การศึกษาเปรียบเทียบประสิทธิผลของการใช้ยารับประทาน โรฟีคอกซิบ เทียบกับ ยาฉีดไดโคลฟีแนก ในการรักษาอาการปวดจากการผ่าตัดใหญ่ทางศัลยกรรมออร์โธปิดิกส์

นายพงศ์ศักดิ์ ยุกตะนันทน์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2545

ISBN 974-17-1561-7

A RANDOMIZED, CONTROLLED TRIAL TO COMPARE THE EFFICACY OF ORAL ROFECOXIB AND INTRA-MUSCULAR DICLOFENAC SODIUM FOR THE TREATMENT OF POST-OPERATIVE PAIN AFTER MAJOR ORTHOPEDIC SURGERY

Mr. Pongsak Yuktanandana

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Health Development

Faculty of Medicine

Chulalongkorn University

Academic Year 2002

ISBN 974-17-1561-7

Title	**: A Randomized, Controlled Trial to Compare the Efficacy of Oral Rofecoxib and Intra-muscular Diclofenac Sodium for the Treatment of Post-operative Pain after Major Orthopedic Surgery.**
By	**: Pongsak Yuktanandana M.D.**
Field of Study	**: Health Development**
Thesis advisor	**: Assoc.Prof.Somrat Charulaxananan, M.D., M.Sc.**
Thesis Co-advisor	**: Assoc.Prof.Suwannee Suraseranivongse M.D. Msc.**

Accepted by Faculty of Medicine, Chulalongkorn University in partial Fulfillment of the Requirement for Master's Degree

…….. Dean of Faculty of Medicine

(Prof.Pirom Kamol-ratanakul, M.D., M.Sc.)

Thesis Committee

…… Chairman

(Asst.Prof. Montchai Chalaprawat MD. M.Sc.)

…… Thesis advisor

(Assoc.Prof.Somrat Charulaxananan, M.D., M.Sc.)

…… Thesis co-advisor

(Assoc.Prof.Suwannee Suraseranivongse M.D. Msc)

…… Member

(Assoc.Prof.Pibul Iiravivong MD.)

…… Member

(Dr. Chalaluk Komoltri Ph.D.)

พงศ์ศักดิ์ ยุกตะนันทน์ ; การศึกษาเปรียบเทียบประสิทธิผลของการใช้ยารับประทาน โรฟีคอกซิบ เทียบกับ ยาฉีดไดโคลฟีแนก ในการรักษาอาการปวดจากการผ่าตัดใหญ่ทางศัลยกรรมออร์โธปิดิกส์ (A Randomized, Controlled Trial to Compare the Efficacy of Oral Rofecoxib and Intra-muscular Diclofenac Sodium for the Treatment of Post-operative Pain after Major Orthopedic Surgery.) อาจารย์ที่ปรึกษา : รศ.นพ.สมรัตน์ จารุลักษณานันท์ M.D., MSc., อาจารย์ที่ปรึกษาร่วม : รศ.พญ.สุวรรณี สุรเศรณีวงศ์ MD., MSc.

วัตถุประสงค์ : เพื่อศึกษาเปรียบเทียบประสิทธิผลของการใช้ยารับประทานโรฟีคอกซิบก่อนการผ่าตัดกับยาฉีดไดโคลฟีแนกให้หลังผ่าตัดทุก12ชั่วโมง ในการรักษาอาการปวดจากการผ่าตัดใหญ่ทางศัลยกรรมออร์โธปิดิกส์

