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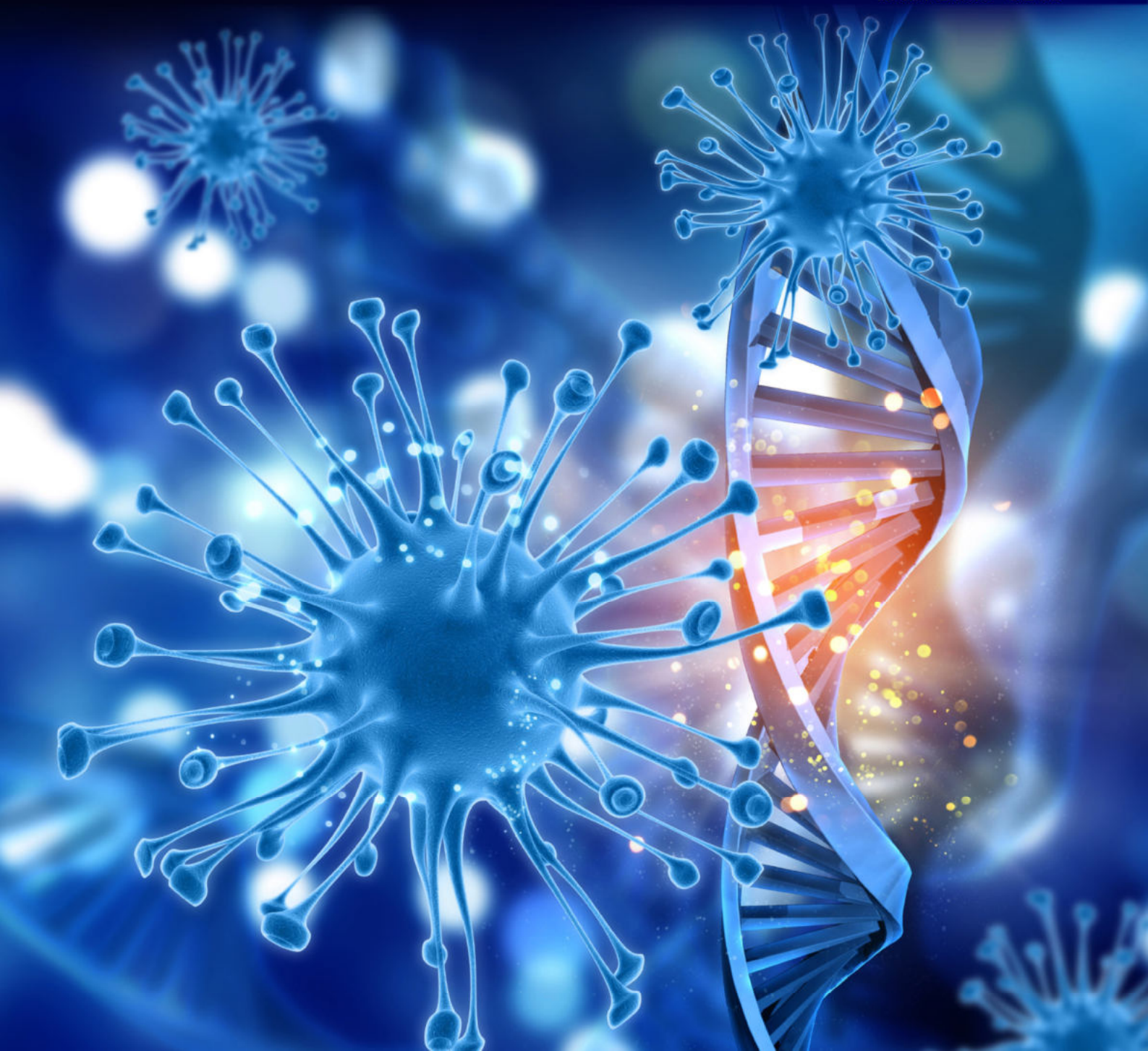

JOURNAL OF
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Introduction

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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CONTENTS

Original Article

EFFICACY OF INTRA-ARTICULAR ANALGESIC INJECTION VERSUS FEMORAL NERVE BLOCK FOR PAIN RELIEF AFTER TOTAL KNEE ARTHROPLASTY

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Abstract

This is a quasiexperimental research which objectives are to study efficiency of intra-articular analgesic injection and compare efficiency for pain relief between intra-articular analgesic injection and femoral nerve block in total knee arthroplasty at SomdechPhrapinklao hospital. 40 patients with operated total knee arthroplasty, randomised to 2 groups (20 patients). Control group received femoral nerve block, another group received intra-articular injection.

Both groups receive spinal morphine nerve block, operated by same surgeon, same surgical technique and same kind of implant. After surgery all patients record VAS score at 1,3,6,12,24,48 hours, doses of injection and oral analgesic drug, degree of knee flexion and hospital stay. Statistics used percentage, mean, standard deviation and independent *t-test*. We found patients received intra-articular analgesic injection had lower VAS pain score, lower dose analgesic drug than patients who received femoral nerve block and more knee flexion postoperatively in statistic significantly. And both Intra-articular analgesic injection and femoral nerve block can decrease VAS pain score, decrease dose analgesic drug postoperatively and improved knee flexion suitable for guideline pain relief in total knee arthroplasty.

Keywords : Intra-articular analgesic injection, Femoral nerve block, Total knee arthroplasty, Pain relief

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Introduction

Osteoarthritis of knee is a major medical problem health in Thailand. It was topten most common disease in elders and incidence 10% of elders more than 55 years old.

In severe stage patients must go total knee arthroplasty for pain relief and improved quality of life. In 2013, 200 patients operated total knee arthroplasty in Somdejphrapinklao hospital. Postoperative pain was a major problem due to delay normal diary activities. Spinal morphine analgesic was standard regimen for all patients. But most patients still severe pain and need more additional analgesic drug such as femoral nerve block.

Lamplot JD et al and Vandittoli PA et al report efficiency and rapid recovery time of additional intra-articular analgesic drug same as Toftdahl et al.

But Tanikawa et al found equal efficiency between intra- articular analgesic and femoral nerve block.

Szczukowski MJ et al found good efficiency of femoral nerve block but Widmer BJ et al shows same efficiency of femoral nerve block and non-femoral nerve block.

In Thailand Yuenyongviwat V et al report good efficiency of intra-articular analgesic drug but Panichkul et al found no efficiency of intra-articular analgesic drug.

Many reports had many results and controversy. Then this study compare efficiency between intra-articular analgesic and femoral nerve block and create guideline pain relief of total knee arthroplasty.

Objectives

1) Study efficacy of intraarticular analgesic injection.
2) Comparative between intra-articularanalgesic injection and femoral nerve block in patients who get total knee arthroplasty in Somdechphrapinklao hospital.

Hypothesis

Pain relief after total knee arthroplasty with intra-articular analgesic injection can relief pain; reduce amount of analgesic drug, ability of knee motion and hospital stay better than patients who received femoral nerve block.

Benefit

1) Guideline for patients who get Total knee arthroplasty received good analgesic drug for relief pain.
2) Study efficacy of intraarticular analgesic injection and femoral nerve block.

Methods

This is a quasi-experimental research. Control group equal characteristic with experimental group and two groups post-test only design

Population

Patient was severe osteoarthritis which does total knee arthroplasty at Somdechphrapinklao Hospital.

Inclusion Criteria

1) Patient was severe osteoarthritis which do got total knee arthroplasty.
2) Female age 60-70 years old.
3) Assign to attend research.
4) Do not previous surgery.
5) Surgery between Oct 2014 to Apr 2015.

Exclusion criteria

1) Patient was severe complication such as shock, severe anaphylactic shock, admitted ICU post.op and prolongs surgical time more than 2 hours.
2) Patients cannot take adequate data.

Samples

Taking female patients which the age between 60-70 years that have been diagnosed to be severe osteoarthritis and they have to do a total knee replacement on October 2014 to April 2015.

The patients were divided into 2 groups by systematic random sampling consists of:

1.Controlled group: Patient who got pain controlled drugs by injected in the femoral nerve block.

2.Experimentd group: Patient who got pain controlled drugs by intraarticular injection.

Equipment for research

A memo report for the patients after finished the total knee replacement surgery.

Part 1 General information: age, height, weight, BMI (Body Mass Index) and congenital disease

Part 2 Information after the surgery: pain level in 1, 3, 6, 12, 24 and 18 hours, using medicine in both injection and eating on the first, second and third day after the surgery, and flexion-extension degree on the fifth day

Examine for the function of the function of the equipment

Testing the content validity and objectivity of the questionnaire by 4 luminaries. (ICO = 0.75)

Researcher suggested the way to collect the data to anesthesiologist, nurse, officer research assistant nurse.

Experiment

Controlled group was injected the spinal morphine in 0.2 mg before the surgery combine with injection 0.25% of marcaine 20 ml to the femoral nerve block by the anesthesiologist. Experimented group was also injected the spinal morphine in 0.2 mg before surgery combine with injection 0.25% of marcaine 20 ml in the intraarticular injection by the surgeon. Using Visual Analog Score (VAS Score) to evaluate the pain level of the knee which 0 means without pain and 10 means the most painful. Both of these groups were taken NSAID (Naproxen) after the surgery. If VAS =1-3 and the patients needed, they were received Paracetamol 1,000 mg. On the other hand, if VAS was more than 3 and patients needed, they were received the injection of Tramadol 50 mg instead. Both of these groups were received the continuous passive motion machine in the day after the surgery follow the clinical pathway and also measured the degree of motion every day.

Results

In this study, pain control method for the patients who have done the total knee replacement surgery can be done by the intraarticular injection and the femoral nerve block. The result shown that in 12 hours after the surgery, patients with the intraarticular injection method is painless than the femoral nerve block method. Moreover, flexion-extension degree of the knee in patient which intraarticular injection method is presented the significant better result compared with the femoral nerve block method as shown in Table 2 and 4.

Table 1. Patient demographic data of the intraarticular injection and the femoral nerve block.

	IAI M(SD)	FNB M(SD)	*p* - valve
Population	20	20	
Age(Yrs.)	66(4)	67(4)	0.63
Height(Cm.)	159(8)	158(7)	0.188
Weight(Kg.)	69(17)	63(9)	0.505
BMI(Kg/m^2)	27(5)	25(4)	0.266

IAI=Intraarticular injection

FNB=Femoral nerve block

Table 2. Pain level comparison of the intraarticular injection and the femoral nerve block after the total knee replacement surgery.

Post.op time	IAI M(SD)	FNB M(SD)	*p* - valve
1st hour	1.9(0.7)	2.2(0.8)	0.307
3rd hour	2.8(0.8)	2.9(0.6)	0.657
6th hour	3.2(1.1)	3.7(1.0)	0.155
12th hour	2.9(1)	4.2(1.2)	0.001*
2nd day	3.1(0.9)	3.6(1.2)	0.150
3rd day	2.7(0.7)	2.9(0.5)	0.174

* *p* - valve < 0.05

IAI=Intraarticular injection

FNB=Femoral nerve block

Table 3. Comparison of injection analgesic drugs and taking analgesic medicine of the intraarticular injection and the femoral nerve block after the total knee replacement surgery.

Post-op. time	IAI		FNB		*p* - valve
	received(%)	not received(%)	received(%)	not received(%)	
Tramal 50 mg iv					
1st day	4(20)	16(80)	8(40)	12(60)	0.176
2nd day	6(30)	14(70)	9(45)	11(55)	0.34
3rd day	3(15)	17(85)	3(15)	17(80)	1.00

Post-op. time	IAI		FNB		*p* - valve
	received(%)	not received(%)	received(%)	not received(%)	
Paracetamal 1000mg.					
1st day	0	20(100)	2(10)	18(90)	0.154
2nd day	3(15)	17(85)	6(30)	14(70)	0.267
3rd day	1(5)	19(95)	0	20(100)	0.324

IAI=Intraarticular injection
FNB=Femoral nerve block

Table 4. Comparison of number of the day that patients stay in the hospital and ability of flexion extension of knee of the intraarticular injection and the femoral nerve block after the total knee replacement surgery.

	IAI M(SD)	FNB M(SD)	*p* - valve
Hospital stay(day)	7.3(1.3)	8.2(1.8)	0.062
Flexion of knee(degree)	104.5(7.6)	95(12.8)	0.007*

* *p* - valve < 0.05
IAI=Intraarticular injection
FNB=Femoral nerve block

Discussion

According to the research, pain control result by using intraarticular injection method is present the significant great result compare with femoral nerve block method by 0.05 statistical. According to Ashraf's research and team [12] and Fu-Yuen Ng and team.[13] Due to during total knee replacement surgery, tissue injury has neurological respond 2 ways consist of peripheral sensitization that increase sensitivity of nociceptive receptor and central sensitization that increase sensitivity of spinal nervous. Intraarticular injection method can reduce central and peripheral sensitization, thus patients have VAS score less than femoral nerve block [14] and intraarticular injection method shows the average of pain less than femoral nerve block method. The result shows that intraarticular injection method has more effectively than femoral nerve block according to research of Lamplot JD and team[4] Venditoli PA and team.[5]

In 3, 6, 24, 48 hours after surgery, intraarticular injection method shows that there is no different of pain compare with femoral nerve block according toTanikawa H and team.[7]

After surgery for 5 days, the 90 degrees knee flexion of patient who gets intraarticular injection is better than patient who gets femoral nerve block because femoral nerve comes from spinal level L2-L4 to quadriceps muscle and receive sensation from front and inside of thigh but the muscle beside and back of thigh receive sensation by sciatic nerve that comes from spinal level L4-S3.[8] So, femoral nerve block method not cover beside and back muscle of thigh that affect to flexion and extension knee of patient according to Peiliang Fu and team[4], Tanaka and team[15] and Antoni and team.[16]

Conclusion

The intraarticular injection shows a better result in flexion of knee and factor affecting the pain is in line with Toftdahlk and team's research that present effective in reduce pain after surgery and rapidity in rehabilitation of knee.

Suggestion

The intraarticular injection during operation can reduce analgesic after the operation and flexion of knee better than femoral nerve block. Both methods can reduce analgesic after operation and show good recovery. This research can be a guideline for appropriate and sufficient pain reducing in total knee replacement surgery.

