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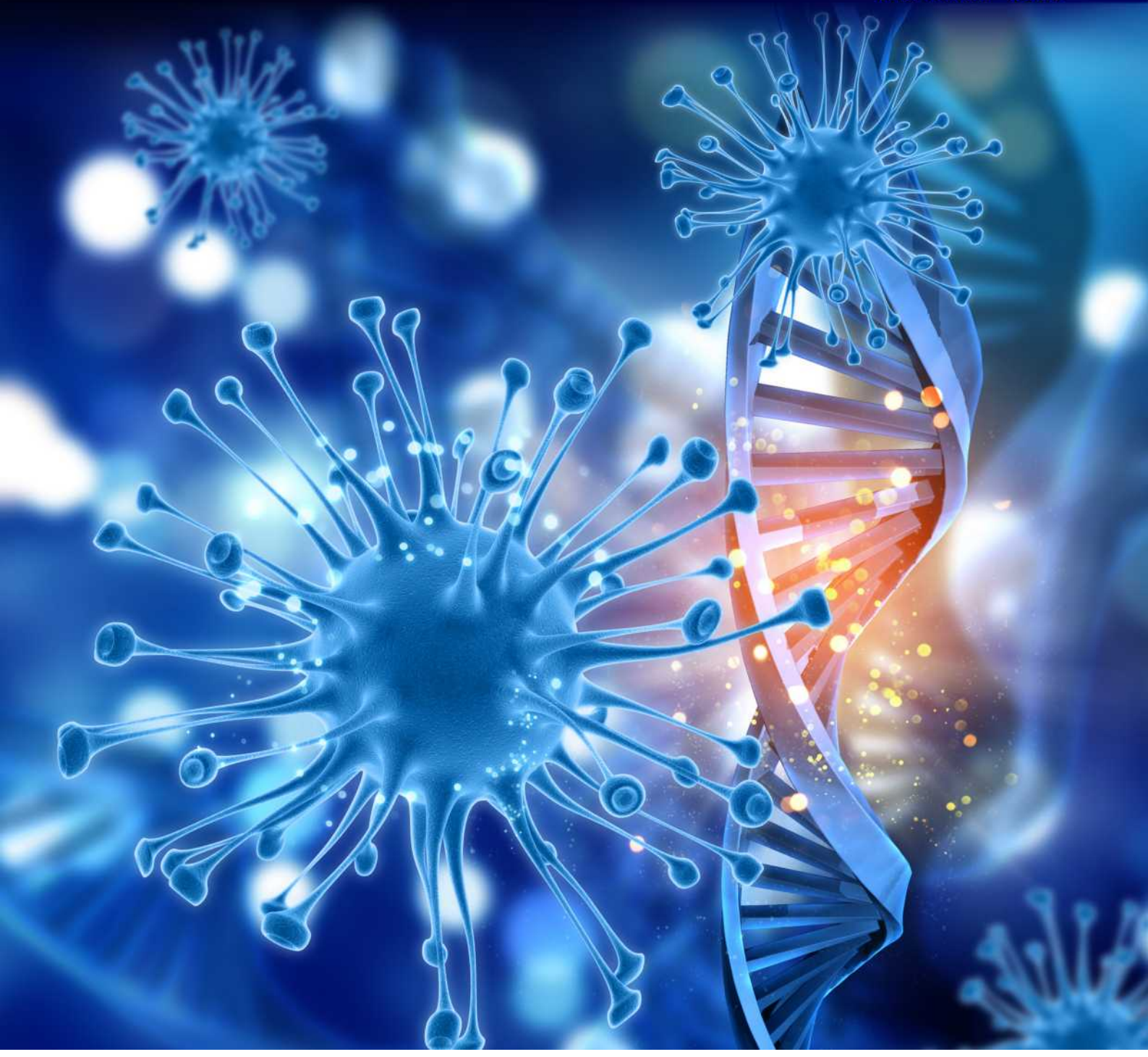

Introduction

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 consists 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.

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A.Original Article

SAFETY AND CLINICAL EFFICACY OF PLATELET RICH GROWTH FACTORS (PRGF) IN MANAGING KNEE OSTEOARTHRITIS AFTER FAILED CONSERVATIVE TREATMENT: EVIDENCE FROM REAL PRACTICES

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Abstract

Background: Platelet rich growth factors (PRGF) comprise a biological treatment of knee osteoarthritis (OA). Due to its limitation concerning the articular cartilage lesions' healing potential, chondrocyte differentiation and external environment factors, clinical improvement of knee OA using PRGF treatment depends on preparation techniques.
Objectives: The study aimed to demonstrate clinical outcomes of PRGF treatment in real practices.

Methods: A prospective cohort study was conducted from February 2018 to 2019 at the Biomedical Technology Research and Development Center, Police General Hospital, Bangkok, Thailand. We enrolled patients above 60 years old with knee OA that failed conservative treatment. The exclusion criteria included meniscus and ligament injury and knee deformity of the tibiofemoral angle more than 5 degrees. The primary endpoint was safe PRGF while secondary endpoints included changes of weight bearing pain and delayed surgery until an appropriate time for intervention.

Results: A total of 240 patients with knee OA, Kellgren-Lawrence (KL) grades II, III or IV were enrolled including 90 males and 150 females. The average age was 68 (60-81) years. Mode of conservative treatment failure included 140 cases of oral medication, 60 cases of oral medication and steroid injection and 40 cases of oral medication, steroid and intra-articular hyaluronic injections (IA-HA). Based on the KL system, 194 were classified as grades II-III, and 46 patients were grade IV. The PRGF was collected according to the protocol. The average initial platelet concentration before and after centrifugation was $165x10^3$ cells/μL (140-$195x10^3$ cells/μL) and $990x10^3$ cells/μL (825-$1,650x10^3$ cells/μL), respectively. At average of 3.3 (3-8) months follow-up, no major complications were observed, but 17 cases (7.9%) had minor complications. Average VAS (visual-analog-scale for pain: 0-100) scores before and after injection were 71 (65-80) and 52 (50-72), respectively. Surgical intervention in KL II-III totaled 11 cases (5.6%) and KL IV totaled 5 cases (10.8%).

Conclusion: Our technique of adjusting platelet concentration, fibrin concentration, leukocyte population and activator status improved clinical efficacy of PRGF treatment. PRGF is a safe, simple and effective treatment for patients with knee OA experiencing conservative treatment failure.

Keywords : Osteoarthritis, Platelet rich plasma, Platelet rich growth factor, Knee arthroplasty, Total knee arthroplasty, Kellgren-Lawrence, Surgical intervention

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Introduction

Knee OA has been steadily increasing affecting patients' quality of life as well as financial impact.[1] Limitation in the healing potential of articular cartilage lesions involves a lack of vessels, chondrocyte differentiation and external environment factors. The repairable process cannot generate properly for cartilage because of its restricted cell migration to repair the lesion. Also, the progressive loss of tissue homeostasis accelerates cartilage degeneration to end stage arthritis.[2] Numerous treatments have been shown to control pain, improve function and quality of life and to modify the natural history of knee OA. Pharmacologic management usually begins with pain relievers and anti-inflammatory agents. However, adverse effects have been noted concerning the gastrointestinal, nephrologic and cardiovascular systems.[3,4] Intra-articular injection of steroids only provides short term improvement for pain and functions. IA-HA injections have been introduced to alleviate pain and delay surgical intervention and recommendation can be found in many guidelines.[5] However, controversies exist related to clinical efficacy and preparations. Platelet rich plasma (PRP) is a popular biologic agent used to treat knee OA and clinical improvements depend on preparation techniques. A recent meta-analysis revealed the outcomes of pain and function assessment of corticosteriod treatment was better than those of PRP treatment while those of PRP treatment were better than those of IA-HA treatment. Many studies have investigated knee OA treatment. However, failure of conservative treatment due to medication and injection techniques has not been widely discussed. Conservative failure and severe damage after surgical intervention could possibly indicate complications including unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA). The recent treatment of PRGF needs to be addressed regarding its safety and clinical effectiveness involving delayed surgical intervention.

Methods

Patient Grouping

After obtaining the approved IRB, a prospective cohort study was conducted from February 2018 to 2019 at the Biomedical Technology Research and Development Center, Police General Hospital, Bangkok, Thailand. All patients were treated in the outpatient clinic and provided written informed consent to participate in this investigation. The inclusion criteria comprised 1) patients above 60 years old, 2) knee OA revealing failure after conservative treatment from physical rehabilitation and pharmacologic management such as pain and NSIADs medication, intra-articular steroid injections, and IA-HA injection, 3) all stages of knee OA severity according to KL classification (II, III, IV); and 4) hemoglobin concentrations greater than 11 g/dL and platelet counts greater than 150 x103 cells/μL. The exclusion criteria comprised 1) patients having meniscus and ligament injuries, 2) having deformity (tibiofemoral angle) more than 5 degrees, 3) having inflammatory arthritis, and 4) having uncontrolled bleeding disorder. The primary end point was safety of treatment after PRGF intra-articular injection. The secondary endpoints were change of weight bearing pain after minimal follow-up after 3 months of injections and delayed surgery until an appropriate for intervention.

PRGF Preparation

Thirty milliliters of venous blood samples were collected from patients. A complete peripheral platelet count was performed at the time of the initial blood draw before and after PRGF preparation. The blood was mixed using appropriate conditions. The first 20 mL of blood were centrifuged twice. The first centrifuge was to separate red blood cell, buffy coat, PRP and platelet poor plasma. The second centrifuge was to concentrate the platelets. The second 10 mL of blood was centrifuged to obtain natural activator, while sterile double syringe injections were prepared for knee injection.

Injection Technique

Patients were placed in the supine position. One knee was flexed 70 degrees and prepared in sterile fashion. The injection site was identified by soft spot at the anteromedial knee. A 22 gauge-needle was inserted through the same area in the joint capsule. In case any effusion presented, the fluid was aspirated. The needle remained in place and then the two syringes prefilled with PRGF were injected. When pain persisted, 2 tablets of paracetamol were given for rescue medication.

Results

Ninety male and 150 female patients with knee OA (KL grade II, III and IV) were enrolled with an average age of 68 years (range 60-81 years). Patients with failed conservative treatment who had been suggested to undergo surgical intervention included 140 cases not responding to oral medication; 60 cases not responding to oral medication and steroid injection and 40 cases not responding to oral medication, steroid and IA-HA injection. One hundred and ninety-four patients were KL grades II-III, 46 patients were KL grade IV (**Table 1**).

Table 1. Baseline demographic data and clinical parameters

Characteristics	Total
Number of patients (male: female)	249 (90:150)
Mean age (years) (range)	68 (60-81)
Body Mass Index (kg/m^2)(mean $\pm$ SD)(range)	24.8$\pm$3.5 (20-35)
Mean height (cm)	165 (160-172)
Number of knees (Right: Left)	240 (130:110)
Number of patients with Kellgren Lawrence II-III: IV	194:46
Mean Tibiofemoral angle (degrees) (range)	3 (0-5)
Failed conservative treatment	
Oral: Oral and Steroid: Oral and Steroid and IAHA	140:60:40
Average follow-up months (range)	3.3 (3-8)

The average initial platelet concentration before centrifugation was 165x103 cells/μL (range from 150-195x10^3 cells/μL). The average initial platelet concentration after centrifugation was 990x103 cells/μL (range from 825-1,650x10^3 cells/μL) (**Table 2**).

Table 2. Baseline clinical parameters of patients

Platelet Rich Growth Factor (PRGF)	Before PRGF	After PRGF
Average platelet concentration x 10^3 cells/uL (range)	165 (150-159)	990 (825-1,650)
VAS pain (points)	73±13	52±15
Range of motion (degrees)	125±10	16±8

At an average of 3.3 (3-8) months follow-up, no major complications were observed after PRGF treatment. In all, 17 cases involved minor complications (7.9%). The VAS score before injection was an average of 73 (60-86) and after injection the average was 52 (43-65).The surgical intervention in KL stages II-III totaled 11 cases (5.6%). All cases were treated by arthroscopic partial meniscectomy for complex tear of the meniscus (medial 9 cases, medial and lateral 2 cases), plica resection and micro drilling technique with PRGF intra-operative injection. KL IV totaled 5 cases (10.8%) and all were treated with TKA (**Table 3**).

