs were used in this study. In compliance with Thailand FDA and relevant private information protection laws, confidentiality of protected health information was maintained by all parties throughout the study. All data were secured against unauthorized access. Data were de-identified with a unique identifier on each patient's CRF and other study records were sent to MSD.

Statistical analysis

Before conducting analyses for specific objectives, descriptive statistics for all demographic characteristics, hospital type and presence of comorbidities were carried out. These included mean, standard deviation, median, interquartile range and minimum/maximum for continuous variables and proportions with standard deviations for categorical variables. Statistical significance was set at $p<0.05$.

Sample Size Calculation

The sample size of 220 was estimated using Yamane's formula. Based on a population of 390 patients, precision of ± 5% and 95% confidence level, at least 197 subjects were required for the study.

Results

The results were reported according to primary and secondary objectives. The primary objectives were to examine the use of drugs to manage pain during pre-operative, operation and postoperative periods. The secondary objectives were to evaluate resource use, pain score, clinical outcomes and waiting time to TKA.

Demographics of study population

Table 1 shows the demographics of eligible patients. Though the baseline characteristics of the patients visiting public and private hospitals were comparable, differences were observed in the presentation of symptoms, with private hospitals seeing more patients presenting severe symptoms. Symptom severity was assessed based on clinical judgment recorded in a chart.

Table 2 depicts the proportion of patients with different insurance schemes. The majority of the patients visiting public hospitals were covered under the CSMBS insurance scheme (66.36%), followed by UCS (10.9%). Approximately 87% patients visiting private hospitals incurred out-of-pocket expense compared with only 20% patients visiting public hospitals.

Table 1. Baseline characteristics of patients visiting public and private hospitals

Characteristics	All patients (%)	Public Hospital (%)	Private Hospital (%)	*p*-value
Arthritis	0.45	0.00	0.91	0.3171
Autoimmune diseases	0.00	0.00	0.00	1
Other metabolic syndrome	10.91	9.09	12.73	0.3876
CNS	0.91	0.91	0.91	1
Respiratory disease	0.45	0.91	0.00	0.3171
Other**	19.55	29.09	10.00	.00038*

*Statistical significance at $p<0.05$

** Others include Delirium, BPH, AIHA, Glaucoma, Anemia and CVA

Table 2. Different insurance schemes and reimbursement statuses

		All patients		**Public Hospital**		**Private Hospital**	
		n	**%**	**n**	**%**	**n**	**%**
Gender	Male	53	24.09	20	18.18	33	30.60
	Female	167	75.91	90	81.82	77	70
Public Insurance Scheme or source of funding for QA treatment	Universal Coverage Scheme (UCS or 30 Baht-Scheme)	12	5.46	12	10.91	0	0
	Social Security Scheme (SSS)	3	1.37	3	2.73	0	0
	Civil Servant Benefit Scheme (CSMBS)	73	33.18	73	66.36	0	0
	None	132	60.0	22	20	110	100
Private insurance	yes	10	4.55	1	0.91	9	8.18
Out-of-pocket	yes	118	53.64	22	20	96	87.27
Reimburse from employer	yes	5	2.28	0	0	5	4.55

Pain management during the pre-operative period

Table 3 compares the patterns of pain management for OA by hospital type (public and private hospitals) at clinical baseline. Public hospitals were more likely to prescribe COX-II inhibitors, tNSAIDs and opioids, as well as combined therapies including tNSAIDS+COX-II inhibitors and tNSAIDS+opioids compared with private hospitals. Private hospitals were also more likely to prescribe paracetamol (9.09%) than public hospitals (4.55%).

Table 4 details the proportion of patients on various therapies by age group (≥70 versus <70 years) at clinical baseline. Patients aged ≥70 years were more likely to be prescribed opioids (5.88%) as compared with patients aged <70 years (2.97%). Similarly, tNSAIDS+COX-II inhibitors were prescribed more frequently among patients aged ≥70 years.