รูปแบบการทดลอง : การศึกษาแบบสุ่มเปรียบเทียบ ปกปิดอาสาสมัครและผู้ประเมิน

สถานที่ทำการวิจัย : โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

วิธีการศึกษา : ผู้ป่วยที่ได้รับการผ่าตัดใหญ่ทางออร์โธปิดิส์จำนวน 102รายเข้าร่วมการศึกษา ได้ข้อมูลผู้ป่วยจำนวน 96รายเพื่อนำมาวิเคราะห์เปรียบเทียบ ผู้ป่วยถูกสุ่มให้รับยาเพื่อทำการศึกษาแบ่งเป็น 3 กลุ่ม กลุ่มแรกได้รับยาหลอก (31ราย) กลุ่มที่สองได้รับยารับประทานโรฟีคอกซิบ 50 มิลลิกรัมครั้งเดียวก่อนการผ่าตัดและยาหลอก (32ราย) กลุ่มที่ 3 ได้รับยาฉีดเข้ากล้ามเนื้อไดโคลฟีแนกหลังผ่าตัดทุก 12 ชั่วโมงและยาหลอก (33ราย) ผู้ป่วยทุกรายได้รับยามอร์ฟีนฉีดเข้าเส้นเลือดชนิดผู้ป่วยควบคุมการใช้ยาเอง การศึกษานี้บันทึก ปริมาณยามอร์ฟีน คะแนนการปวด ความพึงพอใจของผู้ป่วย และผลข้างเคียงที่เกิดขึ้นตลอดระยะเวลา 24 ชั่วโมงหลังการผ่าตัด

ผลการศึกษา : ในผู้ป่วยที่ได้รับการผ่าตัดใหญ่ทางออร์โธปิดิกส์ไม่พบความแตกต่างของปริมาณการใช้มอร์ฟีนระหว่างกลุ่มที่ได้รับยารับประทานโรฟีคอกซิบและกลุ่มที่ได้รับยาฉีดไดโคลฟีแนก (p=0.762) ผู้ป่วยกลุ่มโรฟีคอกซิบใช้มอร์ฟีนน้อยกว่ากลุ่มที่ใช้ยาหลอกร้อยละ 50 ผู้ป่วยกลุ่มไดโคลฟีแนกใช้มอร์ฟีนน้อยกว่ากลุ่มที่ใช้ยาหลอกร้อยละ 43 พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของปริมาณมอร์ฟีนที่ใช้ของกลุ่มโรฟีคอกซิบเมื่อเปรียบเทียบกับกลุ่มยาหลอก (17.5 มก. กับ 35 มก. p=0.003) และกลุ่มไดโคลฟีแนกเมื่อเปรียบเทียบกับกลุ่มยาหลอก (20 มก. กับ 35 มก. P<0.001) พบความแตกต่างของอาการปวดระหว่างกลุ่มไดโคลฟีแนกและกลุ่มยาหลอกที่ 4 ชั่วโมง (p=0.003) ไม่พบความแตกต่างของอาการปวดระหว่างกลุ่มโรฟีคอกซิบและกลุ่มยาหลอก ผู้ป่วยร้อยละ 98 พอใจถึงพอใจมากที่สุดกับการรักษาอาการปวดหลังผ่าตัด ไม่พบผลข้างเคียงที่รุนแรง ผู้ป่วยร้อยละ 11 มีผลข้างเคียงแบ่งเป็นคลื่นไส้อาเจียนร้อยละ 6 หน้ามืดร้อยละ 2 มึนงงร้อยละ 1 คันร้อยละ 1 และ จุกแน่นท้องร้อยละ 1

สรุป : การให้ยาโรฟีคอกซิบ50มิลลิกรัมรับประทานครั้งเดียวก่อนการผ่าตัดมีประสิทธิผลเทียบเท่ากับการใช้ยาฉีดไดโคลฟีแนกหลังผ่าตัดทุก12ชั่วโมง เพื่อรักษาอาการปวดหลังการผ่าตัดใหญ่ทางออร์โธปิดิกส์ในระยะเวลา 24 ชั่วโมงแรก

หลักสูตร	การพัฒนาสุขภาพ	ลายมือชื่อนิสิต.....
สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา	2545	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

447 54272 30: MAJOR HEALTH DEVELOPMENT

KEY WORD: POST-OPERATIVE PAIN/ORTHOPAEDIC SURGERY/PCA MORPHINE/ROFECOXIB/DICLOFINAC SODIUM

PONGSAK YUKYANANDANA: A RANDOMIZED, CONTROLLED TRIAL TO COMPARE THE EFFICACY OF ORAL ROFECOXIB AND INTRA-MUSCULAR DICLOFENAC SODIUM FOR THE TRTEATMENT OF POST-OPERATIVE PAIN AFTER MAJOR ORTHOPEDIC SURGERY.