Table 3. Adverse effects and surgical interventions

Adverse effects and surgical interventions	Number of patients
Injection site pain and pruritus more than 3 days	12
Pain swelling more than 3 days	5
Effusion	2
Hemorrhage and Erythrema	0
Aseptic Athritis	0
Major complication for surgical intervention	0
Surgical intervention Kellgren Lawrence II, III (Anthroscopic Surgery)	11
Surgical Kellgren Lawrence IV (Total Knee Arthroplasty)	5

Discussion

The conservative treatment of knee OA by pharmacologic intervention proved to have clinical efficacy by many guidelines.[6] Most treatments involve oral medication and steroid injections. AI-HA injection is commonly used as stated in standard practices.[7] Because patients now live longer and have more demands, surgical interventions have to be considered at appropriate times. The new biologic interventions have shown potential in improving effective conservative treatment. PRP contains a number of different growth factors including basic metabolic panel (BMP), Platelet-derived growth factor (PDFG), transforming growth factor (TGF), and insulin-like growth factor, which improve chondrocyte proliferation and viability, increase proteoglycan, glycosaminoglycan, hyaluronic acid production, nociceptive, anti-inflammatory role and promote stem cell migration and chondrocyte differentiation.[8] The chemokine constitutions of PRP are growth factors such as PDGF, TGF, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), proteases/antiproteases (alpha-2 macroglobulin), adhesive proteins (fibrinogen, fibronectin), cytokines (interleukin 1 beta, tumor necrosis factor) exhibiting differences resulting from hyaluronic acid.[9] PRP therapies have been reported in many studies regarding its treatment effectiveness in knee OA, and thus, widely used in clinical practices. However, different of platelet concentrations as well as preparation methods can influence the outcomes. Double spin PRP with activator enhanced chondrogenic differentiation concerning cartilage regeneration.[10, 11] Controversy regarding its effective usefulness involved different types of platelet concentrations and preparation methods.[12, 13] Recently, a meta-analysis presented the final accumulative ranks of all knee OA treatment outcomes. The pain and functions from cumulative rank number 1 is naproxen, number 2 is corticosteroid injection, number 3 is PRP and number 7 is IAHA.[14] To increase the capability of the treatment, understanding platelet concentrations, platelet recovery, inclusion of white blood cells (WBCs), platelet activation (thrombin, Ca2+), kinetics of cytokines released from platelets, preservation/function of platelets and WBCs, ratio between fibrinogen and thrombin concentration, formation of the fibrin matrix (fibrin polymerization), microstructure of the final fibrin network (ability to trap cytokines and bioactive factors) and appropriate injection techniques are needed.[15,16] PRGF was developed to improve the treatment quality of knee OA.[17] Understanding all these factors mentioned in the methods section could improve the maximally released growth factors from alpha granules and platelet reservoir to increase sustained releases and pericyte migration by PDGF to activate stem cells.[18,19] Based on our established technique, steps of platelet preparation increased the platelet concentration on an average of 5 to 10 times the normal platelet concentration. The results of this study revealed its easy administration in clinical practices, minimal risks, anti-inflammatory effects and possible effective adjunct to particular arthroscopic procedures. This technique is safe, simple and low cost because no major complications after PRGF treatment were observed except 17 cases (7.9%) presenting minor complications. PRGF treatment improved pain and slightly improved range of motion. The surgical intervention in KL II-III involved 11 cases (5.6%). Most of the pathologies involved complex tear of the meniscus, cartilage lesion in medial femoral condyle and undiagnosed plica. To decrease the failure rate, MRI is recommended in doubtful cases. Five cases (10.8%) comprised KL IV using tri-compartment arthritis as standard TKA.

Even though PRGF is safe, improved VAS scores and delayed surgical intervention, the basic science of the PRGF needs further studies to understand platelet kinematics and functional activity. Further studies should be conducted rgarding tissue biology and stimulating repair or replacing damaged cartilage highlighting a complex regulation of growth factors (GFs) for normal tissue structures and reaction to tissue lesions is recommended. Intermediate and long term follow-up are also suggested for further investigation.

In conclusion, our technique of adjusting the platelet concentration, fibrin concentration, leukocyte population and activator status improved clinical efficacy of PRGF treatment. PRGF is a safe, simple and effective treatment for patients with knee OA who have conservative treatment failure.

Declaration of Conflicting Interests

The authors declare that no potential conflicts of interest exist with respect to the research and/or publication of the article.

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COURSE OF THE RADIAL NERVE IN THE VULNERABLE AREA ALONG THE SHAFT OF THE HUMERUS: A CADAVERIC STUDY

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Abstract

Background: The radial nerve is the most commonly injured nerve associated with humeral fracture. Moreover, the nerve could be iatrogenically injured during fixation of the humerus.

Objective: The study aimed to identify the course of the radial nerve on the posterior and lateral aspects of the humerus.

Methods: Thirty-three adult embalmed cadaveric specimens were included in the study. The humeral length was determined as the distance between the posterior lateral aspect of the acromion and the lateral epicondyle. The distance between the lateral epicondyle to the posterior and lateral course of the nerve were measured.

Results: The average humeral length was 27.7 (±1.8) cm. The mean distance between the lateral epicondyle and posteromedial point, midposterior point, posterolateral point, midlateral point and anterolateral point were 17.4 (±1.2), 15.2 (±1.0), 12.7 (±0.8), 9.5 (±1.0) and 6.4 (±0.8) cm, respectively.

Conclusion: The high variation of the course of the radial nerve along the humerus was confirmed. The results in the present study can be used as a guide to determine the posterior and lateral course of the radial nerve during surgical exploration and prevent the nerve from iatrogenic injury during orthopedic operation.

Keywords : Radial nerve, Course, Humerus, Posterior cortex, Lateral cortex

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Introduction

The radial nerve is the most commonly injured nerve associated with humeral fracture. The close relationship of the nerve to the posterior and lateral cortex of the humerus makes the nerve vulnerable to injury either by trauma such as fracture of the humerus [1-4] or iatrogenic injury during fixation of the humeral fracture using a plate, nail or external fixator. [5-13]

Indications for surgical exposure of the radial nerve include repairing the injured nerve, excising the nerve tumor, decompressing the nerve and identifying the radial nerve during some types of humeral fracture fixation. Thus, knowledge of the location of the radial nerve not only prevents iatrogenic injury but also guides a surgeon when exploring the nerve is necessary.[14]

The current literature has demonstrated a wide variety of reference surgical landmarks.[15-28] For this reason, the exact course of the nerve along the humerus is still inconclusive. The authors have studied the course of the radial nerve in the most vulnerable area and compared the finding with related studies. The authors have attempted to include the English literature regarding the anatomy of the radial nerve as much as possible and summarized them in one conclusion. The suggestions and tips to identify the radial nerve and prevent iatrogentic injury in each study were also included in the present study.

Methods

A total of 33 adult embalmed cadaveric specimens (11 males, 6 females; 16 right, 17 left) were included in the study. The mean age of cadavers was 72 years (range from 65 to 90 years). One specimen was excluded from the study because of a deformity of the humerus.

After removing the skin and subcutaneous fatty tissue of the upper extremity, the posterior course of the radial was identified between the long and lateral head of the triceps. Then the radial nerve was carefully traced along its course distally without disrupting its original position by dividing the lateral head of the triceps and lateral intermuscular septum. After identifying the entire posterior and lateral course of the radial nerve along the humeral shaft, the nerve was then pinned to the surrounding tissue at the postero- medial, postero-lateral and antero-lateral point according to the cortex of the humerus. The lateral epicondyle was used as a reference point to measure the location of the nerve because it serves as a constant anatomical landmark and is easy to identify.

The following distances were evaluated: (1) the humeral length, the posterior tip of the acromion to the lateral epicondyle, (2) the lateral epicondyle to the point where the radial nerve passes the posteromedial margin of the humerus, (3) the lateral epicondyle to the point where the nerve passes the mid-posterior aspect of the humerus, (4) the lateral epicondyle to the point where the nerve passes the posterolateral margin of the humerus, (5) the lateral epicondyle to the point where the nerve passes the midlateral portion of the humerus and (6) the lateral epicondyle to the point where the nerve passes the anterolateral margin of the humerus (**Fig.1**). Each distance was measured and recorded in centimeters by two different surgeons. The mean values, range and standard deviation were calculated. Unpaired t-test was used to compare the data with related studies that used the same anatomical landmarks. A p-value below 0.05 indicated a statistical significance.

Results

The results of measurements are shown in **Table 1**. The comparisons of each parameter to the related studies are shown in **Table 2**. The average humeral length in the present study was 27.7 (± 1.8) cm. The mean distance between posteromedial point and lateral epicondyle in the present study was 17.4 (±1.2) cm. The mean distance between the midposterior point and the lateral epicondyle was 15.2 (±1.0) cm. The mean distance between the posterolateral point and the lateral epicondyle was 12.7 (±0.8) cm. The mean distances from the midlateral point and the anterolateral margin to the lateral epicondyle were 9.5 (±1.0) cm and 6.4 (±0.8) cm, respectively. The average distances from the lateral epicondyle to the point where the radial nerve passes the measuring points along the posterior shaft of the humerus are presented in the **Table 3**. A wide variety of the reported course of the radial nerve in the literature is shown in **Figure 2**.

Fig 1. The anatomic landmarks used to locate the course of the radial nerve along the humeral shaft. (PA = posterior tip of the acromion, PM = posteromedial margin, MP = mid-posterior point, PL = posterolateral margin, ML = mid-lateral point, AL = anterolateral margin, LE = lateral epicondyle)

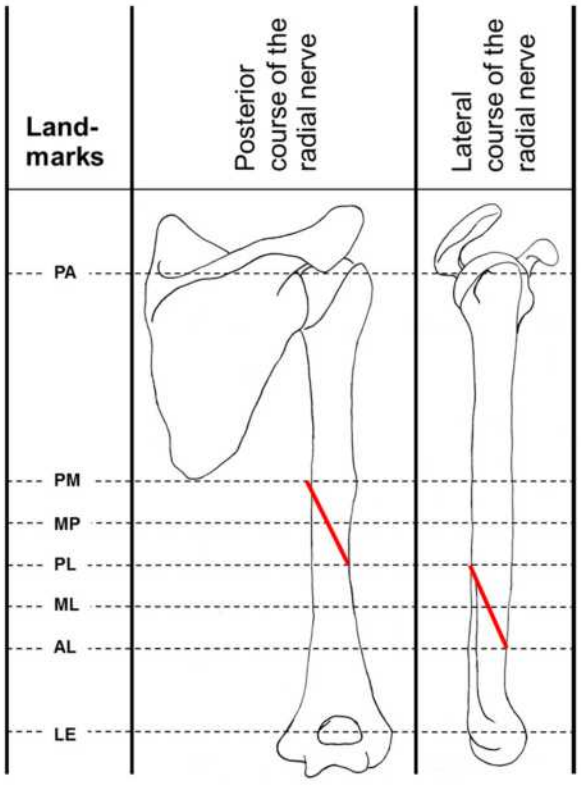


Table 1. Distance from the lateral epicondyle to the measuring point of the radial nerve

	Mean ± SD (cm)	Median (cm)	Min - Max (cm)	Range in % of humeral length
HL	27.7 ± 1.8	27.7	235 - 317	
LE to PM	17.4 ± 1.2	17.5	149 - 202	62.8 ± 4.3
LE to MP	15.2 ± 1.0	15.3	129 - 180	54.9 ± 3.6
LE to PL	12.7 ± 0.9	12.5	113 - 142	45.8 ± 3.2
LE to ML	9.5 ± 1.0	9.5	75 - 110	34.2 ± 3.6
LE to AL	6.4 ± 0.8	6.3	52 - 80	23.1 ± 2.9

HL = humeral length, LE = lateral epicondyle, PM = posteromedial margin, MP = mid-posterior point, PL = posterolateral margin, ML = mid-lateral point, AL = anterolateral margin

Table 2. Location of the radial nerve relative to the lateral epicondyle in the present study compared with previous studies that used the same reference point

	Measurement in cm					
	HL	LE to PM	LE to PL	LE to LIS	LE to ML	LE to AL
This study	27.7 ± 1.8	17.4 ± 1.2	12.7 ± 0.8		9.5 ±1.0	6.4 ± 0.8
33 arms	(23.5 -31.7)	(14.9-20.2)	(11.3-14.2)		(7.5-11.0)	(5.2-8.0)
Guse and Ostrum [15]	30.2 ± 1.8*		12.6 ± 1.1			
24 arms	(26.9-33.5)		(10.1-14.8)			
Gerwin et al [17]			14.2 ± 0.6*			
10 arms						
Fleming et al [19]				10.2 ± 0.8*		
20 arms				(9.1-11.4)		
Carlan et al [20]	28.7 ± 2.5	17.1 ± 1.6		10.9 ± 1.5*		
27 arms						
Chou et al [21]			10.4 ± 2.5*			
120 arms			(6.0-15.6)			
Kamineni et al [22]				10.2 ± 1.0*		
70 arms				(7.5-12.9)		
Artico et al [23]	29.0 ± 0.6*		12.1 ± 1.3*	11.0 ± 2.3*		
30 arms						
Cox et al [26]				11.8 ± 2.1*		
34 arms				(8.9-19.0)		
Wegmann et al [28]			13.5 ± 1.3*		9.7 ± 1.6	6.0 ± 1.8
95 arms			(9.9-17.2)		(6.2-13.9)	(2.7-10.2)