Suggestion for next research

1) Should have studied the effectiveness of sciatic nerve block in conjunction with the injection into the femoral nerve block in patients who received total knee replacement surgery.
2) Should have studied the effectiveness of continuous intraarticular injection for relieving pain of patients who received total knee replacement surgery.

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RENAL INJURY AND DYSFUNCTION AMONG HIV POSITIVE PATIENTS RECEIVING TENOFOVIR BASED ANTI-RETROVIRAL THERAPY

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Abstract

The rate of renal disease among patients with HIV has decreased significantly since the introduction of highly active antiretroviral therapy (HAART). Patients receiving tenofovir, disoproxil, fumarate (TDF) had an increased prevalence of proximal renal tubular dysfunction and injury but its clinical significance remain controversial.To define the renal tubulopathy injury among patients with HIV with and without TDF. A cross-sectional study was conducted among HIV positive patients receiving TDF (N=176) and nonTDF regimen (N=146) at outpatient clinic. All patients were evaluated regarding serum creatinine, electrolytes, phosphate and differing urinary parameters (proteinuria, glycosuria and pyuria). Estimated glomerular filtration rate (GFR) was calculated using CKD-EPI equation. Of 322 participants with mean age of 41.6 ± 11.4 years and HIV duration of 7.2 ± 4.3 years, the TDF and nonTDF groups were similar on most clinical and demographic factors. GFR was 100.6 ± 17.8 mL/min/1.73 m^2 in TDF group and 97.5 ± 19.6 mL/min/1.73 m^2 in non-TDF group (p = 0.143). During evaluation, 3.4% of TDF patients vs. none of the nonTDF - patients had hypophosphataemia (< 2.5 mg/dL), 3.9% of TDF - patients vs. 1.3% of nonTDF had hypokalemia (< 3.5 mg/dL), and 0.68% of TDF - patients vs. none of nonTDF patients had acidosis (<18 mEq/L) with no statistically significant difference between groups. The proportion of patients with evidence of urine abnormalities was also similar in the two groups (Dipstick proteinuria > 1+; TDF: 17.6% vs. non-TDF 20.5%, p = 0.568, and pyuria; TDF: 27.3% vs. nonTDF 20.5%, p = 0.192). Renal impairment, electrolyte disturbances and renal tubulopathy were uncommon among HIV positive patients receiving TDF-based antiretroviral therapy and did not significantly differ between TDF and nonTDF regimens.

Keywords : Tenofovir, Tubulopathy, Acute kidney injury

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Introduction

Highly active antiretroviral therapy (HAART) has reduced the mortality and morbidity associated with human immunodeficiency virus (HIV) infection. Tenofovir disoproxil fumarate, a prodrug of tenofovir (TDF), is a potent nucleotide analogue reverse transcriptase inhibitor and the first line HAART regimens according to a recommendation of the World Health Organization. TDF is mainly elimi- nated by glomerular filtration and 20% to 30% by proximal tubular secretion. Initially, case reports demonstrated TDF - associated acute tubular necrosis, proximal tubular injury and Fanconi syndrome with hypouricemia and hypophosphatemia.[1, 2] In a cohort study, TDF based anti-retroviral therapywas associated with GFR decline during the first years of treatment and relatively mild GFR decline in a long-term follow-up.[3]

Currently, TDF based antiretroviral therapy has been reported infrequently in renal toxicity and renal tubular dysfunction among of HIV positive patients. [4, 5] The high incidence of TDF-associated nephropathy is related to aging, low body weight, low CD4 cell count, advanced HIV disease, preexisting kidney disease, concomitant hepatitis C virus (HCV) infection and concurrent use of other nephrotoxic drugs.[6-9]Little is known about renal safety of TDF among Thai patients on TDF. Here we report the results assessing renal safety of TDF and nonTDF based antiretro- viral therapy among Thai HIV positive patients.

Methods

Study design and population

The cross-sectional study evaluated the renal safety of TDF treatment among HIV positive patients during January 2014 and December 2014. The study protocol was approved by the institutional review boards and ethics committees. Written informed consent was obtained from all patients at screening.The primary objective was to determine the renal function and renal tubular defects between HIV positive patient treatment with TDF and non TDF regimens. Eligibility included male and female patients aged 18 to 85 years diagnosed with HIV receiving antiretroviral therapy treatment at least 12 weeks.

Measurements

The clinical and laboratory data were collected and recorded on case report forms. Safety was assessed by physical examinations, clinical laboratory tests and the incidence and severity of adverse events recorded from treatment. Serum creatinine, electrolytes, calcium, phosphate, uric acid, CD4 + cell count, plasma HIV-1 viral load and urine analysis were measured. The estimated glomerular filtration rate (GFR) was calculated using the CKD-EPI equation.

Urine protein was measured by a urine dipstick. Albuminuria and glycosuria were defined as ≥1+ on a urine dipstick. Pyuria was defined as ≥3 white blood cells per high power field urinalysis.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) and median with interquartile range. Continuous variables were assessed with the Student's *t-test* or Mann-Whitney U test appropriately. Categorical variables were assessed with the Chi-square 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). Statistical significance was determined as a p - value less than 0.05.

Results

A total of 322 (100% Thai ethnicity) with a mean age of 41.6 ± 11.4 years and HIV duration of 7.2 ± 4.3 years were included. Baseline demographics of the TDF and nonTDF patients are shown in Table 1. Compared with the nonTDF group, the TDF group exhibited lower mean age, CD4 count and the comorbid diseases of hypertension and dyslipidemia.The duration of HARRT treatment was significantly longer in the nonTDF group compared with the TDF group. No significant differences in other baseline characteristics were noted between the two groups Table 1 .Common medications and antiretroviral therapy among TDF and nonTDF patients are shown in Table 2. Mean GFR was 100.6 ± 17.8 mL/min/1.73 m^2 in the TDF group and 97.5 ± 19.6mL/min/1.73m^2 in the nonTDF group ($p = 0.143$).

Both serum creatinine and estimated GFR were similar across treatment groups Table 3. Overall tubular dysfunction levels regarding serum electrolytes and urine findings are shown in Fig 1. No significant difference in impaired GFR, hypophosphataemia, hypokalemia and metabolic acidosis incidence between the two groups was apparent. The proportion of patients with evidence of urine abnorma- lities was also similar in the two groups (Dipstick urine albumin>1+; TDF: 17.6% vs. nonTDF 20.5%, p = 0.568, dipstick urine glucose>1+; TDF:17.6% vs. nonTDF 20.5%, p = 0.568 and pyuria; TDF:27.3% vs. nonTDF 20.5%, p = 0.192). Finally, no clear difference in all renal functions and biochemical tubular parameters across treatment in either study was detected. Overall serious renal adverse events were not reported in both group.

Table 1. Baseline characteristics

	TDF (N=176)	Non-TDF (N=146)	p-value
Age (yr)	38.4±11.5	45.3±10.0	0.000
Male (N, %)	127 (72.2%)	96 (65.8%)	0.227
Body weight (kg)	61.4±12.2	61.1±10.5	0.775
Body mass index (kg/m^2)	22.0±3.9	22.4±3.5	0.395
Systolic blood pressure (mmHg)	123.8±14.2	126.3±16.4	0.152
Diastolic blood pressure (mmHg)	77.0±11.4	78.8±12.1	0.192
Duration of antiretroviral therapy (yr)	5.4±4.0	9.5±3.5	0.000
Co-morbid diseases (N, %)			
- Hypertension	14 (8%)	39 (26.7%)	0.000
- Dyslipidemia	32 (18.2%)	76 (52.1%)	0.000
- Type 2 diabetes	5 (2.8%)	9 (6.2%)	0.175
- Ischemic heart disease	9 (7.9%)	12 (12.1%)	0.333
Common co-infection (N, %)			
-*Mycobacterium tuberculosis*	59 (33.5%)	49 (33.6%)	1.000
-*Pneumocystis jiroveci*	33 (18.8%)	23 (15.8%)	0.555
-*Cryptococcus neoformans*	13 (7.4%)	11 (7.5%)	1.000
-*Treponema pallidum*	12 (6.8%)	6 (4.1%)	0.338
- *Candida albicans*	12 (6.8%)	4 (2.7%)	0.123
CD4 count (cell/mm^3)	437.2±227.1	543.8±234.5	0.000
HIV RNA viral load (copies/mL)	560±3226	1509.6±16365.2	0.505

Data are expressed as mean SD, median (interquartile) or as number (percentage) of patients. Comparisons between treatment groups employed the Independent *t-test* (continuous variables) and Chi-square test (Categorical variables).

Table 2. Medical treatments among HIV positive patients receiving TDF and nonTDF regimens

	TDF (N=176)	Non-TDF (N=146)	p-value
Antiretroviral medications (N, %)			
Zidovudine (AZT)	9 (5.1%)	95 (65.1%)	0.000
Lamivudine (3TC)	165 (93.8%)	114 (78.1%)	0.000
Nevirapine (NVP)	19 (10.8%)	40 (27.4%)	0.000
Efavirenz (EFV)	123 (69.9%)	52 (35.6%)	0.000
Stavudine (D4T)	1 (0.6%)	19 (13%)	0.000
Didanosine (DDI)	1 (0.6%)	3 (2.1%)	0.333
Lopinavir (LPV)	28 (15.9%)	24 (16.4%)	1.000
Atazanavir (ATV)	6 (3.4%)	4 (2.7%)	1.000
Other medications (N, %)			
Statin	13 (7.4%)	44 (30.1%)	0.000
Fibrate	20 (11.4%)	33 (22.6%)	0.010
Co-trimoxazole	18 (10.2%)	2 (2.1%)	0.003
Fluconazole	17 (9.7%)	1 (0.7%)	0.000

Data are expressed as number (percentage) of patients. Comparisons between treatment groups employed the Chi-square test (Categorical variables).

Table 3. Renal function and serum electrolytes among HIV positive patients receiving TDF and nonTDF regimens

	TDF (N=176)	Non-TDF (N=146)	p-value
BUN (mg/dL)	10.9±4.2	12±6.9	0.091
Serum Cr (mg/dL)	0.9±0.2	0.91±0.6	0.842
Estimated GFR (mL/min/1.73 m^2)	100.7±17.8	97.5±19.6	0.134
Na (mEq/L)	139±2.1	139±1.9	0.432
K (mEq/L)	4.1±0.4	4.1±0.3	0.329
Cl (mEq/L)	102±2.5	102±2.2	0.101
HCO3 (mEq/L)	26.2±2.6	25.85±2.5	0.225
Ca (mg/dL)	9.2±0.4	9.2±0.5	0.415
PO4 (mg/dL)	3.2±0.5	3.4±0.5	0.160
Uric (mg/dL)	5.1±1.5	5.2±1.6	0.565

Data are expressed as mean SD. Comparisons between treatment groups using the Independent *t-test* (continuous variables).

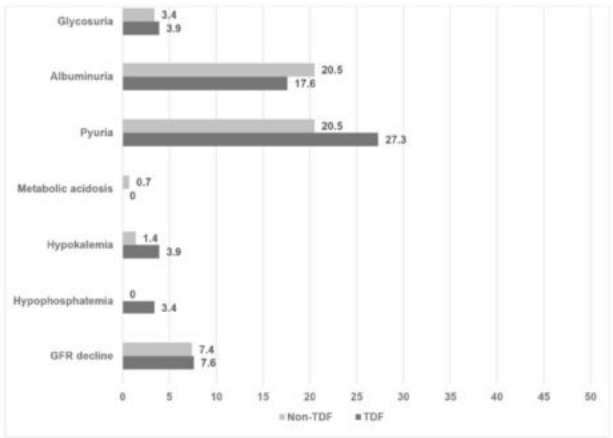

Fig 1. Percentage of renal tubular dysfunction among HIV positive patients receiving TDF (N=176) and nonTDF regimens (N=146). All parameters in both groups did not significantly differ ($p > 0.05$).

Data are expressed as number (percentage) of patients. Comparisons between treatment groups employed the Chi-square test (Categorical variables). Albuminuria was defined as urine dipstick >+ 1, glucosuria was defined as urine glucose >+ 1, hypophosphatemia was defined as serum phosphorus < 2.5 mg/dL; hypokalemia was defined as serum potassium < 3.5 mg/dL; GFR decline was defined as GFR < 60 mL/min/.173m^2, metabolic acidosis was defined as serum HCO3 < 18 mEq/L and pyuria was defined as WBC < 3 cells/HPF.

Discussion

This study evaluated the renal safety of TDF among HIV positive patients. Overall, results of this study showed that receiving TDF based antiretroviral therapy exhibited equivalent renal safety as nonTDF based antiretroviral therapy in this patient population. Low frequency of treatment limiting renal impairment and tubular dysfunction was observed among HIV positive patients receiving TDF in Thailand. No statistically significant difference in mean GFR and tubular defect markers was observed between the two groups. Data on the renal safety of TDF in developing countries is limited. Two clinical studies in Caucasian populations reported a low incidence of TDF-associated renal injury and tubular dysfunction. [4, 5] Several clinical studies in African populations have also reported approximately 1 to 2% of TDF-associated nephropathy among HIV positive patients. [6, 10, 11] One study in a Chinese population showed that patients exposed to TDF regimen exhibited greater renal function decline than the control, but renal function always fluctuated within normal range.[12] Recently, a meta-analysis among 7,496 subjects reported that the risk for acute kidney injury was 0.7% higher (95% CI, 0.2 to 1.2) among TDF-treated subjects than among subjects receiving HARRT without TDF.[13] Similar to our findings, our patients on TDF based antiretroviral therapy were not more likely to experience renal dysfunction than those receiving other regimens.