THESIS ADVISOR: ASSOC.PROF. SOMRAT CHARULUXNANAN, M.D.,M.Sc.,

THESIS CO-ADVISOR: ASSOC.PROF.SUWANNEE SURASERANIVONGSE M.D., M.Sc.

Objective: To compare the efficacy of oral rofecoxib, intramuscular diclofenac and placebo in the amount of PCA morphine used during postoperative orthopedic surgery period.

Design: Randomized (1:1:1) double-blind controlled trial

Setting: King Chulalongkorn Memorial Hospital

Methods: One hundred and two healthy patients undergoing major orthopedic surgery were recruited for the study and 96 patients completed the study. Patients were randomized into three treatment groups; placebo group (n=31) received oral placebo and placebo injection, rofecoxib group (n=32) received 50 mg preoperative oral rofecoxib and placebo injection, and diclofenac group (n=33) received oral placebo and post-operative intramuscular diclofenac injection 12 hourly. All patient received intravenous morphine by patient controlled analgesia (PCA) system. Amount of morphine used, numerical pain score and patient satisfaction were recorded for 24 hours. Adverse event was also monitored.

Results: There was no statistical significant different of the amount of PCA morphine used between rofecoxib group and diclofenac group (p=0.762). The amount of PCA morphine used at 24 hours in patients who received oral rofecoxib and placebo was significantly different (17.5 mg vs 35 mg, p=0.003, 50% less) and the amount of PCA morphine used at 24 hours in patients who received diclofenac injection and patients in placebo group was significantly different (20 mg vs 35 mg, p<0.001, 43% less). Numerical pain scores between rofecoxib group and placebo group were not different. Numerical pain scores between diclofenac group and placebo group were significantly different at 4 hour post-operatively (p=0.003). Ninety eight percent of the patients reported satisfactory score between “satisfy”, “very satisfy” and “most satisfy” to the treatment of postoperative pain. No serious adverse event occurred and there were 11% adverse events (6% nausea, 2% hypotension, 1% dizziness, 1% pruritus and 1% dyspepsia).

Conclusion: Single dose preoperatively administered rofecoxib is as efficacious for the treatment of postoperative pain as post-operative injection of diclofenac sodium 12 hourly in the first 24 hours after major orthopedic surgery.

Department……Health Development…… Student’s Signature……..

Field of Study…Health Development…… Advisor’s Signature……..

Academic Year…2002…… Co-advisor’s Signature…….

ACKNOWLEDGEMENTS

First of all, I would like to thank all of the patients who were willing to participate in this study, without their patience and understanding, this study could not be possible. I also would like to thank all the nurses who work hard and take care of the patient very well.

Many thank to Ms. Kusolsri Torleb, registered nurse in pain unit department of anesthesiology, who prepared intravenous morphine and PCA machine and help solved problems according to PCA machine.

I would like to thank Assoc. Prof. Somrat Charuluxananan MD. MSc, who introduced me to this course and accepted to be my advisor, and also guided me for this research project. I also would like to extend my grateful appreciation to all teachers in Thai CERTC Consortium, who were very busy but spare sometime to teach and share their knowledge and give invaluable comments and suggestion.

This study was partial financially support by Rachadapisakesompoj Research Fund, Faculty of Medicine, Chulalongkorn University. I also would like to thank BLH and Novatis companies for their support of trial medications.

CONTENTS

Pages

LIST OF TABLES

Tables **Page**

LIST OF FIGURES

Figure **Page**

CHAPTER 1

INTRODUCTION

Patients underwent orthopedic surgery suffered severe postoperative pain. Usually orthopedic surgery is performed with large soft tissue dissection, periosteum stripping and sometimes osteotomy of the bone. Post-operative pain caused suffering, dissatisfaction and delayed postoperative mobility, which may affect the result of the surgery. Postoperative pain caused by tissue damage during surgery. These tissue damaged trigger tissue inflammation, which might sensitize peripheral and central receptors for pain. The noxious stimuli from surgery and the result of inflammatory response elicit change in the periphery leading to hypersensitivity of nociceptors both in peripheral and central nervous system. Postoperative pain can be control by central acting drug such as narcotic drugs or peripheral acting drug such as anti-inflammatory drugs, which prevent inflammatory response and production of noxious stimulus.