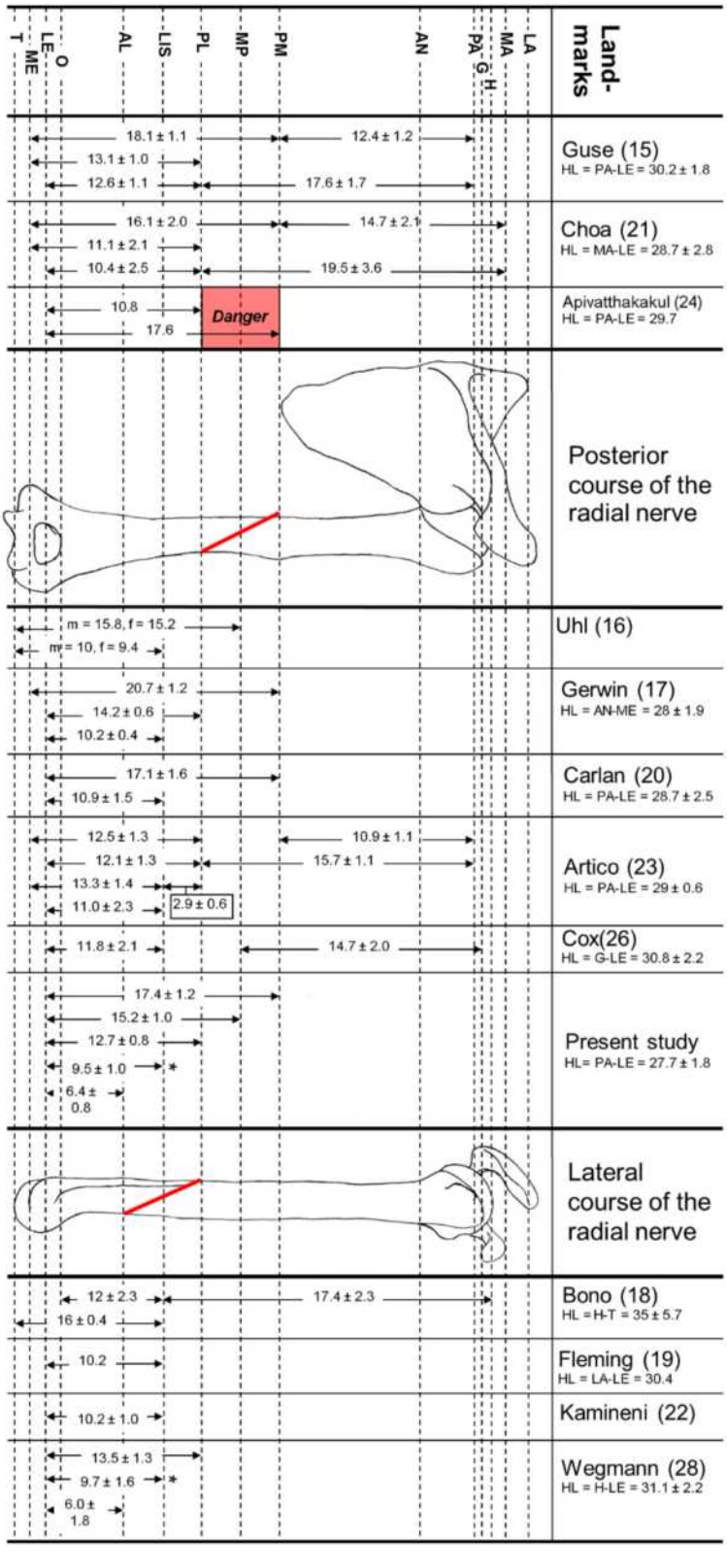
Values expressed as mean ± standard deviation, with range in parentheses, * significant difference ($p < 0.05$), HL = humeral length, LE = lateral epicondyle, PM = posteromedial margin, PL = posterolateral margin, LIS = lateral intermuscular septum, ML = mid-lateral point, AL = anterolateral margin

Table 3. Average and range of the distance from the lateral epicondyle to the measuring point of the radial nerve

Distance	Average (cm)		Range (cm)	
	Min	Max	Min	Max
LE to PM	17.1 ± 1.6 [20]	17.4 ± 1.2 [PS]	14.9 [PS]	20.2 [PS]
LE to MP	15.2 ± 1.0 [PS]		12.9 [PS]	18 [PS]
LE to PL	10.4 ± 2.5 [21]	13.5 ± 1.3 [28]	6 [21]	17.2 [28]
LE to LIS	10.2 ± 1.0 [19]	11.8 ± 2.1 [26]	7.5 [22]	19.0 [26]
LE to ML	9.5 ± 1.0 [PS]	9.7 ± 1.6 [28]	6.2 [28]	13.9 [28]
LE to AL	6.0 ± 1.8 [28]	6.4 ± 0.8 [PS]	2.7 [28]	10.2 [28]

LE = lateral epicondyle, PM = posteromedial margin, MP = mid-posterior point, PL = posterolateral margin, LIS = lateral intermuscular septum, ML = mid-lateral point, AL = anterolateral margin, [ ] = reference number, PS = the present study

Fig 2. A wide variety of the reported course of the radial nerve in the literature. HL = humeral length, LA = lateral acromion, MA = middle point of acromion, H = proximal humerus, G = greater tuberosity, PA = posterior tip of the acromion, AN = medial aspect of anatomical neck, PM = posteromedial margin, MP = mid-posterior point, PL = posterolateral margin, LIS = lateral intermuscular septum, AL = anterolateral margin, o = olecranon fossa, LE = lateral epicondyle, ME = medial epicondyle, T = trochlear,



Discussion

The proximity of the radial nerve to the humeral shaft makes it vulnerable in two areas: posteriorly, where it runs in the spiral groove and laterally, where it passes from the posterior compartment to the anterior through the lateral intermuscular septum. [1-4] The course of the radial nerve in these two areas has been documented in various studies but the results are inconsistent. One possibility for this phenomenon is the difference in using the reference bony landmark in the literature reviewed (**Fig. 2**).

The distal reference point, for instance, includes the olecranon fossa [18], lateral epicondyle [15, 17, 19-24, 26, 28] medial epicondyle [15, 17, 21, 23], trochlea [16-18] and triceps aponeurosis. [25, 27] Among them, the lateral epicondyle is used the most commonly. With this reference point, some conclusions about the course of the radial nerve along the humeral shaft have been made.

Posterior course of the radial nerve

Other than the knowledge of the reported distance, many methods can help to identify or protect the radial nerve in this area. Guse and Ostrum [15] described the mid-posterior point was close to the point midway between the posterior tip of the acromion and medial epicondyle. Cox et al.[26] showed the radial nerve at the posterior spiral groove was located at 50% of the distance between the greater tuberosity and lateral epicondyle. Carlan et al.[20] demonstrated that the center of the posterior course of the nerve, 6.3 ± 1.7 cm in distance, was close to the level of the distal aspect of the deltoid tuberosity. The triceps aponeurosis can also be used as a surgical landmark. Chaudhry et al.[25] found that posteriorly, the radial nerve ran 2.2 to 2.7 mm lateral to the lateral triceps aponeurosis and was always greater than 13 ± 1 mm from this boundary. They proposed that the immediate area parallel (<10 mm) to the aponeurosis represented a "safe zone". Arora et al.[27] described the radial nerve as lying 2.5 cm proximal to the apex of the triceps aponeurosis. This information and these techniques are useful when the posterior approach of the humerus is indicated either for operative fixation or radial nerve exploration. Moreover, the radial nerve can also be injured from drills or screws when anterior plating is applied either by a standard open technique or minimally invasive plate osteosynthesis (MIPO). Apivatthakakul et al. [24] described the danger zone of the radial nerve during placement of the locking screw in fixating the humeral shaft fracture using the MIPO technique, as an area 10.8 to 17.59 cm proximal to the lateral epicondyle. In their study, the most dangerous area lay 14.03 to 15.8 cm proximal to lateral epicondyle. They suggested that a uni-cortical screw should be used in this danger zone.

Lateral course of the radial nerve

The average distances from the lateral epicondyle to the point where the radial nerve passes the measuring points along the lateral shaft of the humerus are presented in **Table 3.** The two most commonly used landmarks to describe the lateral course of the radial nerve include the point where the radial nerve traverses the lateral intermuscular septum [16-20, 22, 23, 26] and the point where the radial nerve passes the midlateral point of the humerus. [28] The mean distance from the mid-lateral point to the lateral epicondyle is shorter than the distance between the point where the nerve traverses the lateral intermuscular septum and lateral epicondyle. [19-21, 23, 28]

In the present study, the midlateral aspect of the humerus was used as a reference point and the nerve passes this point near the junction between the middle and distal thirds. This point is lower than the point where the radial nerve traverses the lateral intermuscular septum.

Fleming et al.[19] found that the point where the radial nerve pierces the lateral intermuscular septum is within 5 mm of the junction of the distal and middle thirds of the distance between the lateral epicondyle and lateral point of the acromion. Artico et al.[23] reported that the point where the nerve crosses the lateral aspect of the humeral shaft was close to the middle of a line drawn from the acromion angle to the lateral epicondyle. Cox et al. [26] described that when the humeral length was defined as the distance between the greater tuberosity and lateral epicondyle, the radial nerve passes the lateral intermuscular septum at a location 40% of this length proximal to the lateral epicondyle. Kamineni et al.[22] used transepicondylar distance to define a safe zone for the radial nerve. In their study, the average transepicondylar distance (62 ± 6 mm, range 52 to 78 mm) was less than the distance measured from the lateral epicondyle to the point where the nerve traverses the lateral intermuscular septum (102±10 mm, range 75 to 129 mm).

They concluded that the distance of 75 mm from the lateral epicondyle could be applied as a safe zone to all patients. Interestingly, iatrogenic injuries to the radial nerve below these reported points have been reported. Baumann et al. [12] reported 3 cases of iatrogenic radial disruption following the surgical technique using a hinge elbow external fixator. The distance, where the injury occurred from the distal pin, ranged from 3.2 to 4.7 cm proximal to the lateral epicondyle. Caldwell et al.[13] reported a case of radial nerve injury using the distal half pin of a hinge elbow external fixator. The nerve was undisrupted but was tensioned by the distal pin at 3.5 cm proximal to the lateral epicondyle. These reported cases confirmed the risk of radial nerve injury found in a cadaveric study conducted by Clement et al.[29] In their study, the radial nerve passed at or below the point 5 cm proximal to the lateral epicondyle in more than one half (14 of 20) of their specimens. Moreover, among 25% their specimens, the nerve was found at or distal to the point 3 cm proximal to the lateral epicondyle. Wegmann et al. [28] emphasized a high variety of the distal portion of the radial nerve. Therefore, these relative safe zones should be applied with caution especially in the case of humeral fracture, especially fracture around the elbow and elbow dislocation with or without fracture. Displacement of the bony structure can distort the normal anatomy of the nerve. Moreover, disruption to the supporting tissue around the nerve, swelling of the surrounding tissue and hematoma from the fracture all can create challenges to locate the nerve. Thus, the authors agree with the recommendation that an open incision followed by a carefully blunt dissection, allowing direct visualization to the cortex of the humerus, should be performed before drilling and aligning the pin. A drill sleeve or soft tissue protector must be used when the drill or half pin was drilled in to the humeral shaft to prevent spinning soft tissue nearby the nerve. This technique should also be applied when inserting the distal locking bolt of the intramedullary locking nail. Applying a medial plate can damage the radial nerve on the lateral cortex by drills, taps or screws that are inserted from the medial to the lateral direction. In this situation, a subperiosteal or submuscular retraction should be used to protect the nerve along the lateral aspect of the humerus.[20] Identifying the radial nerve during open reduction and internal fixation of a humeral fracture using plates is recommended for both the posterior or anterolateral approach in some literature. [11, 14,16-18, 27, 30] However, this maneuver does not promise the postoperative recovery will be free of radial nerve dysfunction. Instead, it can provide a high level of confidence to the surgeon that the radial nerve would not be directly damaged and full recovery of the nerve function could follow. [9-11]

One limitation in the present study was being conducted using the embalmed cadaveric humeri, so surgeons should keep in mind that these measured anatomical landmarks could be distorted in the case of humeral fracture.

Conclusion

The high variation in the course of the radial nerve along the humerus was confirmed. Even though some contrasts were found regarding related reports, the present study could create simple guidelines. The radial nerve passed the midposterior point of the humerus at just above the middle of the distance between the lateral epicondyle and posterior tip of the acromion. In addition, the nerve passed the midlateral point of the humerus around the junction between the middle and distal thirds of the interval between the described bony landmarks. These guidelines could help surgeons when identifying the radial nerve is needed especially in cases without humeral fracture or elbow injury. However, in cases associated with elbow injuries or fracture of the humerus, this information should be used with caution to avoid iatrogenic radial nerve injury.

Disclosure

No conflicts of interest were declared by the authors.

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HETEROTOPIC OSSIFICATION FOLLOWING NONCEMENTED HIP REPLACEMENT: A COMPARATIVE STUDY USING MINIMAL INVASIVE SURGERY VS. CONVENTIONAL ANTEROLATERAL APPROACH

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Abstract

Background: A conventional anterolateral approach was previously a remedy for total hip replacement. Currently, an intermuscular approach is relatively safe, provides excellent exposure and causes less soft tissue damage than the traditional approach.