Table 3. Percentage of patients on pain drug therapy at clinical baseline by hospital type

Drug Class	% of patients receiving drug therapy at clinical baseline			
	All patients (n=220)	Public Hospital (n=110)	Private Hospital (n=110)	*p*-value
Paracetamol	6.82	4.55	9.09	0.1827
tNSAIDs	10.45	11.82	9.09	0.5091
COX-II inhibitors	17.27	23.64	10.91	0.0127*
Opioids	4.55	6.36	2.73	0.1972
Paracetamol+ tNSAIDs	1.82	0.91	2.73	0.3137
Paracetamol+ COX-II inhibitors	5.91	9.09	2.73	0.0460*
Paracetamol+ Opioids	1.82	2.73	0.91	0.3137
tNSAIDs+ COX-II inhibitors	3.64	6.36	0.91	0.0312*
tNSAIDs+ Opioids	1.82	3.64	0	0.0439*
COX-II inhibitors + Opioids	1.36	2.73	0	0.0817
Paracetamol+ tNSAIDs+ COX-II inhibitors	1.36	0.91	1.82	0.5617
Other medications	9.55	10.91	8.18	0.4918
No pain medication	33.64	16.36	50.91	<0.0001*

*Statistical significance at $p<0.05$

Table 4. Proportion of patients on drug class at medication after operation by hospital type (discharge clinical baseline by age group medication)

Drug Class	% of patients on therapy at clinical baseline by age group		
	≥70 years old (n=119)	≤70 years old (n=101)	*p*-value
Paracetamol	9.24	3.96	0.1223
tNSAIDs	11.76	8.91	0.4921
COX-II inhibitors	19.333	14.85	0.3821
Opioids	5.88	2.97	0.3028
Paracetamol+ tNSAIDs	0	3.96	0.0288*
Paracetamol+ COX-II inhibitors	5.04	6.93	0.5544
Paracetamol+ Opioids	1.68	1.98	0.8685
tNSAIDs+ COX-II inhibitors	4.20	2.97	0.6279
tNSAIDs+ Opioids	1.68	1.98	0.8685
COX-II inhibitors + Opioids	1.68	0.99	0.6608
Paracetamol+ tNSAIDs+ COX-II inhibitors	0.84	1.98	0.4685
Other medications	10.92	7.92	0.4514
None prescribed	27.73	40.59	0.0447

*Statistical significance at $p<0.05$

Pain management during operation

Drug use pattern related to TKA during operation by hospital type. While both public and private hospitals prescribed antibiotics, differences were observed in the prescription of other concomitant drugs. While antihistamines and bone and muscle-related drugs were often prescribed in public hospitals, private hospitals were more likely to prescribe antithrombotic and GI-related drugs than public hospitals.

The use of pain control drugs at discharge was almost similar in both public and private hospitals. Among concomitant drugs, the use of bone-related drugs (38% vs. 5%, $p<0.0001$) and antibiotics (77% vs. 35%, $p<0.0001$) were higher in public hospitals compared with private hospitals. However, the use of antithrombotic drugs was almost twice as high in private hospitals compared with public hospitals (65% vs. 35%, $p<0.0001$). On average, physicians prescribed discharge pain medication for 9.13 days across hospitals.

Table 5 shows the pain control drug prescription during discharge by hospital type. In public hospitals, the majority of patients received analgesic drugs (71%) or analgesic +opioids (50%), whereas patients in private hospitals were more likely to receive COX-II inhibitors during discharge. At discharge, private hospitals prescribed more COX-II inhibitors than public hospitals ($p=0.0006$).