Narcotic analgesic drugs such as morphine or pethidine were used in patients with unbearable postoperative pain effectively. Narcotic analgesic drugs may cause addiction, respiratory depression and other complications. Patients who take narcotic analgesic drugs may be drowsy and difficult for rehabilitation, which will delay hospital stay. Classical NSAIDs and many of the new class selective COX-2 inhibitors were proven to be effective in the treatment of postoperative pain without opioid side effects. One effective way to improve the quality of the orthopedic patients care, is to control post-operative pain by using less narcotic drugs and encourage patient mobility.

Intra-muscular diclofenac sodium injection is common classical NSAIDs used for post-operative pain after orthopedic surgery in Thailand and rofecoxib is a new selective COX-2 inhibitor registered for treatment of post-operative pain. This study aim at comparison of the efficacy of oral rofecoxib with intra-muscular diclofenac sodium injection in the treatment of post-operative pain by measuring the amount of morhpine used postoperatively.

CHAPTER 2

LITERATURE REVIEW

Literature search strategy

The literature search strategy used to locate the information in this review is in the MEDLINE reference database and additionally by going through the reference lists of other articles and institutional database. The keywords used were post-operative pain, PCA morphine, rofecoxib, diclofenac and orthopedic surgery. The year covered by the search was from 1985 – 2003.

Mechanism of post-operative pain

The phenomenon of pain is complex, incorporating biological factors as well as sociological, cultural and psychological influences. After initial transmission of sharp pain by fast conducting myelinated Aδ fibers from the afferent nerve endings, a complex myriad of change then occurs, both in the periphery as well as in the central nervous system, resulting in slow dull pain as well as other phenomena, including primary and secondary hyperalgesia, allodynia, sensitization, wind up, expansion of receptor field, and enhancement of flexor reflex.

Many of these changes are brought about by chemical mediators that either act directly on neuronal cell membrane (e.g., H^+ ions, adenosine triphosphate, and serotonin), or react with membrane receptors to invoke intracellular second messengers. Example of these receptor binding mediators included: bradykinin reacting with beta receptors; tachykinins, such as substance P, with NK receptors; histamine with H_1-receptors; serotonin with 5-HT_1-receptors; glutamate and aspatate with NMDA receptors, nitric oxide, cytokines, and eicosanoids. Platelet-activating factor (PAF), which mediate vasodilatation, may also involved. In response to tissue damage, eicosanoid are products of metabolism of arachinodic acid released from membrane phospholipid by phospholipase A_2. The cyclooxygenase(COX) and lipooxygenase pathways lead to formation of cyclic prostaglandins and leukotrienes[1].

Prostaglandins are algogenic by several mechanisms: (1) acting on prostaglandin receptors and being second messengers to sensitize sensory neurons; (2) direcly increasing the activity of nociceptors; and (3) stimulating the release of substance P from sensory neurons. The release, level, and activity of prostaglandins are enhanced by other algogenic substances release during inflammation, such as bradykinins and cytokines.