Objective: The study aimed to compare heterotopic ossification (HO) between minimal invasive surgery (MIS) and conventional anterolateral approach among patients having noncemented total hip replacement.

Methods: A retrospective study was conducted among 47 patients (52 sites) with noncemented total hip replacement who were randomly divided in 2 groups. The first group received treatment with MIS whereas the second group received the conventional anterolateral approach. The incidence of HO was recorded and followed-up for a minimum of 12 months. The demographic data of both groups were analyzed using the chi-square test and the discrete data were analyzed using the chi-square test and Fisher's exact test.

Results: The incidence of HO in the MIS and conventional anterolateral approach group were within 37.9 and 56.5%, respectively. After 12 months of followed-up, the incidence of HO in the MIS group did not significantly differ compared with that of the conventional group (p=0.291). Severe HO was within 13.79 and 8.69%, respectively (p=0.682) and neither group required further surgery.

Conclusion: The MIS group showed a lower incidence of HO than that found in the conventional anterolateral approach group without statistical significance.

Keywords : Heterotopic ossification, Minimal invasive surgery, Conventional anterolateral approach

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Introduction

The indications of total hip arthroplasty (THA) include osteoarthritis, rheumatoid arthritis, avascular necrosis as well as developmental dysplasia. Progressive innovations include many designs of implants such as cemented, noncemented, resurfaces and reconstructed such as endoprosthesis. On the other hand, various styles of approaches are performed depending on the experiences of surgeons. The goal of surgery is excellent or good result and diminished complications. Serious complications including infection, aseptic loosening, dislocation and heterotopic ossification (HO) can disturb patients'daily life activities. The incidence of HO was 24 to 32%, and mostly asymptomatic even though patients with severe grades had limited motion and painful progression. The hypothesis of HO could occur as described below. First is the process of reaming the femoral canal before inserting the cemented implants that could contaminate the bone marrow surrounding the operative field. Second, modern noncemented implants require impacted broaching. Third, complications may stem from exposure at the hip abductor area in a muscular man. Biz et al. reported risk factors of HO included being male, having a gonarthrosis hip joint or contralateral hip with HO and using the lateral approach.[1] Using meta-analysis, Zhu et al. showed that being male, using cemented implants, bilateral THA, ankylosed hip and ankylosing spondylitis also constituted risks of HO.[2]

The severity of HO depends on the kind of approach employed, which could vary soft tissue dissection and contribute to different grades of HO. Alijanipour et al. reported the incidence of HO was higher regarding the direct lateral approach than the direct anterior approach. The incidences were 36.1 and 19.4%, respectively, although without significance concerning high grade HO.[3] Similar results to this study were shown by Kutzner et al. reporting that the incidence of HO after minimal invasive surgery (MIS) using a modified anterolateral approach with short stem was only 7.8% with excellent Harris Hip Score.[4] In addition, Tan et al. demonstrated that patients could obtain good abductor strength and function in the early postoperative period of 2 years.[5] The objective of this study was to compare HO between MIS using the conventional anterolateral approach among patients having noncemented total hip replacement.

Methods

A retrospective study was conducted at Pakchongnana Hospital with approval obtained from the Ethics Committee of the Nakhon Ratchasima Provincial Public Health Office (Identity number = KHE 2018-010). The inclusion criteria comprised patients having of the followings: fractured neck of the femur, end stage of gonarthrosis hip, avascular necrosis of the femoral head, Ficat and Arlet stage IV or severe hip dysplasia. The exclusion criteria included patients having one of the followings: traumatic brain injury, stroke, spinal cord injury, severe injury severity score (ISS), ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis (DISH).

From July 2012 to December 2016, the cemented and noncemented total hip replacements and hemiarthroplasty at Pakchongnana Hospital totaled 92 cases. Of these, noncemented THA comprised 48 cases (53 sites). All participants were enrolled in the study (n=53 sites), and one was lost to follow-up due to death. After that, the patients were randomly divided in two groups depending on the date of treatment. The MIS anterolateral approach participants (29 sites) constituted the study group while the conventional anterolateral approach participants (23 sites) constituted the control group. All the study operations were conducted by one surgeon. The appearance of HO was assessed using Brooker classification, which is a common rating scale to score the extent of ectopic bone formation around the hip joint. This classification defines four levels as shown below.

Class 1: bone islands inside tissue around the hip joints
Class 2: bone spur from the pelvis or proximal femur and bony gap more than 1 cm.
Class 3: bone spur from the pelvis or proximal femur and bony gap less than 1 cm.
Class 4: hip ankylosis

A computerized tomography (CT) scan was employed to evaluate HO in cases of neurologic injury and acetabulum fracture fixation.[6]

The severity of HO related to decreased range of motion and hip function. After treatment, the initial protocol advised by physical therapists in both groups were isometric exercises followed by increased hip range of motion and

strengthening exercises. Both groups did not take any nonsteroidal anti-inflammatory drugs (NSAIDs) 10 days for prophylaxis of HO due to gastrointestinal side effects.

Pelvis x-ray imaging was conducted in the antero-posterior (AP) plain and checked periodically after treatment. After at least 12 months of follow-up, x-ray imaging was reviewed by a radiologist uninvolved in the procedures to avoid inter-observer variation and outcome bias. The data were collected by reviewing medical records and x-ray imaging of 48 participants who had underwent noncemented total hip replacement. Medical records were reviewed for demographic data, i.e., sex, age, side of fracture and HO grade.

Statistical analysis

The demographic data of both groups were analyzed using the chi-square test and the discrete data were analyzed using the chi-square test and Fisher's exact test. A *p*-value lower than 0.05 was considered statistically significant.

Results

Demographic data of both groups such as sex, age and side of fracture are shown in **Table 1**. No significant differences were found in the demographic data (sex, age, side of fracture) between the two groups and mean follow-up time was 1.3 (0.60) years in the MIS group and 2.6 (1.50) years in the conventional approach group. No statistically significant differences were found in the cause of noncemented THA (hip dysplasia, hypertrophic gonarthrosis, avascular necrosis, femoral neck fracture) in both groups (**Table 2**). HO of the MIS and conventional antero-lateral groups totaled 37.9 and 56.5%, respectively (p=0.291) as shown in **Table 3**. Severe HO in both groups totaled 13.8 and 8.7%, respectively (p=0.682) (**Table 4**). Although HO occurred in the conventional group more than in the MIS group, these results were not statistically significant. Neither of the two groups experienced serious complications nor any infections.

Table1. Demographic data among the MIS and conventional groups

Data	MIS group (29 cases)	Conventional group (23 cases)	*p*-value
Sex (%)			
female	12 (41.4)	11 (47.8)	0.854
male	17 (58.6)	12 (52.2)	
Age year (Mean±SD)	54.07(11.64)	49.57(12.56)	0.187
Side of fracture (%)			
left	16 (55.2)	14 (60.9)	0.896
right	13 (44.8)	9 (39.1)	

*The chi-square test: gender, side of fracture
Independent t- test: age

Table 2. Indication of total hip arthroplasty (THA)

Indicator	Noncemented total hip replacement		*p*-value
	MIS (29cases)	Conventional (23 cases)	
Hip dysplasia (%)	9(31.03)	11(47.82)	0.343
Non hip dysplasia (%)	20(68.97)	12(52.18)	
Hypertrophic gonarthrosis (%)	5(17.24)	4(17.39)	1.000*
Non hypertrophic gonarthrosis (%)	24(82.76)	19(82.61)	
AVN of head femur (%)	5(17.24)	4(17.39)	1.000*
Non AVN of head femur (%)	24(82.76)	19(82.61)	
Fracture femoral neck of femur (%)	10(34.48)	4(17.39)	0.287
Non fracture femoral neck of femur (%)	19(65.52)	19(82.61)	

The chi-square test
*Fisher's exact test

Table 3. Incidence of heterotopic osssification (HO) between the MIS and conventional approaches

Noncemented THA	Indicator		*p*-value
	HO Amount(%)	Non HO amount(%)	
MIS (29 sites)	11(37.9)	18(62.1)	
Conventional (23 sites)	13(56.5)	10(43.5)	0.291*

*The chi-square test

Table 4. Incidence of severe heterotopic ossification (HO) (Brooker classification ≥3) between the MIS and conventional approaches

	Indicator		
Noncemented THA	Severe HO number (%)	Non severe HO number (%)	*p*-value
MIS approach (29 sites)	4 (13.8)	25 (86.2)	
Conventional approach (23 sites)	2 (8.7)	21 (91.3)	0.682*

MIS= Minimal invasive surgery
Fisher's exact test: incidence of severe HO

Discussion

One of the serious complications related to the selected method of approach is HO. HO involves bone inside soft tissue which occurs from osteoinductive growth factor released from soft tissue injury and induced formation of HO. HO is believed to reach its complete formation after 6 to 12 weeks postoperative and not progress anymore after this period. The limited range motion of the hip joint and pain were found only in severe HO (9%), leading to unsatisfactory outcomes after total hip replacement.[7] This study implied a lower rate of HO using the MIS (37.9%) when compared with conventional anterolateral approaches (56.5%) (p=0.291) while severe HO totaled 13.8 and 8.7%, respectively (p=0.682). However, results of HO using the two methods were not statistically significant.

Numerous research works have reported that the posterior approach was associated with a lower rate of periprosthetic ossification than the anterolateral or trans-trochanteric approach. Moreover, the amount of soft tissue trauma is recognized as a critical risk factor favoring HO occurrence. In 2004, Bertin and Rottinger described the anterolateral muscle-sparing minimally invasive THA that passed through the interval between the tensor fascia latae and gluteus medius. The popularity of this approach has increased because it provides the potential for reduced blood loss, reduced soft tissue damage, short hospitalization, faster recovery and especially, excellent exposure of the femoral neck and less trochanter. The safe area was defined regarding the distance between the caudal branch of the superior gluteal nerve (SGN) and the apex of the greater trochanter was 5.47 (1.61) cm.[8] SGN injury occurs in hip surgery including overstretching the nerve, while retracting or detaching the muscles, thereby causing abductor weakness and a postoperative limp with a positive Trendelenburg's sign.

Presently, the MIS approach is believed to cause less trauma to the soft tissue. Patients could return to work earlier than using standard approaches; however, the incidence of HO remains controversial. Repantis et al. reported the results of a midterm (4 years) study of both clinical and functional aspects between the MIS and conventional anterolateral approaches of THA did not differ regarding functional outcomes and walking endurance except for postoperative pain without reporting the incidence of HO.[9] Hürlimann et al. also reported highest incidence of HO in a standard modified anterolateral (STD-Watson-Jones) group (45.2%) and revealed significant

difference compared with the AMIS (23.1 %) and the STD-Bauer approaches (14.3 %). However, no statistical significance was observed using the MIS-AL approach (24.0 %).[10]

Those who had acute revision total hip replacement within 3 weeks were at high risk of extensive HO. They needed prophylactic treatment because 14% of Brooker IV and 42.8% of unsatisfied severe limited motion were observed. [11] The use of extensive surgical wound lavage (>3000 mL) could decrease the incidence of HO by 73 to 41% and no severe class of HO was observed.[12] Likewise, other high risk groups, i.e., diffuse idiopathic skeletal hyperostosis, hypertrophic osteoarthritis, ankylosing spondylitis and previous occurrence of HO, were treated with radiation after surgery. The results of applying the 700 cGy radiation could significantly decrease HO more than the 400 cGy with no wound complications.[13] In addition, a short course of indomethacin therapy for 10 days prevented some significant grades of HO and was effective in reducing the incidence of HO in about one half to two thirds of cases. However, meta-analysis showed no statistical difference was observed when using selective NSAIDs compared with nonselective NSAIDs groups to reduce the incidence of HO.[14]

Some limitations of the present should be noted. This study employed a retrospective and observational review with involving a small number of cases. However, the sample size was sufficient for statistical analysis. This study showed the outcomes of the comparative study concerning the occurrence of HO between the MIS and conventional anterolateral approaches among patients with noncemented hip replacement.

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Potential conflicts of interest

No conflicts of interest were declared by the author.

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PREVALENCE AND ASSOCIATED FACTORS OF ACNE VULGARIS AMONG HIGH SCHOOL STUDENTS IN RURAL AND URBAN AREAS OF THAILAND: A CROSS-SECTIONAL STUDY

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Abstract

Background: Acne is the most common skin disorder affecting teenagers. Current knowledge of acne is continuously evolving with particular food especially skim milk, which has been recently recognized as a causative factor while environmental factors have not been clearly investigated.

Objectives: A cross-sectional study was conducted concerning the prevalence of acne among secondary school students living in rural and urban areas of Thailand. Associated risk factors were also evaluated as basic knowledge about acne.

Methods: We developed a questionnaire comprising baseline data, body mass index (BMI) and dietary, sleeping and exercise habits. Acne severity was assessed based on the Investigator's Global Assessment (IGA).