However, the heterogeneity of renal outcomes with TDF reflected differences in our study design. A high incidence of TDF associated nephropathy have been reported in case control studies or retrospective cohort studies[14], but renal function decline was lower in the studies that systematically reported adverse effects and in randomized clinical trials.[13]

Therefore, biochemical laboratory monitoring in terms of long term safety is required regarding randomized control studies. Based on our results and related studies, TDF appeared to be comparable regarding renal safety with other antiretroviral treatments. Concerning normal renal function, TDF-based antiretroviral therapy may be less harmful than previously thought. TDF-induced nephropathy is a reversible form of proximal tubular injury, manifesting distinctive proximal tubular eosinophilic inclusions and ultrastructural mitochondrial abnormalities. [15] Apoptosis and mitochondrial DNA depletion of tubular cells might be involved in the pathogenesis of TDF-induced nephropathy. [16] Clinical manifestation of proximal tubular dysfunction including albuminuria, hypophosphatemia, hypouricemia and tubular acidosis have been described among patients receiving TDF.[9, 17, 18] Because acid base and electrolyte disturbances are quite common among HIV positive patients and have many possible causes, concluding whether these complications are a direct consequence of TDF is difficult. The etiology of these abnormalities seems to be multifactorial and unrelated to TDF or renal dysfunction. [13, 19] In addition, our findings and previous meta-analysis confirm that all proximal tubular dysfunction biomarkers did not differ between TDF-treated and nontreated patients. This study had some limitations. First, because of the crosssectional study, we could not evaluate long term renal outcomes, and we could not assess the mechanisms of TDF associated nephropathy and tubular cell injury. Second, the outcomes of this study were based on primarily Asian patients with normal renal function and may not be generalizable to a special population, e.g., impaired renal function and high comorbid illnesses. Finally, noting that urine electrolytes, uric acid, phosphate and albumin and creatinine ratio were not obtained and measured is important, which may make diagnosis of tubular defects less reliable.

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Conclusion

In conclusion, among HIV positive patients receiving TDF, mean renal function and electrolyte abnormalities were similar to nonTDF treatment. The authors of this study conclude that TDF-based first line ART can be safely given even without renal monitoring in settings with normal renal function. The renal safety of TDF treatment will require further evaluation in longer duration studies and high risk groups regarding kidney injury.

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THE EFFICACY OF PROGESTERONE IN TREATMENT OF TRAUMATIC OPTIC NEUROPATHY (PROTON STUDY)

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Abstract

To evaluate the visual function improvement by progesterone for treatment of indirect traumatic optic neuropathy Study design was comparative historical controlled trial. Seven patients newly diagnosed with indirect traumatic optic neuropathy (TON) were enrolled for progesterone group. Nineteen indirect TON patients were reviewed medical records for steroid group (N=12) and observation group (N=7). Patients in progesterone group were given Depot medroxyprogesterone acetate (DMPA) 1 mg/kg. intramuscular injection every 12 hrs. for 5 days and observed for side effects. All patients were examined and reviewed for visual acuity by ETDRS chart, color vision test by Ishihara test, visual field testing by Humphrey automated perimetry, fundus and optic disc examination at baseline, follow-up 1 week, 1 month and 3 months. Demographic and clinical characteristic of patients in 3 groups were not different in terms of age, sex, underlying disease, side of eye, type of injury, baseline visual acuity, associated orbital fracture, history of amnesia, time to visit hospital and time to start treatment. Improvement in best-corrected visual acuity (BCVA) compared at 3 months from baseline showed no difference between 3 groups ($p = 0.891$). Analysis within steroid group showed statistically significant improvement of BCVA at 1 and 3 months ($p = 0.015$, 0.028 respectively). No improvement was shown in color vision and visual field in progesterone group. Only better baseline BCVA was the protective factor for better visual outcome ($p = 0.027$, Odds ratio = 0.004, 95%CI = 0.000 - 0.537). No side effects of progesterone were found in this study. Progesterone is a safe and promising neuroprotective agent that could be adjunctive or alternative to steroid in case of contraindication to corticosteroid treatment. This study showed no difference among choices of treatment therefore study in larger population is required. Steroid remains an effective option contrast with recent studies.

Keywords : Visual function, Optic neuropathy

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Introduction

IntroductionTraumatic optic neuropathy (TON) is a rare condition found 2.3% of head injury[1] but often devastating cause of permanent visual loss after blunt or penetrating injury. While projectiles or other sharp objects injure the optic nerve directly, the most common form of traumatic optic neuropathy is indirect, as a result of concussive force to the head, particularly the forehead.[2] This impact is thought to transmit a shock wave to the optic canal, damaging the optic nerve.[3] In some cases a relatively mild concussive impact can result in indirect traumatic optic neuropathy. Typically, the retina and optic disc initially appear normal, and the only objective finding is the presence of a relative afferent pupillary defect. The severity and range of the initial visual loss can vary widely. Optic atrophy does not become apparent for 3 - 4 weeks.[4] While the diagnosis of indirect traumatic optic neuropathy can usually be made with the aid of a careful history and examination; its optimal management is far less well defined. Evidence for the relative benefits of these approaches has mainly been based on small retrospective studies, and there fore a convincing rationale for treatment is lacking. The management of traumatic optic neuropathy (TON) is controversial. Various options include high - dose or low - dose corticosteroids, immediate decompression of the canalicular portion of the optic nerve (via intracranial, transethmoidal, endonasal, sublabial, or other approaches), decompression of the canalicular optic nerve after a course of systemic corticosteroids, opticnerve sheath fenestration and observation.[5,6] A comparative nonrandomized interventional study found no clear benefit for either corticosteroid therapy, optic canal decompression, or observation in the treatment of TON.[7] Progesterone is a hormone which has steroidal, neuroactive and neurosteroidal action in the central neuronal system. Neuroprotective effects of progesterone have recently been shown in a variety of animal models, including ischemic and traumatic brain insult models.[8,9] Postinjury administration of progesterone in experimental models of head injury confers significant protection against TBI - induced cerebral edema and secondary neuronal death, promoting behavioral recovery.

Experimental evidence suggests that postinjury treatment with progesterone decreases brain edema, attenuates free radical damage, and reduces neuronal loss in TBI animal models. Progesterone also reduces the inflammatory response and attenuates neurological abnormalities after ischemia and spinal cord injury.[10-35] In a recently published controlled study of progesterone, Wright and colleagues conducted a phase II, randomized, double-blind, placebo controlled trial to assess the safety and benefit of administering progesterone to patients with acute TBI. [36] No serious adverse events were found in the 77 patients who received progesterone, and the patients with moderate TBI who received progesterone were more likely to have a moderate to good outcome than those were randomized to placebo at 30 days post injury. This outcome suggests that progesterone causes no harms and may be a beneficial treatment for TBI.[36-38]

The optic nerve is the second of twelve paired cranial nerves and is technically part of the central nervous system, ensheathed in all three meningeal layers (dura, arachnoid, and pia mater). The fibers of the optic nerve are covered with myelin produced by oligodendrocytes rather than Schwann cells of the peripheral nervous system, and are encased within the meninges. Despite potential advantages and the good safety profile of progesterone described in studies utilizing animals or humans as subjects, there is relatively no clinical information available for assessing neuroprotective properties of progesterone in the patients with traumatic optic neuropathy. The purpose of the present pilot clinical study was to assess the longer-term efficacy of progesterone on improving the visual outcome of patients with indirect traumatic optic neuropathy.

Methods

The study was conducted in compliance with the clinical protocol approved by the Institutional Review Board of Royal Thai Army Medical Department. Protocol was followed as in flow chart Fig 1.

Participant selection

All of newly diagnosed indirect traumatic optic neuropathy patients visited at Phramongkutklao hospital were enrolled during February to August 2015. Male or female patients between the ages of 18 and 65 years were studied.

The patients received progesterone within 8 hours after the documented time of injury.

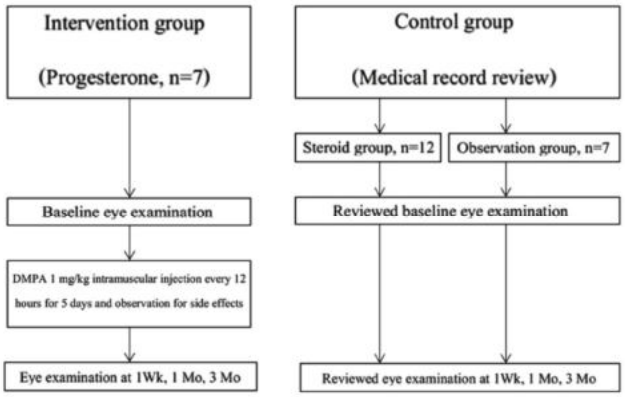

Fig1. Flow chart indicating patient allocation, intervention and follow-up

Inclusion criteria

1. Male or female patient, aged 18 - 65 years old.
2. Diagnosed with indirect traumatic optic neuropathy within 7 days
3. No other ocular or visual pathway effecting visual function

Exclusion criteria

1. Low level of consciousness and unable to evaluated visual acuity
2. Other system injury such as cardiovascular, pulmonary injury
3. Progesterone administration with in 30 days
4. Contraindicated to progesterone as following
    1) Pregnancy or lactation
    2) Abnormal vaginal bleeding
    3) Breast mass or history of breastcancer
    4) Uncontrolled blood pressure > 180/110 mmHg.
    5) Diabetes mellitus with complications
    6) Diagnosed or history of is chemic heart disease
    7) Occlusive vascular diseases
    8) Active viral hepatitis, cirrhosis, liver cancer
    9) Coagulopathy, deep vein thrombosis, pulmonary embolism

Screening for eligible subjects

After informed consents were obtained, participants were examined and investigated for eligible subject indicated for drug administration.

1. Blood pressure
2. Complete blood count, Coagulograms, Fasting plasma glucose, Liver function test
3. Electrocardiogram
4. For female patient: History taking about menstrual period, contraception, abnormal vaginal bleeding, urine pregnancy test, complete breast exam
    1) Age 18 - 39 years old: Ultrasound breast
    2) Age 40 - 65 years old: Mammogram

Baseline eye examination

All patients in progesterone group were examined as following for comparing to follow-up eye examination

1. Visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) chart
2. Fundus and optic disc examination
3. Color vision test by Ishihara test
4. Visual field testing by Humphreyautomated perimetry (Swedish Interactive Threshold Algorithm (SITA) standard program 30 - 2)

Patients in steroid and observation groups were review medical record for visual acuity for baseline data.

Drug administration All eligible subject in progesterone group diagnosed with indirect traumatic optic neuropathy within 7 days were received Depot medroxy progesterone acetate (DMPA) 1 mg/kg intramuscular injection every 12 hours for 5 days either outpatient or inpatient. All patients received the medication were observed for side effects such as headache, fatigue, nausea, vomiting, hair loss, weight gain/ loss, depression, abnormal menstruation and vaginal bleeding.

Follow up Patients in progesterone group were followed up and examined same as baseline eye examination at 1 week, 1 month and 3 months from last time of drug administration and also screened for side effects, physical examination and laboratory testing as following at 1 and 3 months

1. Blood pressure
2. Complete blood count,

Coagulograms, Fasting plasma glucose, Liver function test

Patients in steroid and observation group were also reviewed for visual acuity at approximate time of follow-up at 1 week, 1 month and 3 months.

Statistical analyses

For evaluating visual improvement, visual acuities were converted to logarithm of the minimum angle of resolution (logMAR) equivalents.

Poor visual acuity was assumed as the following: No light perception = 1.9, Light perception = 1.8, Hand motion = 1.7, Counting finger = 1.6 for purpose of analysis. Recovery of visual acuity was defined as a decrease of at least 0.4 log MAR in visual acuity after 3 months. We compared clinical characteristics of patients in each group and improvement of visual acuity in different groups by chi-square test, and we used *t-test* and paired *t-test* for comparison of initial and final mean visual acuities in those groups. The effect of treatment on final BCVA was evaluated by ANOVA test after adjustment for confounding factors. Statistical level of significance was set at 0.05.

Results

Seven patients newly diagnosed with indirect traumatic optic neuropathy were enrolled for progesterone group. Table 1 demonstrates basic characteristic data of all patients in progesterone group. All patients in this group were male and mean age was 34.29 ± 16.19 years (range from 20 to 61 years). No side effect of progesterone was found in patient received progesterone. Nineteen indirect TON patients were reviewed medical records for steroid group (N=12) and observation group (N=7). Demographic and clinical characteristic of patients in 3 groups were not different in terms of age, sex, underlying disease, side of eye, type of injury, baseline visual acuity, associated orbital fracture, history of amnesia, time to visit hospital and time to start treatment.

Table 1 Basic characteristic of patients in progesterone group

Patient	Sex	Age (yrs)	Eye	Type of injury	Initial BCVA	Final BCVA	Disc palor	Side effects	Medications
1	M	24	LE	VA	20/125	20/20	3Mo	No	DMPA 1mg/kg IM Q 12 hrs for 5 days
2	M	54	RE	Fall	HM	HM	1Mo	No	MP 1 g IV for 3 days then DMPA 1mg/kg IM Q 12 hrs for 5 days
3	M	27	RE	VA	NPL	PL	1Mo	No	DMPA 1mg/kg IM Q 12 hrs for 5 days
4	M	26	LE	VA	PL	20/200	3Mo	No	MP 1 g IV for 3 days then DMPA 1mg/kg IM Q 12 hrs for 5 days
5	M	28	LE	VA	HM	CF	1Mo	No	DMPA 1mg/kg IM Q 12 hrs for 5 days
6	M	20	LE	VA	NPL	PL	1Mo	No	DMPA 1mg/kg IM Q 12 hrs for 5 days
7	M	61	LE	Fall	NPL	NPL	1Mo	No	MP 30 mg/kg loading dose then MP 5.4 mg/kg/h for 24 hrs then DMPA 1mg/kg IM Q 12 hrs for 5 days

BCVA = Best-corrected visual acuity, M = Male, RE = Right eye, LE = Left eye, VA = Vehicle accident, NPL = No light perception, PL = Light perception, HM = Hand motion, CF = Counting finger, DMPA=Depot medroxy progesterone acetate, MP = Methylprednisolone, IV = intravenous, IM = intramuscular, Q = every, Mo = month.