Opioid receptors are absent in undamaged tissue, but they appear in damage tissue within minutes to hours. Inflammatory mediators, such as prostaglandin E2, activate adenylate cyclase via stimulatory G protein, causing nociceptor sensitization. Opioid, such as morphine, provide multi-mechanism of pain treatment. The anti-nociceptive and anti-inflammatory effects may prevent bradykinin-induced sensitization. Bradykinin stimulates the release of nociceptor-sensitzing agents from the postganglionic sympathetic nerves. This discovery led to the use of intra-articular morphine for analgesia after knee arthroscopy. The goal of effective opioid administration is to provide constant, sustained analgesia over regular intervals[2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of agents with similar actions but diverse chemical structures[3]. Aspirin (acetylsalicylic acid) and sodium salicylate were the first drugs of this type to be used clinically. However, over the past 3 decades there has been a dramatic increase in the number of NSAIDs available for the treatment of postoperative pain. Tissue injury occured with surgical intervention, is associated with the release of numerous inflammatory mediators including prostaglandins. Prostaglandins derived from the arachidonic acid cascade are implicated in the production of inflammatory pain, and in sensitising nociceptors to the actions of other mediators. They are synthesised from arachidonic acid via the endoperoxide biosynthesis pathway, the initial step of which is catalysed by the enzyme cyclo-oxygenase. Two forms of the cyclo-oxygenase enzyme (COX-1 and COX-2) have been characterised. COX-1 is important in circumstances where prostaglandins have a protective effect such as gastric mucus production and renal blood flow maintenance. NSAIDs inhibit the synthesis of prostaglandins at 1 or more points in the endoperoxide pathway. Three mechanisms of inhibition of the biosynthetic enzymes have been proposed: (i) rapid, reversible competitive inhibition; (ii) irreversible, time-dependent inhibition; and (iii) rapid, reversible noncompetitive (free radical trapping) inhibition. In addition, there is evidence that NSAIDs have a central antinociceptive mechanism of action that augments the peripheral effect. This may involve inhibition of central nervous system prostaglandins or inhibition of excitatory amino acids or bradykinins. There is considerable variability in the pain relief obtained from NSAIDs. Such variability in drug response may be explained in terms of differences between agents with respect to

either pharmacodynamic actions or pharmacokinetic parameters or a combination of both. Stereoisomerism, where preparations exist as racemic mixtures and where only 1 enantiomer is active, may also be important. However, chiral inversion from inactive to active enantiomer may occur and may be rapid or slow. NSAIDs have numerous adverse effects. Gastrointestinal disturbances including ulceration are the commonest adverse responses to NSAIDs and carry the greatest risk of death. Other significant side effects are renal impairment and an increased risk of postoperative haemorrhage. Asthma and allergic reactions are uncommon.

Analgesia by NSAIDs has been attributed primarily to peripheral inhibition of COX and decreased level of prostaglandins[4, 5]. The inhibition can be reversible (e.g., by ibuprofen) or irreversible (e.g., by aspirin). NSAIDs may also directly uncouple membrane receptor and G-protein-mediated signal transduction. Finally, there may be central anti-nociceptive action by a decrease in central prostaglandin synthesis, an opoid-like effect, a decrease in central serotoninergic mechanism, and a decrease in spinal N-methyl-D-aspatate (NMDA) excitatory mechanism. The analgesic effect of NSAIDs bears no direct relationship to the anti-inflammatory potency. For example, acetaminophen has little peripheral anti-inflammatory effect, but is effective analgesic and anti-pyretic.

The absence of significant depressant effect on respiration, cardiac function, and sensorium are the major advantage of NSAIDs over opioid analgesics in treatment of acute pain. For mild to moderate acute pain, such as minor musculoskeletal trauma, soft tissue inflammation, and pain after dental procedures, superficial surgery, and minor gynecologic procedures, NSAIDs are efficacious and comparable to opioid analgesics, although the onset is typically delayed by 15 to 30 minutes. NSAIDs appear to exhibit a “ceiling effect” in analgesic efficacy and are clearly less effective than opioid analgesics for patients who have undergone major surgical procedures. Even so, they may reduce both visual analog pain scores and postoperative opioid requirements and permit a more rapid return of bowel function. Administering NSAIDs prior to or during surgery may, however, compensate for the delayed onset of analgesia postoperatively, and takes advantage of the opoid-sparing effect, which reduces adverse effects such as respiratory depression and nausea. NSAIDs can significantly improve analgesia in the early postoperative period, especially for ambulatory surgery patients. The efficacy of the NSAID depends on the timing, route of administration, and type of surgical procedure. NSAIDs have also been used as adjuvant to epidural and intrathecal opioid analgesia and morphine patient-controlled analgesia (PCA) to lower pain scores and reduce postoperative opioid requirement[5].