Results: A total of 526 students completed the questionnaires. Of these, 287 (54.6%) lived in rural areas. In all, 172 (32.7%) students had moderate to severe acne. No statistical significance was found between the proportion of moderate to severe acne and none to mild acne cases among students living in rural areas 94/287 (32.7%) and those living in urban area 78/239 (32.6%) (p =0.977). Being male and high BMI were associated with moderate to severe acne using the adjusted odds ratio (OR) =2.05 (95% CI, 1.38-3.05) and adjusted OR =1.06 (95% CI, 1.01-1.11). Milk consumption did not affect acne severity.

Conclusion: Students residing in urban and rural areas had about equal prevalence of moderate to severe acne. Dietary habits especially milk consumption and living environment had no influence on acne severity.

Keywords : Acne, Milk consumption, Teenagers

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Introduction

Acne is a chronic inflammatory skin disorder found in all age groups with the highest prevalence among adolescents and young adults. Clinical manifestation usually presents with mild to moderate acne with open or closed comedones and a smaller proportion with more severe acne including inflammatory papules, pustules, cysts or nodules. Acne pathogenesis is multifactorial affecting the pilosebaceous units of the skin.

The current understanding of acne has been continuously evolving, especially the aspect of causative or aggravating factors. No harmful morbidity is associated with acne, but has quite significant physical and psychological consequences, such as permanent scarring, low self-esteem, anxiety disorders, depression, and emotional distress.[1-3] A related large epidemiological study of the prevalence of acne among Chinese adolescents reported that 3,163 students aged 10 to 18 years from 7 schools had an overall prevalence of 53.5%, with 51.3% among males and 58.6% among females.[4]

Many predisposing factors of acne have been studied. An interesting study by Goulden et al. suggested that family or genetic factors were important to susceptibility to adult persistent acne.[5] Furthermore, Ghodsi et al. also stressed the correlation of genetic background and acne severity especially with mother's acne history.[6] Other risk factors that are known to aggravate acne include insufficient sleep, smoking, the use of oral contraceptives, skin care products or cosmetics use, particular food consumption such as sweet and oily foods and occupation.[4-8] Consumption of a high glycemic index diet such as cow's milk, chocolate and fatty foods may also increase the risk of acne.[8,9]

The hypothesis that dairy products or milk consumption can cause acne has been explored during the past decade. LaRosa et al. recently reported that consumption of lowfat/ skim milk, but not full fat milk among teenagers, was significantly associated with acne eruptions.[9] Other studies have also supported this association.[10-12] Hormonal constituents or other biological substances in skim milk may affect endogenous hormones and cause acne.[13]

We report a cross-sectional descriptive study regarding the prevalence and risk factors of acne vulgaris among secondary school students aged 14 to 19 years residing in two different areas, urban and rural of Thailand. In addition, basic knowledge about acne and skin care practices during acne eruptions in these populations were explored.

Methods

Study Population

This study was approved by the Institutional Review Board of the Royal Thai Army Medical Department and the Ethics Committee. The Thai Clinical trial registration number was TCTR20180102001. Secondary school students, aged 14 to 19 years living in rural and urban areas of Thailand, participated in this study. A high school, located in Chachoengsao Province, 190 km from Bangkok, was chosen as the rural area school, whereas a school in Samut Prakan Province, approximately 30 km from Bangkok, was selected as the urban area school. The appropriate sample size calculated totaled 400 students. After obtaining permission from the directors of both schools, the investigators approached students in their assigned classrooms to inform them about the study objectives. Students who declined to answer the questionnaire or were unable to answer the questionnaire by themselves were excluded from the study.

Data Collection

We developed the questionnaire comprising two sets of questions. The first part comprised general baseline data, students' self-evaluation of acne severity (none to mild acne or moderate to severe acne), intake of particular foods (high glycemic index diet, i.e., chocolate, amount and type of cow's milk consumption) and activities or personal habits including smoking, exercise, sleeping and cosmetics use. A second set of ten true-false questions was developed covering basic knowledge of acne and proper skin care practices during acne eruptions. The questionnaire was pilot-tested by volunteers to develop a final version before launching to the study population. The investigator was trained by a pediatric dermatologist to grade the severity of acne based on the Investigator's Global Assessment (IGA) scale for acne severity. The investigator had to evaluate each individual student one by one and classify as either none to mild acne (IGA scales 0, 1, 2) or moderate to severe acne (IGA scales 3, 4) before providing the questionnaire. The students were informed they could decide by themselves

if they did not want to be included, and could leave the questionnaire without completing it. This survey was voluntary, and no information could be traced back to the subjects.

Statistical analysis

Prevalence was analyzed using descriptive statistics. Associated factors were analyzed between groups by univariate and multiple logistic regression, presented in odds ratio (OR) and 95% CI. Knowledge about acne was analyzed using descriptive statistics presenting the average scores. All data was analyzed using the STATA Program, Version 12.

Results

The assigned questionnaires were 100% completed by 526 students, including 287 (54.5%) students from the rural area in Chachoengsao Province and 239 (45.4%) students from the urban area in Samut Prakan Province. Baseline demographic data of the two groups were compared as shown in **Table 1**.

Table 1. Baseline demographic characteristics of subjects according to acne severity groups

Characteristics	Acne Severity	
	None – Mild Acne (n = 354) n (%)	Moderate – Severe Acne (n = 172) n (%)
Location		
Rural	193 (67.25)	94 (32.75)
Urban	161 (67.36)	78 (32.64)
Sex		
Male	127 (58.26)	91 (41.74)
Female	227 (73.70)	81 (26.30)
Class		
Ninth grade	97 (72.39)	37 (27.61)
Tenth grade	122 (65.59)	64 (34.41)
Eleventh grade	46 (69.70)	20 (30.30)
Twelfth grade	89 (63.57)	51 (36.43)
Age, years old		
14	72 (73.47)	26 (26.53)
15	93 (64.58)	51 (35.42)
16	95 (68.35)	44 (31.65)
17	63 (63.00)	37 (37.00)
18	30 (69.77)	13 (30.23)
Average (SD)	**15.68 (1.23)**	**15.75 (1.20)**
BMI, kg/m^2		
Underweight (< 18.5)	153 (79.69)	39 (20.31)
Normal (18.5-22.9)	144 (61.54)	90 (38.46)
Overweight (23-25)	18 (52.94)	16 (47.06)
Obese (> 25)	36 (60.00)	24 (40.00)
Average BMI (SD)	**19.92 (3.92)**	**21.18 (4.47)**

The mean age of all students was 15.7 years (14-18). Overall, 172 (32.7%) students were evaluated to have moderate to severe acne (IGA scales 3, 4). The proportion of moderate to severe acne (IGA scales 3, 4) and none to mild acne (IGA scales 0, 1, 2) comparing rural living students, 94/287 (32.7%) and urban living students, 78/239 (32.6%) did not significantly differ (p=0.977). Male students (91/218, 41.7%) were more significantly affected by moderate to severe acne than female students (81/308, 26.3%; p <0.001).

Regarding body mass index (BMI) and acne severity, the overweight (16/34, 47.0%) and obese groups (24/60, 40.0%) were noted to have a higher proportion of more severe acne than that of the underweight (39/192, 20.3%) and normal BMI student groups (90/234, 38.4%; p <0.001). Furthermore, the group of more severe acne had higher average BMI, 21.18 compared with 19.92 kg/m^2.

The univariate analysis of acne severity is shown in **Table 2**.

Table 2. Univariable logistic regression analysis of associated factors correlated with acne severity

	None – Mild (n = 354) n (%)	Moderate – Severe (n = 172) n (%)	Crude OR (95% CI)	*p*-value
Living area				
urban	161 (67.36)	78 (32.64)	0.99 (0.69, 1.43)	0.977
Sex				
male	127 (58.26)	91 (41.74)	2.01 (1.39, 2.91)	0.000
Age, years old				
mean (SD)	15.68 (1.23)	15.75 (1.20)	1.06 (0.91, 1.23)	0.476
BMI, kg/m^2				
mean (SD)	19.92 (3.92)	21.18 (4.47)	1.07 (1.03, 1.12)	0.002
Self – evaluation to have				
none / mild acne	194 (84.72)	35 (15.28)	1	
moderate / severe acne	160 (53.87)	137 (46.13)	4.75 (3.10, 7.27)	0.000
Family history of acne				
father with acne	63 (67.74)	30 (32.26)	0.98 (0.60, 1.58)	0.920
mother with acne	77 (63.11)	45 (36.89)	1.27 (0.83, 1.95)	0.261
brother or sister with acne	138 (67.98)	65 (32.02)	0.95 (0.65, 1.38)	0.792
Smoking	51 (68)	24 (32)	0.96 (0.57, 1.63)	0.889
Dietary habits				
Sweets (snack)/soft drinks (> 2 days/week)	304 (67.26)	148 (32.74)	1.01 (0.60, 1.71)	0.958
Chocolate (> 2 days/week)	214 (69.71)	93 (30.29)	0.77 (0.53, 1.11)	0.164
Milk (> 250 ml/day)	184 (67.65)	88 (32.35)	0.97 (0.67, 1.39)	0.861
Type of milk				
low-fat milk or skim milk	46 (58.23)	33 (41.77)	0.63 (0.39, 1.03)	0.064
full-fat milk	308 (68.9)	139 (31.1)	1	
Exercise				
(> 2 days/week)	186 (66.43)	94 (33.57)	1.09 (0.76, 1.57)	0.649
Hours of sleep				
(< 6 hours/night)	125 (64.77)	68 (35.23)	1.20 (0.82, 1.74)	0.346

The parameters that displayed a significant associated risks with moderate to severe acne included being male (crude OR =2.01, 95% CI, 1.39-2.91; p = 0.000) and high BMI (crude OR= 1.07, 95% CI, 1.03-1.12; p =0.002).

In addition, we found that the moderate to severe acne group had a tendency to self-evaluate their acne severity more correctly than the less severe group with crude OR= 4.75 (95%CI, 3.10-7.27; p = 0.000). Regarding dietary habits, we found no significant association of moderate to severe acne with the particular foods mentioned in the questionnaire including high sugar diets, any type of cow's milk or chocolate consumption. Daily activities such as sleeping hours, exercise habits and smoking were also found to exhibit no significant association with acne severity. Using multiple logistic regression analysis, associated risk factors were identified and summarized in **Table 3**. Being male, high BMI and self-evaluation of having more severe acne tended to indicate risk association with moderate to severe acne after adjusting for relevant factors with OR = 2.05 (95% CI = 1.38-3.05), OR = 1.06 (95% CI =1.01-1.11) and OR = 4.65 (95% CI = 2.99-7.20) (p <0.05), respectively.

Table 3. Multiple logistic regression analysis of risk factors associated with acne severity

	None-Mild **n (%)**	**Moderate-Severe** **n (%)**	**Adjusted OR*** **(95% CI)**	***p*-value**
Sex: male	127 (58.26)	91 (41.74)	2.05 (1.38, 3.05)	< 0.001
BMI (kg/m^2): mean (SD)	19.92 (3.92)	21.18 (4.47)	1.06 (1.01, 1.11)	0.021
Self -evaluation to have moderate / severe acne	160 (53.87)	137 (46.13)	4.65 (2.99, 7.20)	< 0.001
Chocolate (> 2 days/week)	214 (69.71)	93 (30.29)	0.85 (0.57, 1.27)	0.432
Low-fat and skim milk	46 (58.23)	33 (41.77)	1.66 (0.97, 2.85)	0.064

* Adjusted odd ratio for male, BMI, self-evaluation, chocolate consumption, and milk consumption

A set of true or false questions regarding acne basic knowledge and proper skin care during acne eruptions was answered by all students. Overall average scores totaled 46%.No significant difference was found by comparing the average scores between the none to mild acne group and the moderate to severe acne group with scores 45.5% and 46.7%, respectively (mean difference = 0.12, 95% CI = 0.11-0.37, p = 0.299). The most correct answers were found for the question, "*pressing or squeezing acne can cause acne scars and pits, true or false*" (502/526, 95.4%). The most incorrect answers were when students answered "true" to the question, "*cleansing your face with facial cleansing scrub can prevent acne, true or false*" (230/526, 43.7%)

Discussion

In this study, 526 Thai adolescents aged between 14 and 19 years from two different areas of Thailand had an overall prevalence of moderate to severe acne (IGA scales 3, 4) of 32.7%, with similar proportions among students residing in rural and urban areas. This was the first study comparing acne epidemiological data among teenagers in rural and urban areas in Thailand. However, this study failed to provide any evidence supporting the hypothesis

that differences in environment or dietary culture in different residential areas could affect acne prevalence. However, teenagers living in urban areas were more likely to be in contact with more environmental pollution or consume higher fat foods, higher glycemic diets and seemed to drink more milk than those living in rural areas. However, rapid changes and growth in many rural areas of Thailand could have changed environment, life styles and eating habits of people residing in rural areas.