Table 2 Demographic and clinical characteristic

Characteristics	Progesterone n=7	Steroid n=12	Observation n=7	Total n=26	P-value
Age, mean (SD)	34.29 (16.19)	25.58 (11.50)	39.14 (18.89)	31.58 (15.56)	0.163
Sex Male, n(%)	7 (100)	11 (91.7)	6 (85.5)	24 (92.3)	0.601
Female, n(%)	0 (0)	1 (8.3)	1 (14.3)	2 (7.7)	
Eye RE, n(%)	2 (28.6)	3 (25.0)	3 (42.9)	8 (30.7)	0.711
LE, n(%)	5 (71.4)	9 (75.0)	4 (57.1)	18 (69.2)	
Injury type, n(%)					
Vehicle accident	5 (71.4)	11 (91.7)	2 (28.6)	18 (69.2)	0.055
Fall	2 (28.6)	0 (0)	2 (28.6)	4 (15.4)	
Assault	0 (0)	1 (8.3)	1 (14.3)	2 (7.7)	
Blast injury	0 (0)	0 (0)	2 (28.6)	2 (7.7)	
Baseline BCVA,n(%)					
NPL	3 (42.9)	5 (41.7)	0 (0)	8 (30.8)	0.554
PL	1 (14.3)	2 (16.7)	2 (28.6)	5 (19.2)	
HM	2 (28.6)	1 (8.3)	2 (28.6)	5 (19.2)	
<20/200-CF	0 (0)	3 (25.0)	2 (28.6)	5 (19.2)	
<20/40-≥20/200	1 (14.3)	1 (8.3)	1 (14.3)	3 (11.5)	
≥20/40	0 (0)	0 (0)	0 (0)	0 (0)	
Categorized baseline BCVA, n(%)					
≤HM	6 (85.7)	8 (66.7)	4 (57.1)	18 (69.2)	0.494
> HM	1 (14.3)	4 (33.3)	3 (42.9)	8 (30.8)	
Time to visit hospital, Hr. (SD)	8.71 (5.59)	3.92 (2.91)	9.29 (10.19)	6.65 (6.55)	0.141
Time to treatment, Hr. (SD)	82.71 (56.36)	61.08 (44.88)	-	69.05 (49.04)	0.369
Underlying DM, n(%)					
Yes	1 (14.3)	1 (8.3)	1 (14.3)	3 (11.5)	0.894
No	6 (85.7)	11 (91.7)	6 (85.7)	23 (88.5)	
Underlying HT, n(%)					
Yes	1 (14.3)	1 (8.3)	1 (14.3)	3 (11.5)	0.894
No	6 (85.7)	11 (91.7)	6 (85.7)	23 (88.5)	
Underlying DLP, n(%)					
Yes	0 (0)	1 (8.3)	0 (0)	1 (3.8)	0.545
No	7 (100)	11 (91.7)	7 (100)	25 (96.2)	
Orbital wall fracture, n(%)					
No	5 (71.4)	4 (33.3)	5 (71.4)	14 (53.8)	0.272
1 wall	1 (14.3)	1 (8.3)	0 (0)	2 (7.7)	
> 1 walls	1 (14.3)	7 (58.3)	2 (28.6)	10 (38.5)	
History of amnesia, n(%)					
Yes	5 (71.4)	9 (75.0)	4 (57.1)	18 (69.2)	0.711
No	2 (28.6)	3 (25.0)	3 (42.9)	8 (30.8)	
Development of disc palor, n(%)					
1Wk	0 (0)	0 (0)	0 (0)	0 (0)	0.196
1Mo	5 (71.4)	8 (66.7)	3 (42.9)	16 (61.5)	
3Mo	2 (28.6)	4 (33.3)	2 (28.6)	8 (30.8)	
>3Mo	0 (0)	0 (0)	2 (28.6)	2 (7.7)	

BCVA = Best-corrected visual acuity, RE = Right eye, LE = Left eye, VA = Vehicle accident, NPL = No light perception, PL = Light perception, HM = Hand motion, CF = Counting finger, DM = Diabetes mellitus, HT = Hypertension, DLP = Dyslipidemia

An interesting case example of a patient in progesterone group, showing a surprising visual improvement in many parameters: A 24 year-old Thai male with history of motorcycle accident and forehead contusion came to hospital with symptom of blurred vision on his left eye after the accident. Initial best-corrected visual acuity of his left eye was 20/125, positive relative afferent pupillary defect on left eye. Neuroimaging showed no abnormalities. He was diagnosed with indirect traumatic optic neuropathy and enrolled to the study. He was given Depot medroxyprogesterone acetate 1 mg/kg intramuscular injection every 12 hours for 5 days and no side effects were observed.

After follow-up, the final best-corrected visual acuity at 3 months was 20/20. There was persistently positive relative afferent pupillary defect on left eye and optic disc photography showed left optic nerve atrophy developed in 3 months Fig 2. Color vision test showed increased in number of plate from 0 plate at baseline, 12 plates at 1 week and 25 plates at both 1 and 3 months of follow-up. Visual field testing showed improvement in mean deviation and pattern standard deviation demonstrated by the gray scale in Fig 2.

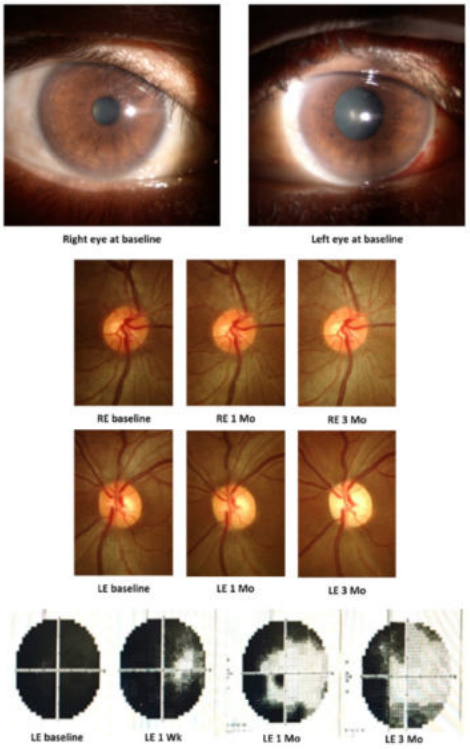

Fig. 2 Patient example: Patient number 1: Anterior segment photograph at baseline, disc photograph and gray scale of visual field test during follow-ups.

Repeated measure ANOVA was utilized for analysis of improvement in best-corrected visual acuity after adjustment for confounding factors. Statistical level of significance was set at 0.05. Best-corrected visual acuity mea- sured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was converted to visual acuity in LogMAR unit for purpose of analysis. Table 3 shows analysis for primary outcome. No statistically significant change in mean best-corrected visual acuity between patients of all 3 groups in each follow-up ($p = 0.891$).

Analysis within steroid group showed statistically significant change in mean best-corrected visual acuity ($p = 0.002$). Comparing to best-corrected visual acuity in baseline, there were statistically significant improvement of best - corrected visual acuity at 1 and 3 months ($p = 0.015$, 0.028 respectively).

Table 3 Mean best-corrected visual acuity change in 3 groups

Primary outcome	Progesterone n=7	Steroid n=12	Observation n=7	P-value
BCVA (LogMAR)				
Baseline	1.67±0.39	1.66±0.32	1.59±0.31	0.891
1 Wk	1.54±0.60	1.44±0.52	1.40±0.56	
1 Mo.	1.49±0.62	1.26±0.61	1.40±0.53	
3 Mo.	1.40±0.69	1.28±0.66	1.41±0.54	
P-value (within group)	0.055	0.002*	0.138	
BCVA (LogMAR) Analysis within steroid group				P-value
Baseline		1.66±0.32		(Compare with baseline)
1 Wk		1.44±0.52		0.053
1 Mo.		1.26±0.61		0.015*
3 Mo.		1.28±0.66		0.028*

Secondary outcomes for this study were color vision tested by Ishihara test and visual field testing, focused on mean deviation and pattern standard deviation. Analysis for these secondary outcomes Table 4 showed no significant change in number of plate of ishihara test, mean deviation and pattern standard deviation ($p = 0.415$, 0.826, 0.330 respectively).

Table 4 Mean best-corrected visual acuity change in 3 groups

Secondary outcomes	Progesterone, n=7	P-value
Color vision by Ishihara test (Plates)		
Baseline	**0.00±0.00**	**0.415**
1 Wk	**1.71±4.54**	
1 Mo.	**3.57±9.45**	
3 Mo.	**3.57±9.45**	
Visual field (Mean deviation)		
Baseline	**-31.95±3.92**	**0.826**
1 Wk	**-31.96±3.15**	
1 Mo.	**-30.25±7.93**	
3 Mo.	**-30.22±9.63**	
Visual field (Pattern standard deviation)		
Baseline	**2.11±0.45**	**0.330**
1 Wk	**3.25±2.93**	
1 Mo.	**3.18±2.88**	
3 Mo.	**2.68±2.59**	

Improvement of visual acuity was defined as a decrease of at least 0.4 logMAR in visual acuity after 3 months (Decreased BCVA in LogMAR unit reflects better BCVA). Table 5 shows factors effecting visual outcomes on recovery of visual acuity, analyzed by Binary logistic regression analysis. Most of clinical characteristics showed no effect to improvement of visual acuity. Better baseline best-corrected visual acuity was the only factor detected statistically significant to predict better visual outcome ($p = 0.027$, Odds ratio = 0.004, 95% CI = 0.000 - 0.537).

Table 5 Factors effecting visual outcomes

Factors	Improved (n=9)	Not improved (n=17)	P-value	Odds ratio	95% CL
Groups, n(%)					
Progesterone	2(28.6)	5(71.4)	1.000	1.000	0.098-10.166
Steroid	5(41.7)	7(58.3)	0.57	1.786	0.241-13.215
Observation	2(28.6)	5(71.4)		1.000	
Baseline BCVA	1.38±0.04	1.78±0.16	0.027*	0.004	0.000-0.537
Age	25.56±5.48	34.76±18.22	0.174	0.949	0.881-1.023
Sex					
Male	9(37.5)	15(62.5)	0.999	NA	NA
Female	0(0)	2(100)		1.000	
Side of eye					
Right eye	3(37.5)	5(62.5)	0.837	1.200	0.212-6.801
Left eye	6(33.3)	12(66.7)		1.000	
Injury type					
Vehicle accident	8(44.4)	10(55.6)		1.000	
Fall	0(0)	4(100)	0.999	NA	NA
Assault	0(0)	2(100)	0.999	NA	NA
Blast	1(50)	1(50)	0.881	1.250	0.067-23.259
Orbital fractures					
No fracture	6(42.9)	8(57.1)	0.251	3.000	0.459-19.592
1 wall	1(50)	1(50)	0.392	4.000	0.167-95.756
>1 walls	2(20)	8(80)		1.000	
History of amnesia					
Yes	7(38.9)	11(61.1)	0.496	1.909	0.297-12.261
No	2(25)	6(75)		1.000	
Time to visit hospital	7.67±7.75	6.12±6.01	0.562	1.037	0.917-1.172
Time to treatment	50.86±42.04	79.67±51.36	0.219	0.986	0.965-1.008

BCVA = Best-corrected visual acuity, 95% CI = 95% confidence interval, NA = not applicable

Discussion

In our study, most of cases were young men, which is consistent with other studies. [7,39] Vehicle accidents were the most common form of injury in our patients [18] (69.2%), as they were in the studies of Entezari et al. [40] (51.5%) and Steinsapir et al. [41] (45%)

Visual improvement occurred in 28.6 % of cases in progesterone group, 41.7% of steroid and 28.6% of observation groups; this difference was not statistically significant. Moreover, there was no statistically significant change in mean best-corrected visual acuity between patients of all 3 groups in each follow-up (p - value = 0.891). Therefore, our study showed that there was no difference in improvement effect between progesterone, steroid and observation in the treatment of indirect traumatic optic neuropathy. Our results were relevant to those found by Levin et al.[7], which reported results of treatment of 127 cases with TON by observation alone, with corticosteroid treatment, or optic nerve decompression surgery. The results did not show any differences in study groups (32% in the decompression group, 57% in the placebo group, and 52% in the treatment group). In Levin's study, selection of cases was also not randomized and the trial was not double-blind.

Analysis within steroid group showed statistically significant change in mean best-corrected visual acuity (p - value = 0.002). Comparing to best-corrected visual acuity in baseline, there were statistically significant improvement of best- corrected visual acuity at 1 and 3 months (p - value = 0.015, 0.028 respectively). This result that found in our study contrasts to Entezari's study[40] which reported that corticosteroid administration in TON does not improve visual acuity compared to placebo administration (p - value = 0.38). In terms of secondary outcome, the results failed to show the improvement of color vision and visual field testing despite of the selected case of patient number 1.

Progesterone treatment in our study showed no side effect detected by symptom and laboratory results. This finding resembles report the use of progesterone in treatment of traumatic brain injury by Wright et al [36] and Xiao et al.[37,38]

These reports confirm that treatment by progesterone is safe and reflects interesting outcomes. In our study, some of patients received steroid prior to progesterone due to physician's judgement. These events also showed no adverse effect of both medications which imply that progesterone can be used adjunct or combine to steroid treatment. At some circumstance, patients may be contraindicated to corticosteroid treatment; progesterone can be a main or alternative choice of treatment for patient with indirect traumatic optic neuropathy.

After multivariate analysis, only one factor was detected to be statistically significant in our study. Initial BCVA was detected as a predictive factor in improvement of final BCVA. This is similar to Levin's study[7], in which they concluded that initial visual acuity after trauma is a powerful prognostic factor in final visual acuity. This relation was also detected in other studies. [42,43]

Our study shows that progesterone is a safe and promising neuroprotective agent for treatment of indirect traumatic optic neuropathy. Our study was the first to report about clinical use, efficacy and safety of progesterone for traumatic optic neuropathy treatment but showed no difference among choices of treatment. The study design was historical control trial which had problems in validity, time frame for comparison and missing data. To prove a clear effect, we suggest conducting double-blind randomized clinical trial studies with different doses of progesterone and study in larger population.