Table 5. Distribution of pain control drugs related to TKA during operation by hospital type and operation by hospital types (discharge medication)

Drug type	% of patients on discharge medication after operation			
	All patients (n=220)	Public Hospital (n=110)	Private Hospital (n=110)	*p*-value
COX-II inhibitors	40.5	29.1	51.8	0.0006*
tNSAIDS	18.2	1.8	34.5	0.0059*
Muscle relaxant	12.7	12.7	12.7	0.00068*
Opioids	26.4	18.2	34.5	0.138
Analgesic drug plus opioid	47.7	50.0	45.5	0.5
Analgesic drug	62.7	70.9	54.5	0.0121*
Others**	9.1	5.5	12.7	0.064

*Statistical significance at $p<0.05$

** Others include perskindol spray and repagril

Pain management in the postoperative period (follow-up period)

Among all drug classes, opioids were the most frequently prescribed in the postoperative period (at three-month follow-up) in both public and private hospitals. Private hospitals relied more on prescribing COX-II inhibitors (71% vs. 47%, p=0.0004), tNSAIDs (42% vs. 21%, p=0.0009) and analgesics (90% vs. 75%, p=0.0028) as compared with public hospitals.

In pre-operative, during admission, and postoperative periods, both public and private hospitals had similar testing requirements. Therefore, the laboratory measurements were comparable for patients attending public and private hospitals.

The rate of complications in the postoperative setting was higher in public hospitals as compared with private settings (2.73% vs. 0.91%). Private hospital patients were more likely to report urinary tract infection (UTI) while patients from public hospitals were more likely to report deep vein thrombosis (DVT), pulmonary embolism and congestive heart failure (CHF).

Pain score

During the pre-operative period, mean pain score at public and private hospitals were comparable (2.32 vs.2.99, respectively).

Table 6 summarizes the pain score and drug use pattern to control pain after surgery by hospital type. Use of opioids decreased daily in both public and private hospitals.

However, the use decreased at a higher rate in public hospitals as compared with private ones. Pain score was comparatively higher in public hospitals than private hospitals and decreased over subsequent days in both hospital types.

Table 7 shows the mean time from decision to TKA was shorter in private hospitals compared with public hospitals (22.9 days vs. 171.5 days, $p < 0.0001$).

Table 6. Pain score and drugs used to control pain after surgery

Day		All patients	Public Hospital	Private Hospital
Day 1	Mean pain score	3.78	4.79	2.76
	IV tNSAIDs (%)	11.36	13.64	9.09
	Oral tNSAIDs (%)	10.91	2.73	19.09
	Opioids (%)	69.09	70.00	68.18
	COX-II (%)	36.36	22.73	50.00
	Paracetamol (%)	54.55	47.27	61.82
	Others* (%)	22.27	23.64	20.9
Day 2	Mean pain score	3.44	4.15	2.63
	IV tNSAIDs (%)	5.94	5.45	6.42
	Oral tNSAIDs (%)	11.82	1.82	21.82
	Opioids (%)	64.55	62.73	66.36
	COX-II (%)	35.21	24.55	45.87
	Paracetamol (%)	53.64	45.45	61.82
	Others* (%)	22.27	23.64	20.91
Day 3	Mean pain score	2.80	3.22	2.3
	IV tNSAIDs (%)	1.99	1.00	2.97
	Oral tNSAIDs (%)	13.18	1.82	24.55
	Opioids (%)	53.91	50.00	61.82
	COX-II (%)	33.77	22.00	45.54
	Paracetamol (%)	47.73	32.27	58.18
	Others* (%)	14.55	10.00	19.09
Day 4	Mean pain score	2.48	2.78	2.22
	IV tNSAIDs (%)	1.90	0	3.80
	Oral tNSAIDs (%)	8.18	0	16.36
	Opioids (%)	31.36	23.64	39.09
	COX-II (%)	32.05	21.05	43.04
	Paracetamol (%)	37.92	28.57	47.27
	Others* (%)	7.73	4.55	10.91
Day 5	Mean pain score	2.08	2.79	1.73
	IV tNSAIDs (%)	1.45	0	2.90
	Oral tNSAIDs (%)	6.82	0	13.64
	Opioids (%)	20.00	10.91	29.09
	COX-II (%)	25.72	16.67	34.78
	Paracetamol (%)	22.73	8.18	32.27
	Others* (%)	4.55	0.91	8.18

*Others include analgesic combination drugs, neurology, muscle relaxant drugs

Table 7. Mean time to TKA (from TKA decision date to surgery)

Time to TKA (from TKA decision date to surgery)	All patients (%)	Public Hospital (%)	Private Hospital (%)
Mean (day)	97.2	171.5	22.9
Min (day)	0	8	0
Max (day)	695	695	187
SD (day)	130.85	147.2	39.2

Length of hospital stay (post TKA)

Average admission duration (post TKA until discharge) after TKA in both public and private hospitals was also studied. The majority of patients (~85%) stayed in hospitals around three to six days. Only 8% of patients stayed in hospitals for one to two days.