A large epidemiological study on the prevalence of acne among Chinese teenagers showed that among 3,163 students aged 10 to 18 years from 7 schools had an overall prevalence of 53.5%, with 51.3% among males and 58.6% among females.[4] Dreno et al. reviewed several acne epidemiological studies and reported that the prevalence of acne vulgaris was 27.9 to 68.5% among male teenagers and 20.8 to 59.6% among female teenagers.[7] Similar to this study, male students (41.7%) were observed to have more severe acne than female students (26.3%). Concerning secondary outcomes, using multiple logistic regression analysis, risk factors including being male, high BMI and self-evaluation of having severe acne were significantly associated with moderate to severe acne. Contrarily, family history of severe acne, smoking, high sugar diet, chocolate consumption, any kind of milk consumption, physical exercise and hours of sleep did not affect the severity of acne in this study. In 2009, a similar cross-sectional, community-based study conducted in Tehran, Iran, reported numbers of family members with acne especially mothers with acne, seborrhea, mental stress, consumption of sweet and oily foods constituted the risk factors for moderate to severe acne.[6] They also discussed the variations in community-based populations, with different genetic backgrounds, environmental factors and consumption cultures.

Recently, many studies have proposed a positive association between intake of skim milk and acne severity.[9-11,13] A large meta-analysis of 78,529 participants aged less than 30 years showed considerable heterogeneity and bias across studies. Thus, interpretations or conclusions regarding the association between dairy product consumption and acne severity should be made with caution.[14] From our community-based data, the amount of milk consumed was only 250 ml daily on average. Thus, with this cultural dietary variation, the study of the effect of milk on acne severity could not be easily conducted with strong validity in different parts of the world. We suggest that a larger community-based surveillance with appropriate study design to determine associated factors of acne vulgaris among teenagers should be further investigated.

Regarding the basic knowledge testing questions about acne, we found that both students residing in urban and rural areas could achieve less than 50% scores. These results implied the need to implement more knowledge of adolescent medicine including correct skin care practices during acne eruptions among teenagers in school health programs.

Conclusion

The prevalence of moderate to severe acne based on the IGA scale among students aged 14 to 19 years was 32.7%. Students residing in urban and rural areas had about equal risk of moderate to severe acne. In this study, dietary habits including milk consumption and daily activities had no influence on the severity of acne.

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RECOVERY OF HEMOGLOBIN LEVEL FOLLOWING TOTAL KNEE ARTHROPLASTY WITH PERIARTICULAR EPINEPHRINE INJECTION

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Abstract

Background: Anemia is one of the common complications occurring after total knee arthroplasty (TKA). A periarticular epinephrine injection could reduce intraoperative blood loss after TKA. However, the duration of hemoglobin recovery to preoperative level remains uncertain. The hypothesis was based on the concept that epinephrine affects vasoconstriction and reduces blood loss. This study was conducted to compare the duration of hemoglobin recovery to preoperative level between periarticular epinephrine injection and periarticular nonepinephrine injection groups and postoperative blood transfusion.

Methods: A total of 141 participants were randomized to receive a periarticular epinephrine and bupivacaine injection (epinephrine group) or periarticular bupivacaine injection (non-epinephrine group) among patients undergoing TKA. The solution consisted of 10 g of epinephrine 1 ml and 20 ml of 0.25% bupivacaine. In another group, the solution consisted of 20 ml of 0.25% bupivacaine alone. All TKAs were managed under spinal anesthesia using a femoral nerve block. Preoperative and postoperative hemoglobin (Hb) and hematocrit (Hct) levels were assessed 1-day, 3-day and monthly until 6 months. Blood loss and the duration of Hb recovery to preoperative level were compared between the two groups.

Results: The percentage of Hb loss was slightly higher in the epinephrine group than that in the nonepinephrine group but without significance (13.4 ± 6.6% vs. 13.01 ± 5.01%; p=0.703). The duration of Hb recovery to preoperative level was about the same in the epinephrine and nonepinephrine groups (2.52 ± 1.080 months vs. 2.56 ± 1.089 months; p=0.855). The calculated total blood loss in the epinephrine group was lower than that in the nonepinephrine group (570 ± 302 mL vs. 573 ± 228 mL; p=0.955). In this study, surgery was performed without blood transfusions.

Conclusion: The duration of Hb recovery to preoperative level was 2.5 months which was about the same in both groups. Epinephrine injection did not decrease total blood volume loss after TKA under spinal anesthesia.

Keywords : Total knee arthroplasty, Periarticular epinephrine injection, Hemoglobin recovery, Randomized-controlled trial

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Introduction

Total knee arthroplasty (TKA) is one of the most common procedures in orthopedic surgery performed worldwide [1] with an estimated 10.2% increase in the number of TKA annually. The increasing TKA numbers are related to aging population, technical development of surgical procedures and advanced implants.[2] Many comorbidity complications occur during TKA especially perioperative blood loss. This can be reduced by preoperative evaluation and good preparation.

Several strategies have been used to prevent and reduce blood loss in TKA. They can be classified as preoperative, intraoperative and postoperative management. However, anemia is still a common incidence after TKA. Approximately 10% of patients receiving blood transfusion following TKA were at risk of blood-borne infection and transfusion reaction. In addition, prolonged exposure to anemia after TKA may jeopardize these patients and lead to fatigue, late ambulation and extended length of hospital stay.[3]

Periarticular infiltration of analgesia is a method used for postoperative pain control after TKA. Originally, epinephrine is added for local infiltration analgesia (LIA) to delay systemic absorption of the local anesthetic agents to prevent their systemic toxicity.[4, 5] Many studies have investigated the use of epinephrine for LIA to minimize blood loss after TKA.[6] Lombardi et al.[7] reported reducing both postoperative pain and blood loss following TKA using soft tissue and intraarticular injection of bupivacaine, epinephrine and morphine. Anderson et al. [3] reported that a 195 mL (32%) decrease in the amount of drain output and no transfusion rate after intraoperative injection of bupivacaine with epinephrine compared with the control group. However, none of these studies reported the duration of recovery from anemia among patients undergoing TKA.

In this study, we aimed to compare the duration of Hb recovery between the periarticular epinephrine and nonepinephrine injection groups undergoing TKA.

Methods

A double-blind randomized controlled trial was conducted at Phramongkutklao Hospital, Bangkok from May 2015 to April 2016. Patients with a diagnosis of severe osteoarthritis (OA) knee undergoing TKA were included. Exclusion criteria comprised patients who had secondary osteoarthritis from rheumatoid arthritis, or posttraumatic OA including revision TKA, bilateral TKA, using postoperative drainage, hypersensitivity to tranexamic acid or epinephrine, history of infection, history of abnormal bleeding or coagulopathy and preoperative anemia (Hb level <10 mg%). In addition to these exclusions, patients who could not take anticoagulant agents or had creatinine clearance <30 mL/min were excluded. Patients were randomly divided in two groups. First, the intervention or epinephrine group with epinephrine and bupivacaine injection received 0.25% bupivacaine 20 mL and epinephrine 10 g. Second, the control or nonepinephrine group received only 0.25% bupivacaine 20 mL. Age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative Hb level, Hct level and comorbidity were recorded. All operations were performed using a cemented prosthesis (Attune or Sigma, posterior stabilized type, manufactured by DePuy Synthes, USA) by the same orthopedist who was blinded between groups.

The same procedures of operation were performed in all TKAs. The anesthetic technique was spinal block with femoral nerve block. The 350 mm Hg tourniquet pressure was applied during the operation using the medial parapatellar approach. After surgery, patients were provided 10 mg rivaroxaban orally daily and performed ankle pumping exercise for thromboembolism prophylaxis. Complete blood count (CBC) was obtained on the first and third days postoperation. One unit of packed red cell was given in case Hb level was lower than 8.0 mg% or lower than 10 mg% with active or ongoing blood loss. When participants required blood transfusion after TKA, they were not excluded from study. Intention to treat analysis was performed to evaluate all participants.

All patients received the same postoperative rehabilitation protocol such as muscle contraction exercise. The ambulation was immediately encouraged on the second day after operation with a walker. Bleedings from other routes were investigated on a follow-up visit and blood supportive agents were not prescribed in the protocol. Patients had their blood examined for Hb and Hct levels the 3rd postoperative day. Gross's formula was used to calculate total blood loss.[14] The threshold Hb level for blood

transfusion was lower than 8 mg% or 8 to 9 mg% with anemic symptoms.

Estimated blood loss by Gross's formula[14] is described below.

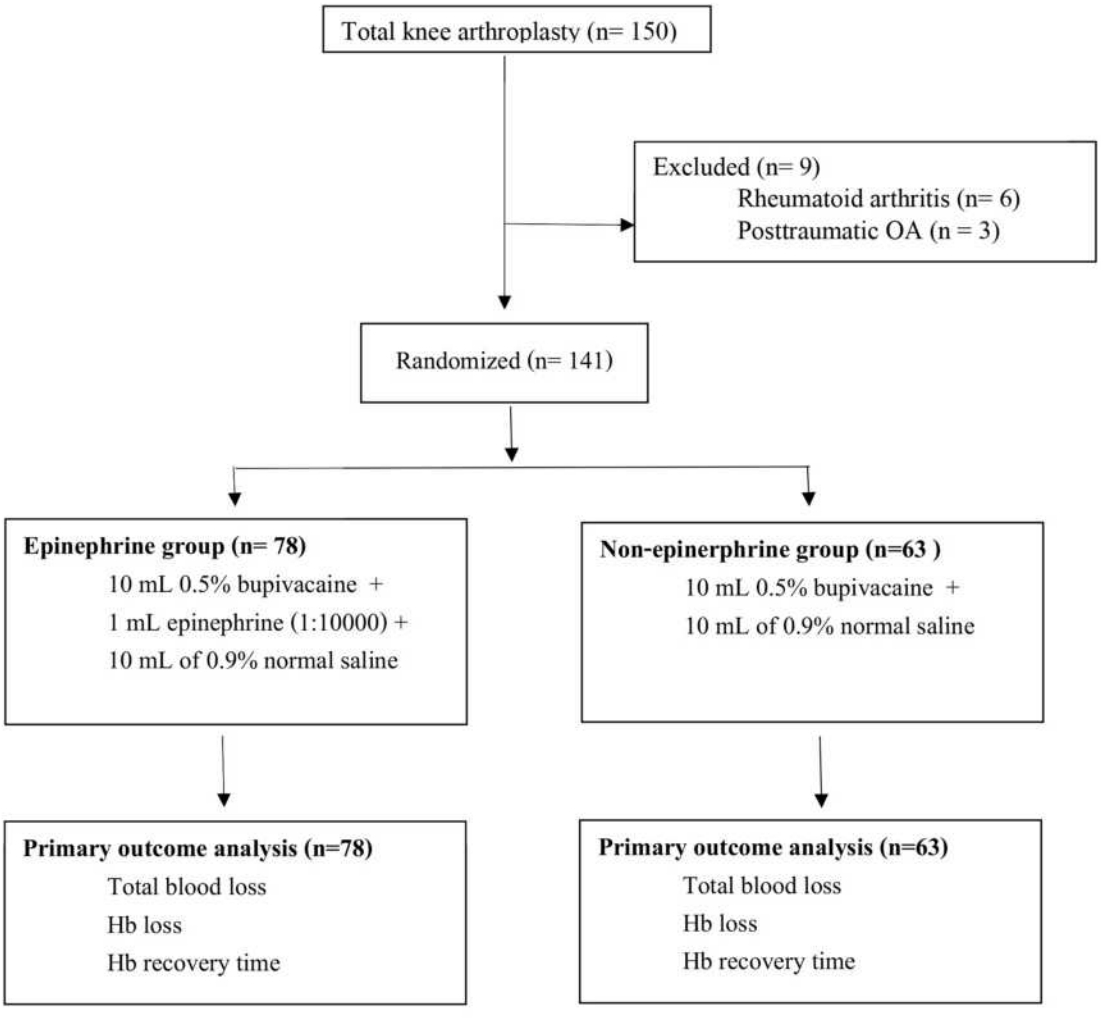
Estimated blood loss = Estimated blood volume x (Hct preoperative - Hct postoperative/ Hct average) + mL of transfused RBC

Estimated blood volume among males: $604 + 0.0003668 \times [\text{height (cm)}]^3 + 32, 2 \times \text{weight (kg)}$

Estimated blood volume among females: $183 + 0.000356 \times [\text{height (cm)}]^3 + 33 \times \text{weight (kg)}$

The duration of Hb recovery to restore preoperative level was calculated from the follow-up data on 1st, 2nd, 3rd, 4th and 5th months postoperatively and until the Hb level returned to normal (the variation of normal Hb level was ±2.46% among males and ± 3.15% among females[8]).

Fig. 1 Flow chart of enrollment and randomization of patients undergoing total knee arthroplasty



The enrolled 150 participants were randomized to 78 in the epinephrine group and 63 in the nonepinephrine group. The demographic data between groups were analyzed regarding age, sex, side of TKA, BMI and preoperative Hb and Hct levels using the Chi Squared test for categorical variables and Student's *t* test for continuous variables. The mean differences in Hb recovery duration and 95% confidence intervals (CI) were calculated using Pearson's Chi Square and independent sample *t*-test. A $p < 0.05$ was considered statistically significant.