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EFFECT OF HUMIDIFIER TEMPERATURE DURING NON-INVASIVE VENTILATION ON WATER CONDENSATE AND AIRWAY PRESSURE: NEWBORN MANIKIN MODEL

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Abstract

Recommendation for setting humidifier temperature when using non-invasive ventilation in newborn infants has been changed from low range (32-34°C) to high range (37°C). However, there is no evidence comparing benefit and hazard between the two settings. To compare the effect of two temperature settings of humidifier during non-invasive ventilation on nasopharyngeal temperature, water condensate and airway pressure. We applied nasal intermittent positive pressure ventilation in a newborn manikin with artificial lungs. The temperature of humidifier was set at high range or low range. We measured nasopharyngeal temperature, water condensate in ventilator circuit and airway pressure in an artificial lung at 0, 8 and 16 hours after starting ventilation. The experiments were conducted 3 times for each setting of humidifier. Comparisons between the groups were analyzed by using unpaired *t-test* or Mann Whitney test. Correlation of water condensate and airway pressure was analyzed by using Pearson's correlation. Nasopharyngeal temperature with humidifier temperature at high range 34.0 ± 0.1 °C was significantly higher than that at low range 32.1 ± 0.2 °C ($p < 0.001$). Volume of water condensate in ventilator circuit was strongly correlated with airway pressure in artificial lungs (r= - 0.828 for PIP, r= - 0.948 for PEEP). Water condensate in ventilator circuit significantly decreased airway pressure and interfered with ventilator function. When using non-invasive ventilation, setting humidifier temperature at high range produces substantial water condensate resulting in significantly decreased airway pressure. Therefore, water drainage should be emphasized as animportant respiratory care. Funding: Phramongkutklao Foundation

Keywords : Humidifier, Non-invasive ventilation

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Introduction

When upper airway is bypassed during invasive ventilation or mechanical ventilation with endotracheal tube in place, warmed and humidified gas is necessary to prevent airway and lung injury. It is suggested that ventilatory devices should provide inspired gas to the lungs at temperature of 37°C and 100% relative humidity (44 mg H_2O/L).[1-5] This recommendation has been generally practiced in all age groups of patients including newborn infants.[6-8] For patients requiring non-invasive ventilation (NIV) via facial mask, nasal prong ornasal cannula, there is no conclusive recommendation for setting optimal temperature and humidity of inspired gas.[4,5] In adult, humidifier temperature is usually set at low range (31 - 34°C) since the inspired gas will be warmed and humidified in the upper airway. Currently, a new guideline for newborn infants receiving NIV has been changed to set humidifier temperature similarly to invasive ventilation at 35.5 - 42°C (average 37°C). A proposed rationale is that newborn infants with rapid respiratory rate may have limited ability to warm inspired gas in their upper airway.

However, there was no study to determine benefit and harm of this guideline. High temperature of inspired gas may result in increased water condensate in ventilator circuit which subsequently increased risk of aspiration and infection. Since appropriate setting of humidifier temperature during NIV in newborn infants was controversial, we conducted an experiment to determine the effect of humidifier temperature on water condensate and airway pressure during NIV in a neonatal manikin model.

Methods

We conducted an experimental model by using a conventional ventilator (Evita V300®, Dräger) with a humidifier (MR 850®, Fisher-Paykel). The humidifier had 2 temperature setting modes: invasive and non-invasive modes Fig 1. A neonatal manikin with artificial lungs was placed in an infant incubator (Isolette 8000®, Dräger). Temperature and humidity at the nasopharyngeal level was measured by using a thermohygrometer (SK - L200THII a® humidity and temperature with SK - LTHII - 3 probe, SATO). Airway pressure in an artificial lung was measured by using a gas flow analyzer (FLUKEVT mobile gas flow analyzer®) (Fig 2). Volume of water condensate was measured directly after disconnecting ventilator circuit.

Nasal intermittent positive pressure ventilation (NIPPV) via nasal prong was set at peak inspiratory pressure (PIP) of 15 mmHg, positive end expiratory pressure (PEEP) of 5 mmHg.

Room temperature and infant incubator were set at 26°C and 32°C, respectively. The experiments were performed by setting humidifier temperature at either invasive or non- inva sive mode Fig 1.

Temperature and relative humidity at the nasopharyngeal level, volume of water condensate in ventilator circuit, airway pressure in an artificial lung and ventilatory pressure were sequentially measured at 8 and 16 hours after starting ventilation Table 1. The experiments were conducted 3 times for each setting of humidifier temperature.

Comparisons within each experiment were analyzed by using paired *t-test* or Wilcoxan sign rank test. Comparisons between the two settings of humidifier temperature were analyzed by using unpaired *t-test* or Mann Whitney test as appropriate. The association between volume of water condensate and airway pressure was analyzed by using Pearson's correlation.

Results

There were no differences in room temperature, relative humidity, and infant incubator temperature between the two groups of experiments. With humidifier setting at invasive mode, average temperatures of the inspiratory limb of venti- lator circuit were significantly higher than those with setting at non-invasive mode Table 2.

With invasive mode, average temperature and relative humidity at nasopharyngeal level were significantly higher than those with non-invasive mode. Volume of water condensate in ventilator circuit was significantly higher with setting at invasive mode Table 3.

Airway pressure, PIP and PEEP, in an artificial lung declined with time with setting at invasive mode whereas they were relatively constant with non-invasive mode. Declined PIP and PEEP returned to baseline levels after draining water condensate from both expiratory and inspiratory limbs of ventilator circuit Fig 3.

PIP and PEEP in an artificial lung were strongly correlated with volume of water condensate in ventilator circuit (correlation coefficient = - 0.828 and - 0.948, respectively).

Ventilatory pressures, PIP and mean pressure (Pmean), read on the monitor during invasive mode were significantly higher than those during non-invasive mode Fig 4 . In addition, waveform of ventilatory pressure on the monitor markedly fluctuated but returned to normal after draining water condensate from ventilator circuit.

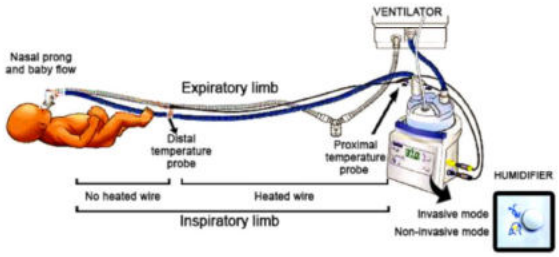

Fig 1 Experimental model: ventilator circuit (inspiratory and expiratory limbs), humidifier with two temperature settings (invasive and non-invasive modes), nasal prong and baby flow and a neonatal manikin

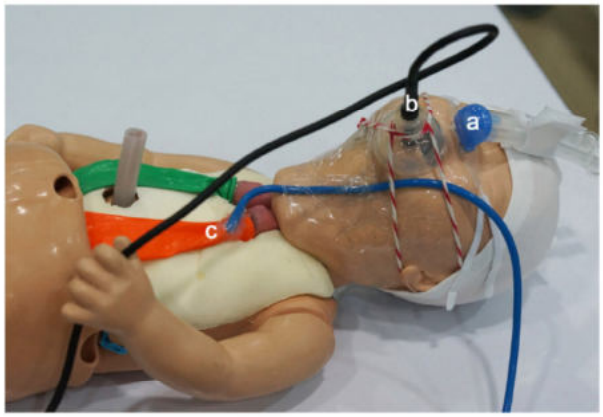

Fig 2 A neonatal manikin with nasal prong (a), thermohygrometer probe for measuring temperature and humidity at the nasopharyngeal level (b) and a gas flow analyzer probe for measuring airway pressure in an artificial lung (c)

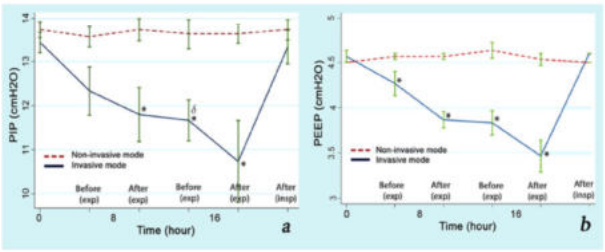

Fig 3 Comparisons of PIP (a) and PEEP (b) in an artificial lung between setting humidifier at invasive mode and non-invasive mode at 8 and 16 hours after starting ventilation (exp): draining water condensate in an expiratory water trap of ventilation

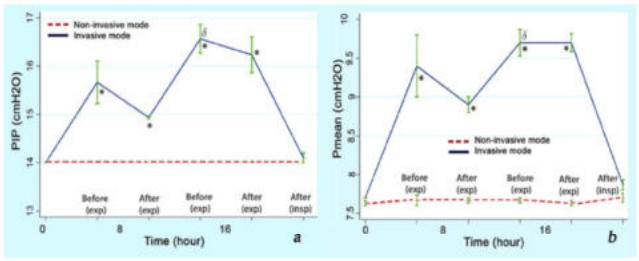

Fig 2 Comparisons of PIP (a) and mean presure (Pmean) (b) of the ventilator between setting humidifier at invasive mode and non-invasive mode at 8 and 16 hours after starting ventilation (exp): draining water condensate in an expiratory water trap o

Table 1 Timing and procedures to measure the outcomes of each experiment

Timing after starting ventilation	Nasopharyngeal		Water condensate (mL)	Airway pressure (cmH_2O)	Ventilator pressure (cmH_2O)
	Temperature (°C)	Humidity (%)			
0 hour	✓	✓		✓	✓
8 hours	✓	✓	✓		
- Before (exp)				✓	✓
- After (exp)				✓	✓
16 hours	✓	✓	✓		
- Before (exp)				✓	✓
- After (exp)				✓	✓
- After (insp)				✓	✓

(exp): Draining water condensate in an expiratory water trap of ventilator circuit

(insp): Draining water condensate in inspiratory limb of ventilator circuit

Table 2 Temperature and humidity of environment and inspiratory limb of circuit

Variables	Humidifier temperature mode		*p* - value
	Invasive	Non-invasive	
Experimental environment			
Room temperature (°C)	26.04 ± 0.04	25.98 ± 0.06	0.391
Room relative humidity (%)	75.29 ± 0.56	76.20 ± 0.68	0.337
Infant incubator temperature (°C)	32.00 ± 0.00	32.01 ± 0.01	0329
Temperature of inspiratory limb			
Proximal probe (°C)	37.11 ± 0.08	31.58 ± 0.25	< 0.001
Distal probe (°C)	39.92 ± 0.03	33.92 ± 0.04	< 0.001

Data presented as mean ± standard error

Table 3 Temperature and humidity at nasopharyngeal level and water condensate in circuit

Variables	Humidifier temperature mode		P value
	Invasive	Non-invasive	
Nasopharyngeal temperature (°C)			
0 hour	34.00 ± 0.006	32.07 ± 0.19	< 0.001
16 hours	34.50 ± 0.06	32.20 ± 0.05	< 0.001
Nasopharyngeal relative humidity (%)			
0 hour	99.00 ± 0.00	73.33 ± 0.67	< 0.001
16 hours	99.00 ± 0.00	73.00 ± 0.29	< 0.001
Volume of water condensate (mL)			
8 hour *	33.23 ± 1.16	2.87 ± 0.13	< 0.001
16 hours **	46.70 ± 0.72	2.53 ± 0.15	< 0.001

Data presented as mean ± standard error

* Water condensate in an expiratory water trap of ventilator circuit

** Water condensate in inspiratory and expiratory limbs of ventilator circuit

Discussion

Currently, NIV including NIPPV, nasal continuous positive airway pressure (NCPAP) and nasal high flow was widely recommended for preterm infants requiring ventilatory support. In this study, we conducted an experiment by using NIPPV due to technical limitation in measuring airway pressure in a non-breathing manikin. This study demonstrated that humidifier setting at invasive mode generated gas temperature and humidity at the nasopharyngeal level close to recommendation. However, it is difficult to conclude that setting humidifier at invasive mode is better than non-invasive mode during NIV. In newborn infants with spontaneous breathing, temperature and humidity of inspired gas may increase in the nasal cavity and upper airway.[3,4] With invasive mode, there was significant amount of water condensate in ventilator circuit including in the baby flow and nasal prong attached to the manikin. Water condensate decreased airway pressure in an artificial lung which was opposite to a previous study. Youngquist et al reported that water condensate in the expiratory limb of ventilator circuit increased airway pressure in the trachea.[9] The contrary may be due to different ventilator circuit and methodology. The declined PIP and PEEP returned to baseline after draining water condensate from both the expiratory and inspiratory limbs of ventilator circuit. In addition, water condensate interfered with normal function of the mechanical ventilator.

The experiment was conducted in a manikin model under well-controlled environment. In a neonatal intensive care unit, lower room and incubator temperatures as well as exhaled gas may result in larger amount of water condensate and greater effect on the infant airway pressure.[10,11]

Conclusion

Our study demonstrated high humidifier temperature results in better airway temperature and humidity. However, it produces a large amount of water condensate which interrupts mechanical ventilator function and disturbs infant ventilation. Physicians should be aware of the benefit and harm of humidifier setting during receiving NIV. When setting humidifier temperature at high range, good respiratory care to minimize accumulation of water condensate in ventilator circuit should be emphasized.

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Conflict of Interest

The authors declare no conflict of interest.

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PROTEUS SYNDROME: REPORT OF A CASE WITH VASCULAR MALFORMATION SUCCESSFULLY TREATED WITH ENDOVENOUS RADIOFREQUENCY ABLATION

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Abstract

We reported a case of a 10 year-old Thai boy diagnosed as Proteus syndrome, presented with progressive enlarging of extremities with asymmetric disproportionate overgrowth and distorting of the feet and toes. Skin examination showed marked thickening of the soles without characteristic cerebriform appearance, and well-defined purplish plaques with capillary-microcystic lymphatic malformation on the right hip and thigh. MRI/MRA of extremities showed disproportionate overgrowth with combined lymphatic-venous malformation at the right buttock and right lower extremity. He was treated with endovenous radiofrequency ablation (EV-RFA) by using VNUS® Radiofrequency Generator Model RFG2 (VNUS Medical Technologies Inc., San Jose, California, USA and foam sclerotherapy after ablation as an adjunctive treatment for the venous malformation of the right leg with favorable outcomes.

Keywords : Proteus syndrome, Cerebriform connective tissue nevus, Endovenous radiofrequency ablation

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Introduction

Proteus syndrome is characterized by variable manifestations, including vascular malformations, cerebriform connective tissue nevus, epidermal nevi, lipomas or dysregulated adipose tissue, dermal hypoplasia, asymmetric disproportionate overgrowth of body parts, facial phenotype and hyperpigmentation. Cerebriform connective tissue nevus is the pathognomonic sign of Proteus syndrome. Proteus syndrome is caused by an activating somatic mutation of the AKT1 gene (c. 49G > A or p. Glu17Lys). The clinical variability emphasizes the mosaic basis for this syndrome. Treatment of Proteus syndrome is challenging.