Clinical Assessment of knee function after TKA during the postoperative (follow-up) period

Table 8 reports the clinical assessment and patient reported outcomes (PRO) including pain assessment during the postoperative (follow-up) period in both public and private hospitals. More patients in public hospitals experienced pain as compared with private hospitals, albeit not statistically significant (6.4% vs. 3.6%, p = 0.3412). A significantly higher proportion of patients were found able to walk but with a cane in private hospitals compared with public hospitals (17.3% vs. 7.3%, p = 0.0238).

Overall, patients who were prescribed analgesics only were the most likely to experience pain (21%), followed by analgesics+ analgesics plus opioid combination (12%). A high proportion of patients (ranging from 64% to 79%) reported overall good outcomes while on COX-II inhibitor combinations. A lower proportion of patients on COX-II inhibitor combinations (ranging from 0%-14%) reported issues with flexion/extension compared with the overall range of 0% to 63%. No patient reported issues with surgery wound while on COX-II inhibitor combination, except for COX-II inhibitors + analgesics plus opioid (12% of patients reported some issues).

Table 8. Pain outcomes in public and private hospitals after TKA during the postoperative (follow-up) period

Assessment	All patients (%) (n=220)	Public Hospitals (%) (n=110)	Private Hospitals (%) (n=110)	p-value
Reported pain	5.0	6.4	3.6	0.3412
Overall good outcomes	63.2	60.9	65.5	0.4777
Reported some issue with flextion/extention	15.9	18.2	13.6	0.3523
Able to walk but need cane	12.3	7.3	17.3	0.0238*
Reported some issue with flextion/extention	2.3	0.9	3.6	0.1770

*Statistical significance at p<0.05

Discussion

The objectives of the study were to examine the patterns of pain management during pre-operative, hospital admission for TKA, and postoperative periods among patients with knee OA receiving unilateral TKA in public and private hospitals. The baseline characteristics for patients visiting public and private hospitals were largely comparable. Notable differences between the two groups were: (i) severity of OA, with more patients presenting severe OA in private hospitals (78%) than in public hospitals (59%) and (ii) out-of-pocket expenses, with more private hospital patients (87%) incurring private expenses than public hospital patients (20%).