Results

Of 150 patients, 9 were excluded because 6 had rheumatoid arthritis and 3 had posttraumatic OA knee. The enrolled 141 patients were randomized to the epinephrine (n=78) and the nonepinephrine groups (n=63) according to the flow chart of participants shown in **Figure 1**. Demographic data such as age, sex, side of TKA, BMI including preoperative Hb and Hct levels are shown in **Table 1**. Patients were mostly female and exhibited no significant differences between groups (p=0.09 among males, p=0.236 among females). Preoperative Hb levels between the two groups did not significantly differ (12.62 ± 1.11 vs. 12.64 ± 1.15; p=0.891) and demographic data and clinical characteristics did not significantly differ between groups.

From **Table 2**, no significant difference was observed between the epinephrine and nonepinephrine groups concerning total blood loss volume (570.95 ± 302.93 ml vs. 573.56 ± 228 mL; p=0.955), postoperative percent Hb loss (13.40 ± 6.66 g/dl vs. 13.01 ± 5.01 g/dl; p=0.703) and Hb recovery time (2.52 ± 1.08 months vs. 2.56 ± 1.09 months; p=0.855). None of these patients had Hb levels <8.0 g/dl. Thus, no patients received blood transfusion. **Table 2**. Comparison of hemoglobin, hematocrit and hemoglobin recovery time between groups. The Hb level gradually increased to preoperative level at 2.54+1.08 months in both groups as shown in **Figures 2 and 3**. All patients were clinically stable without receiving blood transfusion.

Table1. Demographic and clinical characteristics of the patients in both intervention and control groups

	Epinephrine group (n=78) Mean (SD)	Non-epinephrine group (n=63) Mean (SD)	Total (n=141) Mean (SD)	*p*-value
AGE, years	70.7 (8.29)	69.11 (7.39)	69.99(7.92)	0.236
SEX, MALE	11 (14.10)	16 (25.40)	27 (19.10)	0.090
SEX, FEMALE	67 (85.90)	47 (74.60)	114 (80.90)	0.236
BMI (kg/m^2)	26.42 (3.52)	25.76 (3.54)	26.13 (3.53)	0.272
Lt	44 (56.40)	26 (41.30)	70 (49.60)	0.074
Rt	34 (43.60)	37 (58.70)	71 (50.40)	0.095
PREOP Hct	38.69 (3.44)	39.00 (3.59)	38.83 (3.50)	0.606
PREOP Hb	12.62 (1.11)	12.64 (1.15)	12.63(1.13)	0.891

Table 2. Comparison of hemoglobin, hematocrit levels and hemoglobin recovery time between groups

	Epinephrine group (n=78) Mean (SD)	Non-epinephrine group (n=63) Mean (SD)	Total (n=141) Mean (SD)	*p*-value
Hb at Day 3	10.92 (1.24)	10.99 (1.13)	10.95 (1.19)	0.733
Hct at Day 3	33.26 (3.70)	33.53 (3.50)	33.38 (3.60)	0.661
Hb loss	1.69 (0.84)	1.65 (0.67)	1.67 (0.77)	0.743
Hct loss	5.43 (2.68)	5.47 (1.84)	5.45 (2.33)	0.920
% Hb loss	13.40 (6.66)	13.01 (5.01)	13.23 (5.96)	0.703
% Hct loss	13.99 (6.78)	14.02 (4.46)	14.00 (5.84)	0.968
TVB loss	570.95 (302.93)	573.56 (228.00)	572.12(271.10)	0.955
Hb recovery time (month)	2.52 (1.08)	2.56 (1.09)	2.54 (1.08)	0.855

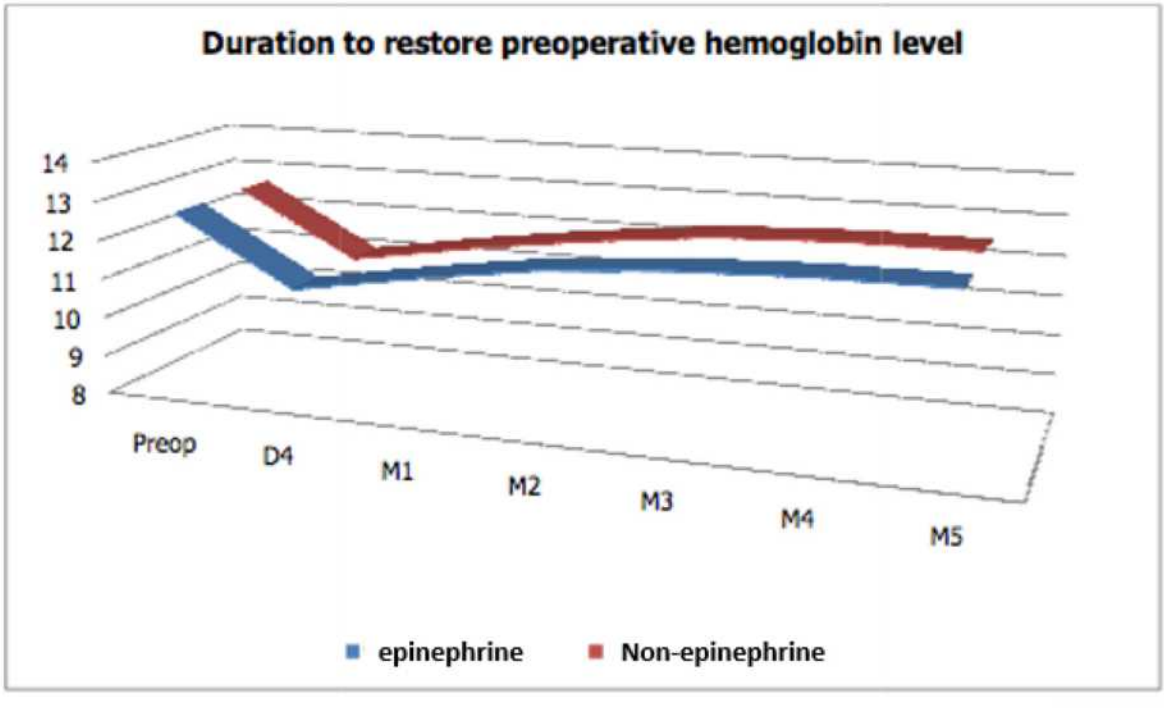


Fig 2. The duration to restore preoperative haemoglobin levels

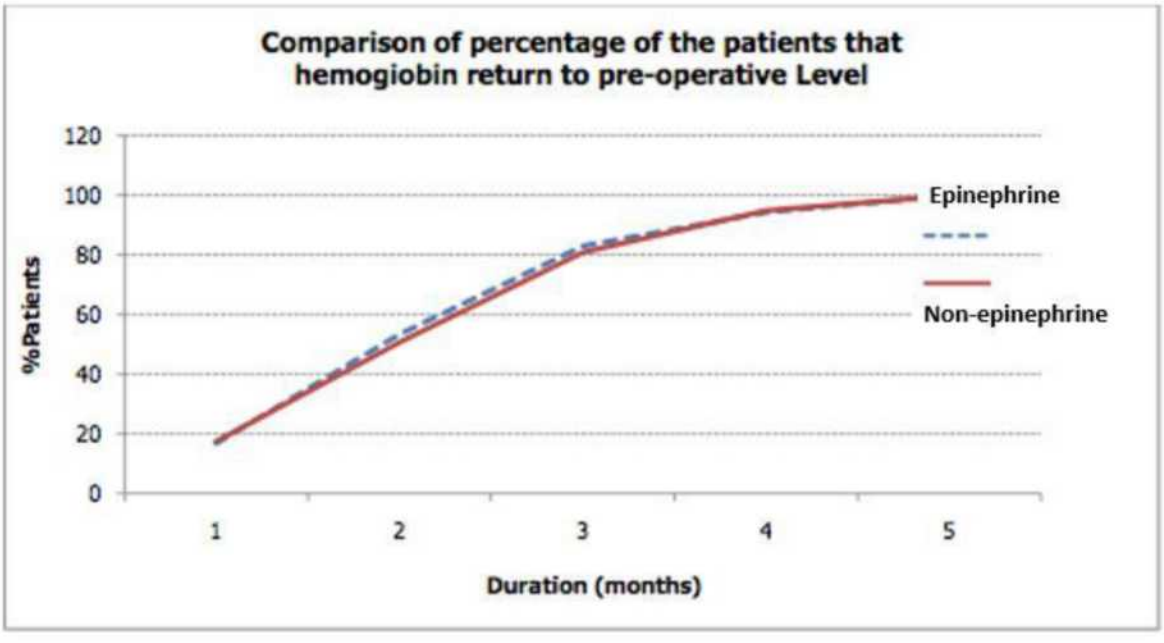


Fig 3. Comparison of percentage of Hb preoperative recovery between groups

Discussion

Recently, technology and surgical techniques involving TKA have been improved using computer navigation, minimal invasive surgery and patient specific implants. Minimal pain, early knee motion, early ambulation, shorter length of hospital stays are beneficial results of surgery and one of the important outcomes is minimal blood loss. Blood loss in TKA usually totals about 500 to 1900 mL. Concealed hemorrhage constitutes one important reason, mainly caused by blood remaining in the intraarticular space up to 500 mL.[9, 10] With hidden blood loss in the tissue, total blood loss amount could be 765 mL.[11] Several techniques have been employed to reduce blood loss in TKA such as drain clamping, intravenous or intraarticular tranexamic acid injection and periarticular epinephrine injection. However, anemia is one of the common postoperative sequelae in TKA.

The 1992 to 1995 baseline data of tourniquet and drain clamping after surgery showed blood in the bottle of the first 24 hours totaled 600 mL with blood transfusion at about 18%. In 2006, we started to use a clamp drain from 1 to 4 hours and eventually 4 hours for primary TKA and 5 hours for revision TKA.[12] Using a tourniquet, drainage with 4-hour clamp including less operative time could reduce blood transfusion to less than 5%.

To compare computer navigation with minimal invasive surgeries, TKA showed the amount of drainage within 24 hours was 338 mL and 361 mL, respectively.[13] Regarding patient specific instrument (PSI) compared with the conventional TKA, postoperative blood loss within 24 hours was 294.3 mL and 311.8 mL as well as Hb loss was 1.7 g/dl and 2.7 g/dl, respectively.[14] In 2014, our related study showed that the use of a tourniquet, drainage and 2 gm tranexamic acid by intravascular injection yielded blood transfusion less than 1% and postoperative Hb levels before blood transfusion were reduced from 10 to 9 g/dl. Patients receiving blood transfusion mostly had preoperative Hct levels less than 33%. These patients showed a Hb loss of 1.7 g/dl.

In this study, TKA was performed without drainage. The most accurate way to determine the total or true blood loss from the operation was the use of calculation. Gibon et al. reviewed using a formula and found that Gross' formula proved reliable and easy to use.[15] We used a safety dose of epinephrine injection to reduce blood loss from TKA operation. Our results showed no significant difference concerning the aspect of reducing blood loss regarding Gross' formula.

Similar results have been reported from other studies. Anderson et al. and Lombadi et al. studied the use of bupivacaine injection along with epinephrine and reported no significant difference in reducing Hb or the bleeding index.[3, 6] However, one advantage of epinephrine injection was demonstrated. Gao et al. reported the use of local tranexamic acid combined with epinephrine injection and observed significantly reduced blood loss and transfusion rate.[16] Epinephrine combined directly with tranexamic acid could increase the tranexamic acid reaction.

In this study, we found no significant differences between the epinephrine and nonepinephrine groups regarding total blood volume loss (518.89 ± 174.19 vs. 521.7 ± 209.12; p=0.953), % Hb loss (13.69 ± 4.61 vs. 13.67 ± 4.39 mL; p=0.986). About 77.8% of TKA patients had anemia but remained asymptomatic. The duration to restore preoperative hemoglobin levels were about the same (2.52 vs. 2.54 months; p=0.855). Periarticular epinephrine injection neither decreased blood loss after TKA nor decreased the duration of anemia.

We used the same threshold for blood transfusion similar to other studies;[16-18] however, surgery was performed without blood transfusion in this study. The limitations of our study involved using an indirect method to calculate blood loss and the safety dose of epinephrine injection was inadequate to have an effect on blood loss control. All techniques previously used included LIA with epinephrine injection and could not reduce further blood loss. All patients who had anemia postoperatively could recover to preoperative Hb levels within 2.54 months without anemic symptoms. Surgical techniques and patient conditions were the main causes of reducing blood loss in TKA.

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OXALIPLATIN RE-INTRODUCTION THERAPY AMONG PATIENTS WITH ADVANCED STAGE COLORECTAL CANCER

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Abstract

Background: : Retreating with prior chemotherapeutic regimens is a possible option for palliative treatment for patients with advanced stage colorectal cancer (CRC).

Objective: This study aimed to examine the feasibility and clinical outcomes of oxaliplatin re-introduction therapy.