Measurement of post-operative pain

Pain is personal experience. It is therefore difficult to define and is not easily measured. Pain involves not only sensory input but also the degree to which that input is modulated by physiological and psychological factors. How the pain is expressed finally depends on the context. Methods for pain measurement have been developed and refined primarily in the research field where they have been used to assess and to compare the efficacy of new and established treatments either in the acute or in the chronic pain setting. At present the most reliable methods for pain measurement depend on recording the patient's report. It is obvious then that the patient must be willing to cooperate, be able to understand the methods and be capable of reliable communication. There are several instruments to measure pain whereas each instrument has inherent limitations, which can restrict or influence the report[6,7].

Patients' reports of pain can be measured by using scales, which analyze only one dimension at a time, usually pain intensity or pain relief. Pain rating scale includes binary scale, categorical verbal rating scales, visual analogue scale and verbal numerical scales. Categorical scales are the oldest of the standard measure of pain. The number of categories most commonly used is 4 (none, slight, moderate and severe). The main advantages of categorical scales are their simplicity and quick scoring. However, a common complaint is that the numbers of description is insufficient and force the patient to choose particular categories. Visual analogue scales are lines whose ends are labeled with extreme descriptions of dimension. Subjects are asked to mark the line at a point corresponding to the magnitude of the dimension, which is being measured. The advantages of visual analogue scales are that they are simple, quick to score, do not involve imprecise description terms and provide many points from which to choose. Disadvantages are that they require both more concentration than the categorical scales and visual and motor coordination, which may be lacking in the post-operative period and in patients with neurological disorders. Verbal numerical scales designed as an alternative or complement to the categorical and visual analogue scales. Patient is asked to express numerically the magnitude of the dimension, which is being assessed. For pain intensity, a scale ranging from 0 (no pain) to 10 ('the worst pain imaginable') showed good correlation with a conventional 10-cm unmarked horizontal visual analogue scale[6,7].

Post-operative orthopedic pain

Orthopedic surgical pain is mediated by increase prostaglandin synthesis[3]. Prostaglandin synthesis in humans is catalyzed by two distinct forms of cyclo-oxygenase (COX), COX-1 and COX-2, which likely mediate distinct biological processes. COX-1 is constitutively active throughout the body[8,9,10] . In contrast, COX-2 expression is limited to the brain and kidney but is markedly up regulated by a variety of inflammatory mediators[8]. These distinct expression patterns have led to proposal that prostaglandin produced by COX-1 are largely responsible for physiologic function[11], whereas COX-2-derived prostaglandin mediate pathophysiologic and inflammatory process, including pain. COX-2 is selectively induced by proinflammatory cytokines at the site of inflammation. The toxicity associated with the clinically useful NSAIDs is caused by the inhibition of COX-1, whereas the anti-inflammatory properties were caused by the inhibition of inducible COX-2. Expression of the inducible COX-2 enzyme is selectively blocked by the potent anti-inflammatory drug dexamethasone. Selective inhibition of COX-2 may produce superior anti-inflammatory drugs with substantial safety over existing NSAIDs. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) nonspecifically inhibit both the COX-1 and COX-2 isoforms[11]. NSAIDs inhibit the synthesis of prostaglandin both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma[12,13].

Clinical studies

Post-operative orthopedic pain had been studied extensively during the last three decade. Most of the studies compared the efficacy of various medications such as NSAIDs, opioid and non-opioid analgesic drugs. The studies included various major orthopedic procedures and multiple medications including: lumbar disectomy with lornoxicam and morphine[14], spinal fusion surgery with rofecoxib and celecoxib[15], spinal laminectomy with lornoxicam and pethidine[16], spinal fusion with propacetamol injection[17], hip arthroplasty with diclofenac and fentanyl[18], arthroscopic knee surgery with intra-articular bupivacaine injection[19], knee arthroplasty with rofecoxib[20], knee arthroplasty with tenoxicam[21], knee arthroscopic surgery with celecoxib and hydrocodone/acetaminophen[22,23], knee arthroscopic surgery with rofecoxib[23] , major orthopedic surgery with rofecoxib[24] etc. Post-operative pain were measured by various method such as visual analog pain score (VAS), verbal analog pain scale (VpAPS), time needed for rescue medication, opioid used during post-operative period etc. Visual analog pain score and verbal numerical pain score were widely used and could measure pain with acceptable reliability. Verbal numerical pain score may classify pain to be four grades including; 0-1 equal to no pain, 2-4 equal to mild pain, 5-7 equal to moderate pain and over 7 equal to severe