In this study, baseline medication was collected to elicit an understanding on the OA treatment before TKA. The present study showed that among patients overall (both public and private hospitals combined), at clinical baseline, use of COX-II inhibitors was highest followed by tNSAIDs. By hospital type, use of COX-II inhibitors and combined therapies including paracetamol+ COX-II inhibitors, tNSAIDS+COX-II inhibitors and tNSAIDS + opioids were higher in public than private hospitals. In contrast, paracetamol prescriptions were almost twice in private hospitals compared with public hospitals (9.09% vs. 4.55%). Of note, 50% of patients from private hospitals had no record of OA medication for pain management. No statistically significant differences were observed in the medications prescribed to both aged ≥70 years and <70 years, which could indicate a consistent treatment guideline regardless of age. However the proportion of patients receiving COX-II inhibitors was higher compared with tNSAIDs. This could be due to the side effect caused by the long term use of tNSAIDs. During the operation period, among patients overall, use of antibiotics followed by GI related drugs and antithrombotics were observed to be high. Use of pain control drugs at operation was similar between public and private hospitals (20% vs. 20.9%). The present study also showed a high use of antithrombotics as concomitant drugs during the perioperative period across hospitals and different age groups. The findings are consistent with the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, which recommend the use of antithrombotic drugs as a prophylaxis measure to reduce the outcomes of fatal and symptomatic pulmonary embolism and symptomatic DVT in patients with TKA.(14) The pattern of drug use at operation was similar across different age groups, except for bone- and muscle-related drugs, which was significantly reported to be higher among patients aged ≥70 years, compared with patients <70 years of age (25.21% vs. 9.9%). The multimodal approach was commonly used to achieve synergistic effects in managing pain for patients with TKA.[15] In this study, various combinations of pain control drugs were used in Thai clinical practice after surgery. Among the different combinations, in both public and private hospitals combined, opioids combinations (with paracetamol and with COX-II inhibitors) were found to be the most common combined pain regimen to be used after surgery. Patients who received COX-II inhibitors as one of their pain control regimens reported lower pain scores than the mean pain scores in the cohort, particularly on Day 1 after surgery and therefore, could be considered as the most effective pain control combined regimen. Patients receiving COX-II inhibitors combined with other drugs reported the lowest average score within five days after surgery. This finding was consistent with the study conducted by Peter Lierz et al. demonstrating that the pain intensity among patients taking COX-II inhibitor (etoricoxib) was reduced during the first postoperative day. Approximately 97% of patients in the etoricoxib group achieved successful pain management compared with only 73% patients in placebo group.[16] It was also observed that use of opioids was gradually decreased in both public and private hospitals. This could be explained by the potential side effects of opioids and the narrow risk-benefit ratio. Opioids should be used sparingly and only for short duration, as long term use may lead to dependence and addiction.[17] In contrast, COX-II inhibitors were consistently prescribed during the first four days after surgery.

The present analysis showed that among different drug categories prescribed at discharge, among patients overall, the highest proportion were on pain control drugs followed by antibiotics. A similar trend was followed by public and private hospitals individually. Among the pain controlled medications prescribed at hospital discharge, analgesics and opioids were used extensively followed by COX-II inhibitors among patients overall as well as in both the public and private hospitals analyzed separately. The prescription

of COX-II inhibitors, tNSAIDs and opioids were higher in private hospitals compared with public hospitals. The use of tNSAIDs was limited during the discharge period in both public and private hospitals. This could be because of the concern for postsurgical gastrointestinal or bleeding complications, the most common adverse event of tNSAIDs.[7, 8, 18] Therefore, COX-II inhibitor is one of the primary choices for controlling pain after surgery. A randomized, double-blind study conducted by Rasmussen and colleagues suggested that the use of etoricoxib (COX-II inhibitor) resulted in superior analgesic effect compared with placebo in the acute postsurgical setting.[19] On average, physicians prescribed discharge pain medication for 9.13 days across studied hospitals. At three-month follow-up, most patients from all studied hospitals had good overall outcomes and were able to walk with a cane. Some were found to have issues with flexion/ extension and experienced mild pain symptoms, which are common symptoms during the first few months after surgery.[20] The prescribing patterns were almost similar for both age groups, except that patients aged <70 years (63.37% vs. 55.46%) being more likely to be prescribed with COX-II inhibitors than those aged ≥70 years. Complication rates were also higher in public hospitals as compared with private settings (2.73% vs. 0.91%). The complications reported were mainly UTI, DVT, pulmonary embolism and CHF. During the follow-up period, among different pain medications prescribed, opioids were the most commonly prescribed drug class among patients overall as well as in public and private hospitals analyzed separately, with the use being higher in private hospitals. Use of COX-II inhibitors, tNSAIDs and opioids was also observed to be higher in private hospitals as observed during the discharge period. These findings were consistent with public and private payers.

Among patients overall (both public and private hospitals combined), clinical outcome distribution during the follow-up period among patients receiving a combination of pain control drugs during discharge tended to be better compared with other combined regimens or analgesics alone. Considering the types of pain control drugs, the results demonstrated that patients with discharge prescriptions of COX-II inhibitors combined with other pain treatments were more likely to achieve pain control than patients receiving analgesics (paracetamol) alone or analgesics plus opioids during the follow-up visit. No patient receiving COX-II inhibitors, tNSAIDs or opioids in both hospital types reported any issues with surgery wound. Patients taking opioids were most likely to report some issues with flexion/extension, while patients on COX-II inhibitors were the least likely. This was consistent with the finding from a study by Arendt-Nielsen et al., reporting that patients with knee OA on COX-II inhibitor (etoricoxib) therapy experienced improvement in pain control during walking/stair climbing and reported lower general pain scores compared with those taking placebo.[21] Although this constituted a retrospective study, the results indicated the potential benefit of using COX-II inhibitors as a postoperative pain management therapy for patients undergoing TKA.