Results

We reported a case of a 10 year-old Thai boy presented with progressive enlarging and distorting of extremities with the diagnosis of Proteus syndrome. He had enlarged and thickened feet with hemihypertrophy of the right buttock and right leg. Asymmetric disproportionate overgrowth and distorting of the toes of both feet were observed with slightly difficulty walking. He can do activities of daily living independently, however, with potential functional impairment. His parents reported that the patient had normal developmental milestones and intelligence. He was born to a healthy mother with term, vaginal delivery with 2,800 grams birthweight. There was neither family history of a similar skin lesion nor known genetic disorders in the family. There was no consanguineous marriage in the family, shown in the pedigree as Fig 1.

His facial appearance was also dysmorphic, including dolichocephaly, long face and downslanting palpebral fissures. Dermatologic examination showed marked thickening of both soles without the characteristic cerebriform appearance and well-defined purplish plaques with clinically capillary-microcystic lymphatic malformation on the right hip and right thigh. The large protruding abdominal mass with superficial vein dilatation was also observed.

The MRI of abdomen found fatty overgrowth along left lateral abdominal wall with splenomegaly. The clinical signs in this patient were shown in Fig 2, 3, 4 and 5.

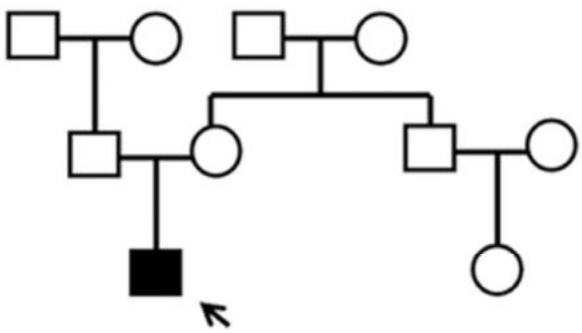

Fig 1 Pedigree of the patient

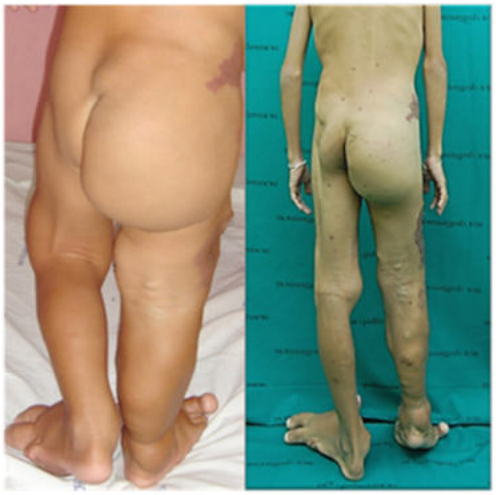

Fig 2 Fig 2 Hemi-hypertrophy of the right buttock and right leg during 3 and 9 years old

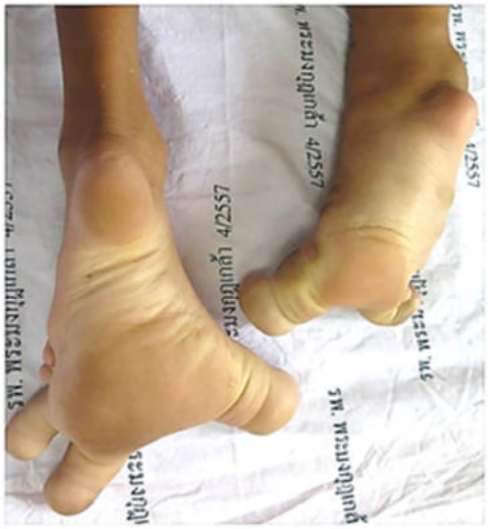

Fig 3 Marked thickening of the soles

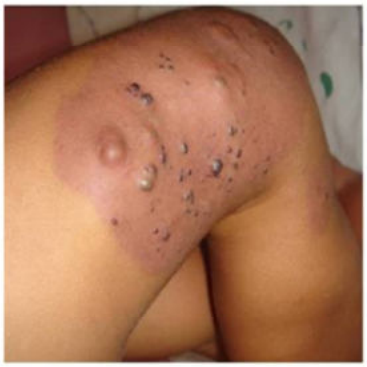

Fig 4 Lymphatic, capillary and venous malformations on the right leg

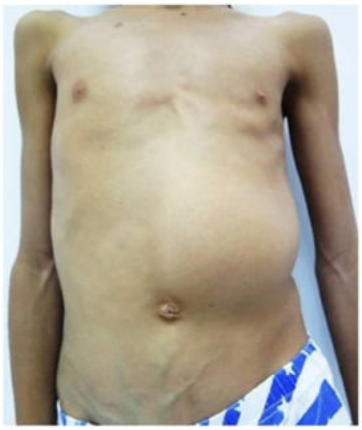

Fig 5 Lipomas with superficial vein dilatation on abdomen

The x-ray of both feet showed enlarging of bones and soft tissue. MRI/MRA of extremities showed disproportionate overgrowth with combined lymphatic-venous malformation at right buttock and right lower extremity.

The venogram of this patient documented patent of deep venous system and incompetent perforating veins at the upper portion of the proximal right leg. Ultrasonography was performed to confirm the segment of venous malformation in which we measured venous diameter and length for the complete preoperative planning.

We treated our patient with endovenous radiofrequency ablation (EV-RFA) by using VNUS® Radiofrequency Generator Model RFG2 (VNUS) Medical Technologies Inc., San Jose, California, USA), and applying the closure with the ablation tip three centimeters in length. He also received the adjunctive treatment with foam sclerotherapy after ablation for the venous malformation of the right leg. Then the limb compression was done with elastic bandage during early postoperative period.

The EV-RFA was performed 3 consecutive times with favorable results. The symptoms and signs including leg pain, feeling of leg heaviness, reducing of the leg size and bleeding problems were very much improved. He also reported the improvement in the abilities for ambulation and in quality of life.

Discussion

Proteus syndrome is a sporadically occurring hamartomatous disorder. It was first described by Cohen and Hayden in 1979 and designated as Proteus syndrome by Wiedemann et al.[1,2] This condition is characterized by cerebriform connective tissue nevus, epidermal nevi, vascular malformations, lipomas, dermal hypoplasia and hyperpigmentation. Progressive, asymmetric disproportionate overgrowth of body parts are also characteristics of Proteus syndrome. Cerebriform connective tissue nevus is considered as unique pathognomonic sign.[3] The average age of onset for connective tissue nevus to develop is 2 years old. However, during the 6 years follow-up, we did not observe this important sign in our patient. Then our patient is a case of Proteus syndrome without the characteristic cerebriform type connective tissue nevus.

Proteus syndrome is an extremely rare disorder with less than 100 affected individuals reported worldwide.[4] Approximately 90% of individuals who meet the clinical criteria were caused by an activating somatic mutation of the AKT1 gene (c.49G>A or p. Glu17Lys).[5] AKT is a member of PI3K/AKT/ mTOR signaling pathway which normally plays an essential role in regulation of normal cell growth and survival. Post - zygotic mutation of AKT1 gene results in mosaic distribution and sporadic occurrence of this syndrome. Clinical variability is correlated with the degree of mosaicism of the mutation in the affected cells and tissues.

The mainstay of management in Proteus syndrome needs multidisciplinary approach focusing on disease progression, possible interventions, complication and enhancing the abilities for activities of daily living without difficulty.

Furthermore, the aim of the treatment is to minimize the physical and psychosocial consequences. The individual hamartomatous and localized overgrowth can sometimes be possibly treated surgically.

Antithrombotic prophylaxis should be considered during surgical procedure because of the potential risks of developing deep venous thromboses and fatal pulmonary emboli.[6] Limb gigantism usuallyrequires vascular imaging and selective embolization. The venogram of ourpatient showed patent of deep venous system and incompetent perforating veins at the upper portion of the proximal right leg. He was a good candidate of receiving treatment with endovenous radiofrequency ablation (EV-RFA) for the venous malformation of his right leg. Then our patient was successfully treated with EV-FRA together with foam sclerotherapy after ablation for the venous malformation of the right leg with favorable outcomes.

Conclusion

We reported a case of Proteus syndrome that fulfilled the diagnostic criteria which included vascular malformations, lipomas, progressive asymmetric, distorting limb overgrowth and the facial phenotype.[7] Our patient was successfully treated with EV-RFA and foam sclerotherapy for the venous malformation of his leg with promising outcomes. Therefore, endovenous radiofrequency ablation may be an effective option providing alternate or adjunctive treatment modality to surgery for the patients with Proteus syndrome.

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THAI CONSENSUS ON VENOUS THROMBOEMBOLISM IN HIP AND KNEE SURGERY

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Abstract

Increasing numbers of hip and knee arthroplasty may associate with higher risk of complications such as venous thromboembolism. Most of Thai orthopedic surgeons ignore thromboprophylaxis because of less symptomatic VTE in Asian population. The "Thai consensus on venous thromboembolism in hip and knee surgery" consist of twenty-four common questions about VTE including their supported literatures. The gold standard of diagnosis is contrast venography although the duplex ultrasound has more role in postoperative patients. Thai patients undergoing hip and knee surgery seem to have lower prevalence of VTE than Caucasian. However, mechanical or chemoprophylaxis should be considered especially in the high risk group and hip fracture in elderly.

Keywords : Venous thromboembolism, Deep vein thrombosis, Hip and knee arthroplasty, Thromboprophylaxis, Chemoprophylaxis

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Introduction

Higher life expectancy in Thai population is associated with increasing of the degenerative disorders. The numbers of osteoarthritis of hip and knee that non-response to conservative treatment, such as medication and physical therapy, are also increasing. Hip and knee arthroplasty in elderly are the major operations which not only improve the quality of life, but also able to create some complications. One of the common complications following hip and knee surgery is venous thromboembolism (VTE) which has several degrees of severity (asymptomatic-life-threa tening).

According to awareness of VTE sequelae, the "Thai consensus conference on venous thromboembolism in hip and knee surgery 2016" was held on 15th - 17th September, 2016 at Lampang, Thailand by the Thai Hip and Knee Association. The participants are Thai orthopedic surgeons who work in different institutions including government hospitals, universities, military services and private hospitals. Modified Delphi method was applied to generate four categories of questions and answers; 1) diagnosis of deep vein thrombosis (DVT)/VTE, 2) risk of DVT/VTE, 3) prevention, and 4) chemoprophylaxis. Finally, twenty-four questions and answers were voted for agreement.

The level-1 evidence-based literature were reviewed by the experts to respond all questions, establishing a consensus. Although the data included in this consensus are suitable for most of Thai patients who undergoing hip and knee surgery. In some situations, the surgeons might have to make different decision for appropriate management.

Question 1: Which investigation is the gold standard for diagnosing DVT after TJA?

Consensus: Contrast venography.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Deep venous thrombosis (DVT) continues to be a source of major morbidity and mortality for surgical patients. The incidence of postoperative DVT is as high as 28% in some series. Indeed, the clinical complications (from post-thrombotic syndrome to fatal pulmonary embolism) as well the risk of anticoagulant treatment require a precise diagnosis. Since clinical diagnosis of DVT is barely sensitive and specific. Thus, the clinical suspicion of DVT needs to be confirmed by objective testing. Venography has been for a long time the reliable technique to confirm or rule-out the clinical suspicion of DVT. Furthermore, venography served as "gold standard" for the validation of diagnostic methods for DVT.[1,2] However, venography is invasive, expensive, not always available, and occasionally inadequate or risky, noninvasive diagnostic strategies for diagnosing DVT have been developed. Non-invasive diagnostic methods (venous ultrasonography) are sufficiently sensitive for venous occlusions. The optimal strategy at individual institutions is dependent on local expertise and cost.[1,3]

Question 2: Should isolated leg swelling be investigated for DVT after TJA?

Consensus: Isolated swelling in the operated limb without other signs of deep vein thrombosis does not require investigation.

Delegate vote: Agree: 95.8%, Disagree: 4.2%, Abstain: 0% (Strong Consensus)

Justification:

Swelling of operated leg is very common after THA and TKA. The postoperative swelling can be caused by direct injury from surgery as well as penetration of intra-articular blood collection into surrounding soft tissue. Although leg swelling is one of clinical signs of deep vein thrombosis, isolated leg swelling after THA and TKA should not be used as an indication for investigation unless other signs of DVT are also presented. Clinical signs of DVT include:[4]

- Swelling
- Pain or tenderness
- Distended veins
- Red or discolored skin
- Firmness or thickening of the vein

Very few clinical studies report correlation between incidence and clinical sings of DVT after THA and TKA. A retrospective study about risk factors for limb swelling after TKA by Gao et al. reveals no correlation between leg swelling (increased circumference) and incidence of DVT.[5] Since there are no strong supporting evidences, decision has to be made based on expert opinion by considering unclear benefit of venographic study in this situation and financial cost of investigation.

Question 3: Does D-dimer have a role for diagnosing VTE after TJA?

Consensus: D-dimer does not have a role for diagnosing VTE after TJA.

Delegate vote: Agree: 95.8%, Disagree: 4.2%, Abstain: 0% (Strong Consensus)

Justification:

D-dimer is the degradation product of crosslinked (by factor XIII) fibrin.[6-13] It is a marker of endogenous fibrinolysis and should therefore be detectable in patients with deep vein thrombosis (DVT). [14-18] Several studies have shown the d-dimer assay to have a high negative predictive value and d-dimer to be a sensitive but nonspecific marker of deep-vein thrombosis.[6-8] D-dimer is a very useful diagno- stic tools for non-surgical patients, however post operation especially in hip and knee surgery, d-dimer result will be all in positive value which ultrasonography confirmation shown to be clear of DVT.[9] There are at least three evidence studies that suggest d-dimer is not useful screening test for VTE or DVT after arthroplasty. Two studies used ultra- sound as reference, while one used venography.

Question 4: Should duplex ultrasound be used as a screening test for diagnosing VTE in clinically suspected patient?

Consensus: Yes.