pain[25]. From those studies, post-operative pain after major orthopedic surgery was measured to be moderate to severe pain and most of the treatment could reduce post-operative orthopedic pain to be mild pain. Patients following major orthopedic surgery needed combination of analgesic medications, which included opioid analgesia and other medication or modality such as NSAIDs or COX-2 inhibitor or intra-articular injection.

NSAIDs are useful as the sole analgesic after minor surgical procedure[13] and may have a significant opioid-sparing effect after major surgery[26]. It is currently recommended that NSAIDs be used in the multimodal analgesic approach for the management of perioperative pain[27,28]. Diclofinac sodium intermittent intramuscular injection following abdominal surgery showed significant morphine sparing effect compare to placebo and pain score were significantly lower at 4 hours and there were no significant within group change of platelet count[29]. Intravenous diclofinac sodium infusion was also shown to be very efficacy in the treatment of postoperative orthopedic surgery pain given pre and postoperatively[18,30]. Diclofinac sodium injection was registered in Thailand for intramuscularly administration. The registered dose for post-operative pain was 75-mg injection follow by another 75-mg injection after 12 hours and the maximum daily dose was 150 mg.

COX-2 selective inhibitor inhibit the COX-2 isoenzyme without effecting the COX-1 isoform[31,32]. Rofecoxib, one of the COX-2 specific inhibitor, is specifically inhibiting COX-2 isoforms[29]. Clinical studies have demonstrated that rofecoxib 50 mg has analgesic efficacy similar to that of maximal single analgesic doses of comparator NSAIDs in study of both post-dental surgery pain and primary dysmenorrhea[33, 34, 35] but with a duration of action longer than ibuprofen[34]. In addition, pooled data from clinical trials comparing use of rofecoxib and nonspecific NSAIDs in treating osteoarthritis have shown improved gastrointestinal safety with use of rofecoxib-as judged by both decreased risk of endoscopically diagnosed ulcers after 6 months of therapy[36] and lower incidence of gastroduodenal perforations, ulcers, and upper gastrointestinal bleeds[37]. A double-blind, randomized, placebo and active-comparator-controlled, parallel-group trial between rofecoxib 50 mg and naproxen sodium 550 mg and placebo in the treatment of post-orthopedic surgery pain showed that rofecoxib was as efficacy as naproxen for single dose treatment of post operative orthopedic surgery pain and better than placebo[24]. Rofecoxib and celecoxib, another COX-2 specific inhibitor, showed opioid sparing effect compare to placebo when administered preoperatively in the patients underwent spinal surgery[15]. Rofecoxib was registered in Thailand for the indication of sign and symptom of osteoarthritis and acute pain. For acute post-operative pain, the registered dose was 50 mg daily and subsequence 25 to 5o mg once daily. The maximum daily dose was 50 mg.

Patient-controlled analgesia (PCA) with intravenous opioids started early in 1980s. Patients with pain and need analgesic drug push an electronic device to deliver a small amount of an analgesic directly into the venous line instead of big bolus dose injection or continuous administer of analgesic drug. Morphine is the most common opioid using with PCA system. A quantitative systematic review[38] showed that perception of pain in patients using PCA with opioid was slightly less than conventional opioid analgesia but the amount of opioids consumed was no different with the two methods. Patient preferred PCA, although they were not necessary more satisfy. There was some evidence that there were few postoperative complications with PCA compare with conventional opioid analgesia. The amount of opioid used during postoperative period was used to quantify the efficacy of non-opioid analgesic when administered during pre and post-operative period.[15, 17,18,29]