Notably, in the present study, among the overall patient population, the average time to TKA from decision to surgery was almost three months. The average waiting time observed to TKA from decision to surgery was almost seven times higher in public hospitals (~6 months) compared with private hospitals (<1 month). The maximum waiting time was almost two years in public hospitals, while less than one year time in private hospitals. Although patients are covered under national health insurance in principle, many chose to seek treatment from private hospitals providing shorter waiting times. The long waiting time at the public hospitals could have also encouraged patients to seek informal care or self-medicate.[22] This could imply a high unmet need in the public sector in view of insufficient facilities, and availability of effective OA treatment in Thailand.

The study results showed approximately one fourth of patients (both public and private hospitals combined) underwent TKA surgery on both knees during the study period; this number was higher in public hospitals compared with private hospitals (33.64% vs. 17.27%). No significant difference was found in the proportion of patients undergoing surgery on the first knee (either left/right) by hospital type. Among patients overall (both private and public hospitals combined), a higher proportion of surgeries were on the left knee compared to the right knee among patients who underwent surgery on the second knee. While private hospitals followed the same trend, the

opposite trend was followed by public hospitals. Several limitations should be noted when interpreting these results. The retrospective nature of the study limited the amount of information for analysis.[23, 24] Particularly, the data could only provide an initial descriptive understanding of the clinical treatment pattern. Therefore, we were unable to conclude a causal relationship between intervention and treatment outcomes. In addition, the hospitals included in this study were located in metropolitan Bangkok. However, given that they were all tertiary care hospitals, they are reflective of the best medical practices in Thailand. Another limitation was the different methods for collecting pain scores. While three hospitals used VAS, one center recorded it as NRS. Nonetheless, since NRS is a segmented numeric version of VAS [25], VAS scores were similar to NRS scores and the final data were represented using the NRS scale. Finally, the study could not capture the data for patients who might have undergone surgery on the second knee after the study period. In addition, patients who underwent surgery in private hospitals may have received drug from elsewhere, which were not recorded in the chart.

Conclusion

At clinical baseline (before TKA), COX-II inhibitors were the most common drugs prescribed for pain management, irrespective of hospital type or age group; the use of COX-II inhibitors monotherapy/combination regimens was higher in the public than the private sector. At operation, the use of pain control drugs was similar for both public and private hospitals; antibiotics were highly prescribed drug during this period. After surgery, use of opioids was highest, followed by COX-II inhibitors and analgesics. COX-II inhibitors were more likely to be used in the private sector. The multimodal approach was found to be effective in managing pain during the different stages of TKA. Pain score after surgery for patients taking combined regimens of COX-II inhibitors was observed to be lower than those taking other drugs. Compared with public hospitals, lower pain scores were observed in private hospitals. At discharge, analgesics and opioids were the most commonly prescribed classes, followed by COX-II inhibitors. In terms of clinical outcomes, patients prescribed with COX-II inhibitors combined with other pain control treatment reported less pain than patients taking only analgesics or analgesics plus opioids. Patients taking COX-II inhibitors reported no issue with surgery wound and were the least likely to report issues with flexion/extension. During follow-up visit, a majority of patients were on opioids followed by analgesics and COX-II inhibitors in both public and private hospitals. In conclusion, this study provided an initial understanding of pain management among patients with OA undergoing TKA in public and private hospitals.

Acknowledgement

The study was supported by Merck Sharp & Dohme Corp.

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JOURNAL OF SOUTHEAST ASIAN MEDICAL RESEARCH

J Southeast Asian Med Res;2018

www.jseamed.org

ISSN 2586-8241