Delegate vote: Agree: 91.6%, Disagree: 4.2%, Abstain: 4.2% (Strong Consensus)

Justification:

The gold standard for VTE diagnosis is venography, but it is not proper for VTE screening in all patients because of cost and the invasiveness. The investigation that is less invasive than venography and widely used to diagnose VTE is duplex ultrasound. From the study of duplex ultrasound in the diagnosis of VTE in patients suspected to have VTE had sensitivity and specificity of 95% and 99%, respectively[19,20], but the value will be reduced to 31.1% and 93%, respectively, in patients who are not suspected VTE.[21,22] Hence, the use of duplex ultrasound for DVT screening should be conducted only in the patients that suspected of DVT. The advantages of duplex ultrasound are inexpensive and less invasive to the patient with high sensitivity and specificity. However, the duplex ultrasound requires an experienced radiologist. The disadvantages of using duplex ultrasound in VTE screening are operator dependent and have low sensitivity in patients who are not suspected DVT.

Question 5: Is it necessary to perform a routine screening test for DVT in patients undergoing TJA?

Consensus: No, it is not necessary to perform a routine screening test for DVT in patients undergoing TJA.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

We do not recommend the routine use of duplex ultrasound or contrast venography for screening of DVT in the patients undergoing hip or knee arthroplasty. The AAOS guideline[23] and two randomized controlled studies[24,25] found no statistically significant difference in symptomatic PE incidence between screening and non- screening group. The available evidences also suggest that d-dimer is not a useful screening test for DVT after arthroplasty, these studies use ultrasound and venography as the standard reference.[10-12]

Question 6: Which factors increase the risk of VTE in TJA patient?

Consensus: Cancer, previous VTE, delayed ambulation (> 4 days), Caucasian, a family history of VTE, hypercoagulable state, hormone replacement therapy, and multiple comorbidities

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Patients undergoing elective hip or knee arthroplasty are at high risk for venous thromboembolic disease (VTE) manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE). Previous history of VTE is the only risk factor that has sufficient evidence indicating that some of these patients may be at even higher risk.[26] Although a previous study in elective hip and knee arthroplasty patients has not clearly demonstrated whether factors other than a previous history of VTE increase the risk of VTE, we still believe that these potential risk factors including cancer, delayed ambulation (> 4 days), Caucasian race, family history of VTE, hypercoagulable state, hormone

replacement therapy and multiple comorbidities may increase the risk of VTE. The practitioner should consider making a prophylaxis of VTE in patients with these risk factors.

Question 7: Does obesity increase the risk of VTE in TJA?
Consensus: It is controversial whether obesity increases the risk of VTE in TJA.
Delegate vote: Agree: 87.4%, Disagree: 4.2%, Abstain: 8.4% (Strong Consensus)

Justification:

According to World Health Organization (WHO) criteria established in 1997 [27], obesity among adults is further classified into three categories: class I obesity is a BMI of 30 - 34.9 kg/m^2; class II is a BMI of 35 – 39.9 kg/m^2; and class III, or morbid obesity, is a BMI $\geq$ 40 kg/m^2. Increasing BMI above normal value has been reported to be associated with a rising risk of VTE.[28-30] Some studies have indicated that mortality among patients with PE appeared to be paradoxically lower among patients who were obese than those who were not.[31,32]

However, it remains obscure whether this phenomenon the so-called "obesity paradox" [33] is attributable to a real protective role of increased body fat because the lower mortality was seen mostly among old people who were obese, but not among young adults and children who were obese.[31,32] By analyzing the relationship of body fat (%) with VTE, a significant association was found in women, but not for men.[34] In summarized, there is the relationship of obesity with some common weak-to moderate risk factors for VTE, including genetic factors, use of sex steroid hormones, inflammation, and insulin resistance.[35,36]

Question 8: Does Thai population have lower prevalence of DVT than Caucasian after TJA?
Consensus: Thai population seems to have lower prevalence of DVT than Caucasian after TJA.
Delegate vote: Agree: 95.8%, Disagree: 4.2%, Abstain: 0% (Strong Consensus)

Justification:

Prevalence of DVT after TKA without any prophylaxis for DVT was reported range from 40 to 88% among the Caucasian population.[37] While prevalence of DVT after THA without prophylaxis in Caucasian was reported range from 8 to 70%.[38] Among of this, proximal DVT was reported around 20% in the western world. For Asian countries including Thailand, prevalence of DVT was reported differently from the western world. From meta-analysis, prevalence of DVT following hip surgery and knee arthroplasty were 25.8% and 42.5%, respectively. Rate of proximal DVT of 9.6% (hip surgery) and 8.7% (knee arthroplasty) were reported in this meta-analysis.[39]

Question 9: Should chemoprophylaxis be administrated in Thai patient undergoing total joint arthroplasty?
Consensus: Yes, chemoprophylaxis should be administrated in high-risk Thai patient.
Delegate vote: Agree: 95.8%, Disagree: 0%, Abstain: 4.2% (Strong Consensus)

Justification:

As we known, patients who undergoing total joint arthroplasty are at high risk for venous thromboembolism.[26] In Thai patients, the incidences of overall and proximal deep vein thrombosis that detected by using venography after total knee arthroplasty are 61% and 12%, respectively.[40] To prevent these complications, we agree to use mechanical prophylaxis in all patients. Because of the two reasons, first, we agree that Thai population has lower prevalence of symptomatic venous thromboembolism than Caucasians[39], and second, bleeding complications of chemoprophylaxis, we therefore suggest using the chemoprophylaxis in high-risk patients. The risk factors are justified in above mention.

Question 10: Does tranexamic acid increase the risk of VTE in TJA patient?
Consensus: Tranexamic acid does not increase the risk of VTE in TJA patient.
Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Tranexamic acid (TXA) is an antifibrinolytic drug used for reducing blood loss in many surgical specialties. Meta-analysis and RCTs conclude that TXA can reduce blood loss, not increase incidence of DVT complications, and should be considered for routine use in primary total knee arthroplasty.[41-43] The route of administration and dosage do not appear to affect complication rates either.

Question 11: Does hip fracture patient carry the same risk of VTE as elective TJA patient?

Consensus: Hip fracture patient does not carry the same risk of VTE as elective TJA patient.

Delegate vote: Agree: 87.4%, Disagree: 8.4%, Abstain: 4.2% (Strong Consensus)

Justification:

Venous thromboembolism (VTE) remains a substantial cause of morbidity and mortality following hip fracture. Asymptomatic deep vein thrombosis (DVT) has been reported in up to 50% of all patients who sustain a hip fracture, with an incidence of fatal pulmonary embolus (PE) of up to 10%.[44-46]

From the study of Hefley FG Jr et al., they found Thirteen (10 percent) of 133 patients who had venography on admission to the hospital for a fracture about the hip had radiographic evidence of deep-vein thrombosis.[47] Only seven (6 percent) of the 122 patients who were seen at the hospital within two days after the fracture had evidence of thrombosis. However, six of the eleven patients who had a delay of more than two days between the fracture and admission to the hospital had evidence of thrombosis.

The study from Korea examined the incidence and trends of clinically relevant VTE including DVT and pulmonary embolism (PE) after hip and knee replacement arthroplasty (HKRA) in Korea. The overall incidence of VTE, DVT, and PE during 90 days were 3.9% (n = 853), 2.7% (n = 597) and 1.5% (n = 327) after HRA, while the incidence was 3.8% (n = 1,990), 3.2% (n = 1,699), and 0.7% (n = 355) after KRA.[48]

Question 12: Does regional anesthesia lower the risk of venous thromboembolism comparing to general anesthesia in total joint arthroplasty?

Consensus: Yes, regional anesthesia has a lower risk of venous thromboembolism than general anesthesia.

Delegate vote: Agree: 79.2%, Disagree: 0%, Abstain: 20.8% (Strong Consensus)

Justification:

Regional anesthesia, including epidural and spinal anesthesia, has several potential advantages over general anesthesia in total joint arthroplasty. From the meta-analysis of 21 independent randomized trials, regional anesthesia can be beneficial in reducing the duration of surgery, the requirement of transfusion, postoperative nausea and vomiting.[49] In terms of venous thromboembolism, regional anesthesia has a lower incidence of deep vein thrombosis and pulmonary embolism when compared to general anesthesia. However, the effects of regional anesthesia on long-term functional outcome after total joint arthroplasty are still unknown due to the lack of high quality evidence.[50]

Question 13: Does tourniquet time (or operative time) affect the risk of VTE in TJA patient?

Consensus: Prolonged tourniquet time (or operative time) increases the risk of VTE in TJA patient.

Delegate vote: Agree: 87.4%, Disagree: 8.4%, Abstain: 4.2% (Strong Consensus)

Justification:

TJA is one of the risk factors of DVT that have post-operative incidence of 20.3%-84%.[51-53] We found that operative time was considered to be significantly associated with the incidence of proximal DVT.[54] Data show that a total operative time which more than 2 hours is correlated with DVT. Incidence of DVT increase when tourniquet time exceeding 60 minutes, age older than 50 years and previous history of DVT.

Question14: Does mechanical prophylaxis have a role in all TJA patients?

Consensus: Yes, mechanical prophylaxis should be performed in all TJA patients.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Mechanical prophylaxis for venous thromboembolism (VTE) act on venous stasis. Mechanical prophylaxis can be static (the graduated compression stockings, elastic stockings or anti-embolism stockings), dynamic (intermittent pneumatic compression and venous foot pump) or both. The main advantage of these methods is lack of bleeding risk. Mechanical prophylaxis is recommended for every patients especially in patients who have high bleeding risk.[55,56] Mechanical and pharmacological methods of VTE prophylaxis are both effective and when used in combination have synergistic effects.[57]

Question 15: Does intermittent pneumatic compressive device (IPCD) have a role for preventing VTE in TJA patient?

Consensus: IPCD have a role for preventing VTE in TJA patient.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Chemoprophylaxis has been recommended to reduce the prevalence of postoperative DVT on the assumption that it will reduce the prevalence of PE, mortality, and thrombophlebitic syndrome. However, chemoprophylaxis carries a bleeding risk, with associated complications of blood loss, blood transfusion, transfusion-related transmission of disease, wound-healing problems, hematoma, slowed rehabilitation, wound drainage, and infection.[58-61]

IPCD is a mechanical device which is not only decrease the venous stasis and increase the blood flow in the lower extremities through external compression, but also can be a good option for avoid bleeding complication. In Asian people, Kim et al, found that patient who received treatment with a mechanical compression device only for prevention of DVT after primary TKA, the prevalence of DVT was only 6.6% compare to Lee et al, who report the incidence of DVT without thromboprophylaxis was 40.4%.[62,63] In a meta-analysis of Pour et al, IPCDs are effective in prevention of venous thromboembolic disease after total hip and knee arthroplasty compared to chemoprophylaxis.[64]

Also, the meta-analysis of Westrich et al, the incidence of DVT after TKA in the patients receiving IPCD was 17% that was significant lower than the patients receiving warfarin (45%) or aspirin (53%).[53] Both AAOS and ACCP guideline agree that mechanical prophylaxis is appropriated.[23] However, there has been a paucity of randomized clinical trial on its efficacy without chemoprophylaxis, therefore ACCP guideline suggest combining chemoprophylaxis with mechanical compression during hospitalization.[65]

Question 16: Which types of chemoprophylaxis are effective for preventing VTE in TJA patient?

Consensus: Aspirin, direct oral anticoagulants (DOAC), vitamin K antagonist and low-molecular-weight heparin (LMWH)

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

According to ACCP guideline, aspirin has been recommended for reducing VTE event in hip and knee replacement.[65] The recent systematic review, including 11 relevant studies with variation of dose regiments, concluded that aspirin can reduce VTE with low risk of bleeding complication.[66] Another large trial (PEP trial) including 13,356 patients underwent surgery for hip fracture and elective hip arthroplasty with use of 160 mg aspirin compare with placebo, they concluded that aspirin can reduce PE of 43% and symptomatic DVT of 29% without increasing death due to bleeding.[67] However, aspirin group increase postoperative transfused bleeding episodes significantly. In compare with other agents, Drescher FS et al included 8 trials compare with anticoagulants and found that aspirin trend to associate with higher risk of VTE and lower risk of bleeding but there was no statistical significant.[68] For economic aspect, Schousboe JT et al showed aspirin is a cost-effective choice for VTE prophylaxis following total hip arthroplasty in patient without history of VTE.[69]

Direct factor Xa inhibitors work by binding to the active site of factor Xa, thus, blocking the interaction with its substrate. Examples of oral direct factor Xa inhibitors are rivaroxaban, apixaban, edoxaban, and betrixaban. Rivaroxaban and apixaban are recommended by the ACCP in the same manner as the fondaparinux.[65] Rivaroxaban is a FDA approved oral direct factor Xa inhibitor that requires no monitoring. Lassen et al. reported that 10 mg of rivaroxaban taken once daily was more effective than 40 mg of enoxaparin administered once daily in reducing overall VTE for TKA patients (RR = 9.2 %; p <0.001).[70] There was no difference in major bleeding between rivaroxaban and enoxaparin groups (0.6 % vs 0.5 %; p > 0.05).).

In a study comparing 10 mg of rivaroxaban taken 6 hours postoperatively against 40 mg enoxaparin administered on the preoperative evening as prophylaxis for THA, rivaroxaban was significantly more effective than enoxaparin in preventing total VTE (1.1 % vs 3.7 %, RR of 2.6 %; p < 0.001) but not in symptomatic events (96.8 % vs 97.0%; p < 0.05).

No difference in occurrence of major bleeding ($p = 0.18$).[71]

Apixaban is a direct oral factor Xa inhibitor that has not been approved by FDA in United States. Lassen et al. conducted a series of studies comparing apixaban against different doses of enoxaparin as prophylaxis for total joint arthroplasty patients. For TKA patients, when 2.5 mg of apixaban taken 6 hours postoperatively twice daily was assessed against 30 mg of enoxaparin administered twice daily, both groups showed extremely low overall VTE rates, but apixaban resulted in significantly less bleeding risk and mortality rate.[72] A meta-analysis, investigated the efficacy of 2.5mg apixaban or 10 mg rivaroxaban against enoxaparin as prophylaxis after total hip and knee arthroplasty, summarized that oral factor Xa inhibitors were superior to enoxaparin in preventing DVT, but there was no difference in the rate of PE, mortality or postoperative wound infection.[73] Another meta-analysis by Guofeng Ma et al. included 6 RCTs with 13,790 patients showed that the incidence of DVT was significantly decreased with the use of direct Xa inhibitors (both twice daily and once daily regimes) comparing with the enoxaparin treatment ($p < 0.01$).[74] However, there was no significant influencing difference between direct Xa inhibitors (twice daily regime) and enoxaparin on the incidence of PE ($p = 0.06$), while significantly lower rate was found for once daily regime of direct Xa inhibitors ($p = 0.02$). With respect to major bleeding, the pooled analysis did not demonstrate a significant difference between groups.