Methods: The present study was a prospective case series of patients with advanced stage colorectal adenocarcinoma who were previously treated and re-treated with oxaliplatin combination therapy at Phramongkutklao Hospital between April 1st, 2011 and March 30th, 2014. Treatment regimens are described below. First, FOLFOX4 (14-day cycles of oxaliplatin 85 mg/ m^2, folinic acid 200 mg/ m^2) was given days 1-2 plus fluorouracil 400 mg/ m^2 (bolus) and 600 mg/ m^2 (continuous 22 hours infusion). Second, modified FOLFOX6 (oxaliplatin 85 mg/ m2) was given day 1 with calcium folinate 400 mg/m^2 as a 2-hour infusion followed by bolus 5-fluorouracil 400 mg/m^2 and a 46-hour infusion of 5-fluorouracil 2,400 mg/m^2). Similarly, XELOX (130 mg/ m^2 intravenous oxaliplatin) was provided for 2 hours day 1 plus oral capecitabine 1,000 mg/ m^2 twice daily for 2 weeks from day 1. Treatment was continued until disease progression (PD), intolerability to therapy, poor performance status, withdrawal of consent or death occurred. Authors evaluated tolerability, feasibility, types and rate of untoward medical occurrences due to adverse reactions of PD.

Results: Thirteen patients with CRC were recruited in the study. The median cycles (range) of receiving oxaliplatin-based chemotherapy before re-introduction therapy was 8 (3-15) cycles. The median age (range) was 50 (27-78) years. Etiologies of treatment cessation were recorded by number of patients as follows: tumor progression (6), lost to follow-up (1), refused to receive further treatment (1), allergic reaction (2) and physical deterioration (2). Efficacy of the treatment was assessed in 10 of 13 patients. Of 10 patients, 2 developed drug allergies and 1 was lost to follow-up. Six patients (60%) had PD while 4 patients (40%) had stabilized disease measured by the Response Evaluation Criteria in Solid Tumors (RECIST).

Conclusion: Reintroducing oxaliplatin combination chemotherapy is one of the treatments in advanced stage CRC. In this study, physical deterioration and tumor progression were the main etiologies of treatment cessation.

Keywords : Oxaliplatin, Reintroduction therapy, Palliative chemotherapy, Advanced colorectal adenocarcinoma, Colorectal cancer

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Introduction

Oxaliplatin has been used worldwide to manage colorectal adenocarcinoma (CRC). Oxaliplatin is classified as an "alkylating agent" indicated for adjuvant or palliative chemotherapy for advanced stage CRC. Oxaliplatin is usually given in combination with other chemotherapeutic drugs, i.e., 5-fluoropyrimidine, capecitabine or irinotecan, with or without biologic targeted therapies, i.e., bevacizumab, cetuximab and panitumumab, as first-line or second-line therapy. Although a median survival rate of 11 to 12 months for fluoropyrimidine single-agent in treating advanced stage CRC was reported, the median survival has doubled to 2 years using novel chemotherapeutic regimens.[1] Problems using chemotherapeutic drugs for palliation in advanced stage CRC include that nearly all patients would eventually experience disease progression (PD) after the second- or third-line therapy. Notwithstanding, many patients would still present good performance status and be ready for further later-line chemotherapy. However, later- line chemotherapy is costly, usually provided at an unaffordable price. For this reason, repeating prior chemotherapy is an option for selected cases to delay tumor progression.

Repeating treatment using prior chemotherapy is a practice that may be justified under limited alternatives. However, little clinical evidence is available concerning the efficacy to support this practice. Further studies are needed to examine the feasibility and tolerability of these patients in real practice. This prospective case series was conducted to gain additional evidence concerning the practical application of repeating prior chemotherapy combined with oxaliplatin therapy for patients with advanced stage CRC.

Patients and Methods

Study design

The present study employed a prospective design among patients with advanced stage CRC who had previously received oxaliplatin and were retreated with oxaliplatin- based regimens at Phramongkutklao Hospital between April 1st, 2011 and March 30th, 2014. This study was approved by the Institutional Review Board of the Medical Department, the Royal Thai Army.

Patients

Patients with a diagnosis of advanced stage CRC that was unable to be treated due to distant site metastasis, infiltration, or adherence to adjacent organs/structures were enrolled. The inclusion criteria of the enrolled participants included 1) previously treated with oxaliplatin and planned to retreat with oxaliplatin-based regimens, 2) age <80 years, 3) good health status evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status within the range of 0 to 2 before starting chemotherapy and 4) adequate organ functions. Functions were defined as **renal**: serum creatinine <1.5 x normal, or creatinine clearance GFR >60 ml/min/1.73 m^2 and **liver**: total bilirubin <1.5 x normal, or SGOT (AST) or SGPT (ALT) <3.0 x normal baseline pretreatment patients' characteristics. In addition, disease status was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST)[2], and laboratory results were also recorded.

Chemotherapy regimens

Three treatment regimens are described below. First, **FOLFOX4** (14-day cycles of oxaliplatin 85 mg/ m^2, folinic acid 200 mg/ m^2) was given days 1 to 2 plus fluorouracil 400 mg/m^2 (bolus) and 600 mg/m^2 (continuous 22-hour infusion). Second, modified **FOLFOX6** (oxaliplatin 85 mg/m^2) was given day 1 with calcium folinate 400 mg/m^2 as a 2-hour infusion followed by a bolus of 5-fluorouracil 400 mg/m^2 and a 46-hour infusion of 5-fluorouracil 2,400 mg/ m^2. Similarly, **XELOX** (130 mg/ m^2 intravenous oxaliplatin for 2 hours) was provided day 1 plus oral capecitabine 1,000 mg/m^2 twice daily for 2 weeks from day 1. Treatment was continued until PD, intolerable adverse drug reactions, poor performance status, withdrawal of consent or death occurred. **ELOXATIN**® (Sanofi-Aventis) was used in the present study. Authors evaluated types and rate of unintended medical events, tolerability, feasibility and efficacy.

Tolerability

Combination regimens may cause different types of side effects. All adverse reactions were identified to determine rate and severity based on the Common Terminology Criteria for Adverse Events, Version 4.0. Rate and reasons of treatment cessation were identified to determine feasibility of retreating with oxaliplatin-based regimens.

Evaluation of efficacy

All patients were given regular follow-up using routine physical examination, serum markers, and imaging studies

to assess treatment response. The efficacy of retreatment with oxaliplatin-based regimens was assessed using routine physical examination, blood test for serum markers, and imaging studies (CT scan/MRI/CXR). RECIST criteria[2] were applied to measure tumor response categorized as: 1) complete response (CR) when all target lesions disappeared, 2) partial response (PR) when a 30% decrease was observed in the sum of the longest diameter of target lesions, 3) PD when a 20% increase was observed in the sum of the longest diameter of target lesions and 4) stable disease (SD) when small changes occurred that did not meet the above criteria. Clinical evaluation was used instead of the imaging study in the case of intolerability or when contraindicated for CT scan/MRI with clear clinical evidence of tumor appearance or progression.

Results

A total of 13 patients with advanced CRT who had been previously treated with oxaliplatin were recruited in this study. The median cycles (range) of received oxaliplatin-based chemotherapy before re-introducing therapy comprised 8 (3-15) cycles. The median age (range) was 50 (27 to 78) years. The most common sites of cancer were the rectum (8/13) and sigmoid colon (3/13). Metastases were detected in different parts of the body. The liver (9/13) and lungs (8/13) were the first two most common metastatic sites. Four patients (30.7%) had more than one metastatic site. Two patients had peritoneal metastases detected during primary tumor resection and 2 patients had local recurrence and peritoneal metastases detected after surgery. Four patients presented primary tumors which were unable to be removed and left in situ. XELOX (130 mg/ m^2 intravenous oxaliplatin) provided for 2 hours on day 1 plus oral capecitabine 1,000 mg/ m^2 twice daily for 2 weeks from day 1 was the most commonly prescribed regimen for this retreatment period. Of a total of 13 patients, 9 (69.3%) received oxaliplatin-based reintroduction on a stop and go strategy to avoid possible cumulative toxicities as resistance had not been proved in this group. In addition, 4 (30.7%) patients received oxaliplatin-based re-introduction after exhibiting previous resistance to the oxaliplatin regimens. The planned 4 cycles of Xerox re-introduction were withheld for 2 patients due to allergic reaction at the 3rd cycle of re-challenge treatment. Efficacy was determined in 10 of 13 cases (two cases presented drug allergy and one case was lost to follow-up). Of these, 6 patients (60%) exhibited PD while 4 patients (40%) had SD measured by RECIST criteria. Grade 3/4 adverse events were found among 7 patients (53%) and some events were anticipated, i.e., organ deterioration or consequences of PD including pericardial effusion, neutropenia, anemia, neuropathy, nausea, vomiting, obstructed uropathy and jaundice. The 4 patients (100%) in the tumor resistance group who had received a diagnosis before receiving re-treatment with oxaliplatin combination therapy had grade 3/4 adverse events compared with 33% of the stop and go treatment group. Three patients were excluded because treatments were withheld due to allergic reactions (2), they refused to continue treatment (1) and were lost to follow-up (1). About 77.8% (7/9) of patients successfully received predefine treatment cycles. Etiologies of treatment cessation by numbers of patient were recorded as: tumor progression (6), lost to follow-up (1), refused to receive further treatment (1), allergic reactions (2) and physical deterioration (2). One patient was defined as having SD while three patients died during the treatment period from PD.

Discussion

For advanced stage CRC, a combination of multiple anti-cancer treatments is given that aims to reduce symptoms and prolong patients' survival. Prolonged treatment with chemotherapy until the cancer ceases to respond usually causes drug related toxicities and compromises quality of life. Stop and restart of aggressive anti-cancer drugs or interspersed with periods of maintenance are acceptable practices to ensure a better quality of life as a continuum of care concept. For patients with advanced stage CRC, experiencing tumor progression beyond multiple line chemotherapy, the best supportive care, clinical trial participation and retreating with the previous regimens are possible options. When clinical trial enrollment is unavailable and patients remain in good physical status, oxaliplatin-based re-introduction may be offered.

Physical deterioration due to the PD and accumulative toxicity after exposure to previous multiple lines of chemotherapy were considered the main obstacles of treatment tolerability. For patients with good performance status,

re-introducing therapy comprised a feasible alternative.[1, 3]

Our study found that approximately 78% of patients could complete 4 cycles of re-introduction therapy. This study found 13% of patients developed hypersensitivity reactions that were comparable to 12.7% from a related study.[4] hao et al.[5] revealed that repeated infusion, younger age, being female, extended period and salvage therapy were factors predicting the occurrence of allergic reactions. Based on the present study, re-introducing oxaliplatin-based chemotherapy was a feasible alternative and could provide clinical benefits when no other alternative choices were available. Selecting suitable patients presenting good physical status with close monitoring by physicians is crucial to achieve treatment objectives. We found a better tolerability of patients with no diagnosis of oxaliplatin resistance. Balancing between prolongation of survival and quality of life must be the primary goal of treatment because organ deterioration and PD are anticipated consequences of advanced unresectable metastatic CRC.

Conclusion

Reintroducing oxaliplatin combination chemotherapy is one of treatments used in advanced stage CRC. We concluded that physical deterioration and tumor progression were the main etiologies of treatment cessation.

Table 1. Patient Characteristics

No.	Sex	Age	Site of Metastases	Regimen	Completion of predefine treatment course	Response	Evaluation of treatment response	Reason for Oxaliplatin Cessation	Grade 3/4 adverse events
1	Male	27	Liver, peritoneum	XELOX	no	N/A	-	Drug allergy	-
2	Female	59	Liver, peritoneum	XELOX	no	PD	Clinical	Dead from PD	Anemia, Obstructive uropathy, Peripheral neuropathy
3	Male	62	Lung	XELOX	no	SD	Imaging	Unable to tolerate side effects	Vomiting
4	Male	50	Liver	FOLFOX4	no	PD	Clinical	Dead from PD	Neutropenia, Renal insufficiency
5	Male	60	Lung	XELOX	yes	SD	Imaging	Dead from PD	Heart failure
6	Male	43	Liver	XELOX	yes	PD	Imaging	PD	-
7	Male	42	Liver	mFOLFOX6	yes	PD	Imaging	PD	-
8	Male	53	Lung, Brain	XELOX	yes	N/A	-	Drug allergy	-
9	Male	46	Lung	mFOLFOX6	yes	PD	Imaging	PD	-
10	Female	40	Lung	XELOX	yes	SD	Imaging	PD	Neutropenia, Peripheral neuropathy
11	Male	37	Liver, peritoneum	XELOX	no	PD	Clinical	PD	Jaundice, Neutropenia
12	Male	55	Lung, peritoneum	XELOX	no	N/A	-	Loss to F/U	-
13	Male	78	Lung	XELOX	yes	SD	Imaging	-	Pericardial effusion, Neutropenia, Peripheral neuropathy

PD=disease progression, SD= stable disease

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