Takeshi FJ et al compared edoxaban, another oral factor Xa inhibitor, with enoxaparin in thromboprophylaxis following TKA.[75] They concluded that edoxaban 30 mg once daily beginning 6 to 24 hours postoperatively was more effective than subcutaneous enoxaparin 20 mg subcutaneously twice daily beginning 24 to 36 hours postoperatively for 11 to 14 days. This study demonstrated a similar incidence of bleeding events.

Direct thrombin inhibitor (dabigatran) work by binding specifically to the active center of thrombin and inactivate free and fibrin-bound thrombin. This process is reversible leaving small amount of free and active thrombin to control hemostasis. In the US, dabigatran etexilate is a FDA approved oral direct thrombin inhibitor for prevention of atrial fibrillation and stroke, but not for VTE prophylaxis after THA and TKA. Eriksson et al compared dabigatran against enoxaparin (oral dabigatran 220 mg, 150 mg and subcutaneous enoxaparin 40 mg; all taken 6 hours postoperatively then once daily).[76] Efficacy outcomes measured were symptomatic DVT, venographic DVT, and/or symptomatic PE. The safety outcome measured was bleeding events during the course of study. The result showed efficacy outcome of 37.7%, 36.4% and 40.5% for enoxaparin, 220 mg dabigatran and 150 mg dabigatran, respectively. The major bleeding occurrence did not differ significantly among 3 groups (1.3% vs 1.5% vs 1.3%; $p > 0.05$).

Warfarin is the first oral anticoagulant that widely used in United States as an anticoagulant agent since 1954. It is vitamin K antagonist that inhibits the synthesis of active vitamin-K-dependent coagulation factors (factors II, VII, IX and X as well as protein C). Therapeutic anticoagulation is reached 24 to 72 hours after the initial dose. Most commonly, 5 or 10 mg is given the night before or the night of surgery and then dosing is adjusted to maintain an International Normalised Ratio (INR) of about 2.0. Rates of DVT using low-dose warfarin range from 35% to 59%.[77] INR levels below 2.0 were associated with a four to five times increase in the risk of VTE.[78] When compare warfarin to LMWH, LMWH was a more effective to prevent DVT formation ($p < 0.05$), but no difference to warfarin in preventing symptomatic events including PE.[79,80] The cautions of usage are bleeding risk, potential drug interaction and requirement for constant monitoring.

Enoxaparin (low-molecular weight heparin: LMWH) has been widely used for thromboprophylaxis in TJA. Several RCTs reported less DVT and symptomatic PE when compared with placebo. Enoxaparin 40 mg subcutaneously once daily or 30 mg subcutaneously twice daily for 7-14 days postoperatively can reduce the incidence of VTE significantly.[81,82] The bleeding complications trend to increase but not statistically significant. A meta-analysis showed 15%-30% of venographic DVT on discharge date although the TJA patients received enoxaparin for 7-14 days.[83] The recurrent DVT occur 10%-25% at 3-4 weeks after THA, while fatal PE can be detected during 1-5 weeks postoperatively.[84] Extended-duration enoxaparin prophylaxis reduced all episodes of DVT and symptomatic venous thromboembolism significantly, especially in THA patients.[83,85]

Question 17: Does other antiplatelets (not aspirin) have a role for preventing VTE in TJA patient?

Consensus: Other antiplatelets do not have a role for preventing VTE in TJA patient.

Delegate vote: Agree: 70.8%, Disagree: 0%, Abstain: 29.2% (Strong Consensus)

Justification:

Currently, other antiplatelets (except aspirin) has not been studied in regard to venous thromboprophylaxis.[86] In theoretically, there are medication with platelet aggregation inhibiting action that little use in the prevention of venous thrombosis, they are essential in the prevention of arterial thrombosis. In TJA patient who continuing other antiplatelets (such as clopidogrel) in the perioperative period can lead to bleeding related complications, so it has been recom- mended that if a patient is to undergo elective surgery and an antiplatelet effect is not desired, should be discontinued at least 5 days prior to surgery.

Question 18: Which conditions should be discontinued chemoprophylaxis of VTE after TJA?

Consensus: If a patient presented with major bleeding or prolonged wound drainage after TJA, chemoprophylaxis of VTE should be discontinued

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

The risk of VTE chemoprophylaxis is associated with bleeding in the perioperative and early post-operative period. There is a potential for long-term problems associated with bleeding, particularly as hematoma is the most important local risk factor for the development of a wound infection after surgery.[87] Saleh et al proposed that both hematoma formation and persistent wound drainage are predicative of superficial surgical site infection, which has a strong correlation with deep-wound infection.[88] Parvizi et al reported the effect of excessive anticoagulation and found that a mean international normalized ratio (INR) of greater than 1.5 was more prevalent in patients who developed post-operative wound complications and subsequent periprosthetic infection and suggested that cautious anticoagulation to prevent periprosthetic infection and its undesirable consequences.[89]

Question 19: Is mechanical prophylaxis alone appropriate for VTE prophylaxis in TJA patients who have bleeding disorders?

Consensus: Yes.

Delegate vote: Agree: 91.6%, Disagree: 8.4%, Abstain: 0% (Strong Consensus)

Justification:

Although mechanical prophylaxis methods have been shown to reduce the risk of VTE, they have been studied less than the major pharmacological treatment options. Mechanical methods of prophylaxis include graduated compression stocking, intermittent pneumatic compression and venous foot pump. However, 10% of surgical and medical patients at risk for VTE were classified as being at high risk for bleeding. According to ACCP 9th edition guideline[65], patients who has bleeding disorders or at risk for it and switch them to anticoagulant prophylaxis as soon as bleeding risk is considered to be low and if they met any of the following criteria ,which were the strongest predictors of bleeding : active gastroduodenal ulcer, bleeding in the 3 months prior to admission, platelet count < 50000 or if they had "multiple risk factors" for bleeding of lesser predictive strength, including age > 84, hepatic failure with INR >1.5, severe renal failure, ICU/CCU admission, a central venous catheter in place, rheumatic /autoimmune disease, current cancer and male sex. NICE clinical guideline[90] concluded that the risk factors for bleeding are acquired bleeding disorders (such as acute liver failure), untreated inherited bleeding disorders (such as haemophilia and von Wille brand's disease), thrombocytopenia (platelets less than 75x109/l), uncontrolled systolic hypertension (230/120 mmhg or higher), acute stroke and concurrent use of anticoagulants known (such as warfarin with INR>2).

Retrospective study of Morris JK, et al. involved 157 consecutive patients TKA who were treated with bilateral intra- and postoperative intermittent pneumatic compres- sion stockings.[91] All patients were followed for at least 6 weeks postoperatively. Postoperative color duplex ultrasound imaging was obtained for 120 patients 2 to 3 days posto- peratively. During hospitalization, 2 (1.7%) patients had acute deep vein thrombosis (DVT) diagnosed, 2 (1.7%) had DVT of indeterminate age, and 4 (3.3%) had chronic DVT. During follow-up, 1 (0.8%) patient had an acute DVT diagnosed at 5 weeks postoperatively and 1 (0.8%) had a superficial phlebitis and subsequently had a nonfatal pulmonary embolism 23 days postoperatively. The predominant chemoprophylaxis used was aspirin alone in 107 (89.2%) patients. The results of this study support the use

of a multimodal approach to VTE prophylaxis in TKA, using bilateral intra and postoperative intermittent pneumatic compression, epidural anesthesia, early mobilization, and postoperative aspirin without the use of major anticoagulation as an effective, safe VTE prophylactic protocol for patients undergoing elective TKA. Retrospective study of Hamilton WG, et al. was to determine the rate of VTE and bleeding complications in a large cohort of patients at a single institution using isolated mechanical thromboembolic prophylaxis in "standard risk" patients, 4,037 TKAs were performed on 3,144 patients at their institution.[92] Mechanical VTE prophylaxis was used for standard risk patients, which included AV impulse foot pumps, thigh high stockings, and early mobilization. Chemoprophylaxis was only given to patients who were at increased thromboembolic risk. The incidence of DVT identified by ultrasound following TKA was 2.1%. A retrospective review showed 1 patient had a fatal pulmonary embolism, and 5 patients had bleeding complications (3 gastrointestinal bleeds, 2 occurred in patients on Coumadin, 1 was in a patient using mechanical prophylaxis only). In addition, there were a severe postoperative wound hematoma in one patient on Coumadin, and an acute knee hemarthrosis six months after surgery in one patient. The result of this study support to use mechanical thromboembolic prophylaxis in risk stratification is safe and effective following TKA and chemoprophylaxis was only given to patients who were at increased thromboembolic risk. Although the supporting evidence to use mechanical prophylaxis alone appropriate for VTE prophylaxis in TJA patients who have bleeding disorders is lacking, avoiding use chemoprophylaxis is good for the safety of patients.

Question 20: Should chemoprophylaxis after knee arthroplasty be given for 2 weeks, if indicated?

Consensus: Yes.

Delegate vote: Agree: 91.6%, Disagree: 8.4%, Abstain: 0% (Strong Consensus)

Justification:

The selection of a regimen for venous thromboembolic prophylaxis after total joint arthroplasty is a balance between efficacy and safety. Bleeding may have a negative impact on clinical outcomes. Recently, both the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) developed new evidence-based guidelines for venous thromboembolic prophylaxis after total joint arthroplasty. On the basis of a review of the available literature, the AAOS guideline panel was unable to make a recommendation with respect to the selection of a specific prophylaxis regimen or duration of prophylaxis following routine total joint arthroplasty. The optimal duration of thromboprophylaxis after total knee replacement remains controversial. It is common practice to administer prophylaxis using low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) until discharge from hospital, usually 7 to 14 days after surgery.[93] International guidelines recommend extending thromboprophylaxis for up to 35 days following major orthopaedic surgery but the recommendation is weak due to moderate quality evidence. In addition, recent oral anticoagulants that exert effect by direct inhibition of thrombin or activated factor X lack the need for monitoring and have few known drug interactions.[94] Interest in this topic remains high.

Question 21: Shouldchemoprophylaxis after hip arthroplasty be given for 4-5weeks, if indicated?

Consensus: Yes, chemoprophylaxis should be given for 4-5 weeks after hip arthroplasty.

Delegate vote: Agree: 91.6%, Disagree: 8.4%, Abstain: 0% (Strong Consensus)

Justification:

One of the common complications after joint replacement surgery is venous thromboembolism. The risk of developing this complication increases with age, weight and previous history of thromboembolic disease. Incidence of symptomatic venous thromboembolism has been reported in the literature in approximately 2.8% of patients undergoing hip arthroplasty and 2.1% of knee arthroplasty patients. The optimal duration of thromboprophylaxis after total hip arthroplasty is still unclear.[95] It is common practice to administer prophylaxis using low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) until discharge from hospital. International guidelines recommend extending thromboprophylaxis for up to 35 days following major orthopaedic surgery.[94]

Question 22: Should a thromboprophylaxis be considered in an elderly hip fracture?

Consensus: A thromboprophylaxis should be considered in

an elderly hip fracture.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Extended (4-week) prophylaxis with fondaparinux can produce a 96% reduction in risk of DVT and an 89% reduction in risk of symptomatic VTE events relative to perioperative (1-week) prophylaxis. As the only anticoagulant approved in the United States for thromboprophylaxis in hip fracture patients, fondaparinux offers more effective prophylaxis against VTE without compromising safety.[96]

Jeong GK et al, compared the clinical efficacy and side-effect profiles of aspirin, dextran 40, and low-molecular-weight heparin (enoxaparin) in preventing thromboembolic phenomena after hip fracture surgery. There were 917 patients. Findings included low incidence of thromboembolic phenomena (deep vein thrombosis, 0.5%-1.7%; pulmonary embolism, 0%-2.0%; fatal pulmonary embolism, 0%-0.5%) and no difference among the 3 pharmacologic agents in thromboembolic prophylaxis efficacy.[97]

Question 23: Should we delay the administration of chemoprophylaxis in TJA patient with massive bleeding?

Consensus: The administration of chemoprophylaxis in TJA patient with massive bleeding (defined as blood loss >500 ml) should be delayed.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

Following total knee arthroplasty (TKA), only the visible blood loss has been measured. The total blood loss might be underestimated because some hemorrhage is "hidden" or "concealed". Concealed hemorrhage has been an important reason for postoperative blood loss in arthroplasty. It is caused by hemolysis, blood permeating into the interstitial fluid, blood remaining in the joint cavity and the damage of red blood cell caused by the surgical trauma and other factors.[98]

Sehat KR et al found that the mean hidden blood loss in THA was about 26% and visible blood loss was 74%. On the other hand, the mean hidden blood loss in TKA was higher as 51%.[99] If the visible blood loss of patient was more than 500 ml that means the total blood loss would be more than 1,000 ml. According to ATLS classification, this amount of hemorrhage has been defined as class II which may increase platelet consumption and result in acute coagulopathy.[100] Acute coagulopathy, characterized by anticoagulation and hyperfibrinolysis, is associated with systemic hypoperfusion. Therefore, the administration of chemoprophylaxis, which is the anticoagulant, in the patients who had massive bleeding (visible blood loss more than 500 ml) should be delay until hemodynamic stable.[101]

Question 24: Does early ambulation decrease the risk of VTE in TJA patients?

Consensus: Yes, early ambulation decreases the risk of VTE in TJA patients.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

The ambulation is defined as sitting at bedside, up standing or walking as able. Specific studies have yet to document the value of early ambulation to reduce VTE risk, yet the ICSI work group recommends it for all patients, including those at high risk.[102] Ambulation within 48 hours was associated with a 70% reduction in the risk of VTE.[103] Several studies demonstrated that early ambulation, a nursing and physical therapy function, directly affects the health care outcome. Although there is no reliable supported evidence, the current AAOS clinical practice guideline recommends that patients should undergo early mobilization following TJA. Early mobilization is of low cost, minimal risk and consistent with current practice.[23]

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