From the previous literature review, selective COX-2 inhibitor was an efficacious medication to use for post-operative orthopedic pain, even the mechanism of action for acute pain relief was not yet well understood. Rofecoxib, a COX-2 inhibitor, has been reviewed and trial for the indication of post-operative extensively. COX-2 inhibitor was well established for the lower gastro-intestinal side effect comparing to classical NSAIDs and also had little effect on bleeding which was very useful for peri-operative used. Dioclofenac sodium injection is very commonly used in Thailand for the indication of acute pain and post-operative pain. Diclofenac sodium injection was quite efficacious but patients may have some risks of peri-operative bleeding, injection side morbidity, gastro-intestinal complication and also labour intensive for nurse personal for injection. There was still be a question whether selective COX-2 inhibitor, which was a new drug, such as rofecoxib better than a classical NSAIDs such as diclofenac in clinical practice or not? There was no study compare the efficacy of intra-muscular diclofenac sodium and rofecoxib, which was a new COX-2 inhibitor, in the treatment of postoperative pain after major orthopedic surgery. This study was designed to compare the efficacy of rofecoxib, intramuscular diclofenac sodium and placebo for post-operative pain by measuring the amount of PCA morphine used, verbal numerical pain score and side effects.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research questions and Objectives

3.1.1 Research Questions

3.1.1.1Primary research question

Were there any differences in the efficacy between oral rofecoxib, intramuscular diclofenac sodium and placebo in postoperative analgesia in orthopedic surgery pain?

3.1.1.2 Secondary research question

Were there any differences in adverse event?

3.1.2 Research Objectives

3.1.2.1 To compare the efficacy of oral rofecoxib, intramuscular diclofenac and placebo in term of the amount us of PCA morphine used during postoperative orthopedic surgery period.

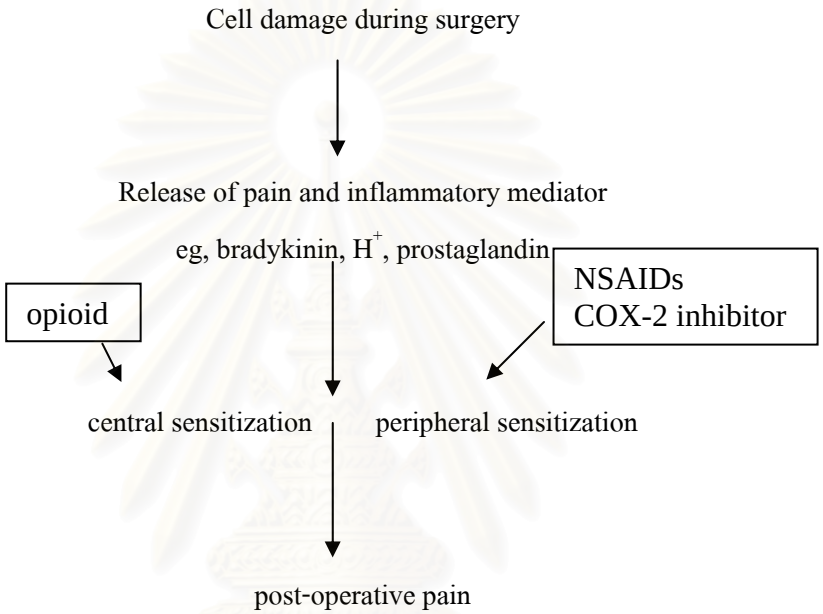
3.1.2.2 To compare postoperative orthopedic surgery pain between patients who received oral rofecoxib, intramuscular diclofenac and placebo.

3.1.2.3 To compare postoperative adverse events between patients who received oral rofecoxib, intramuscular diclofenac and placebo.

3.1.3 Research Hypothesis

There were differences in the efficacy of oral rofecoxib, intramuscular diclofenac sodium and placebo in the treatment of postoperative orthopedic surgery pain in the first 24 hours postoperatively.

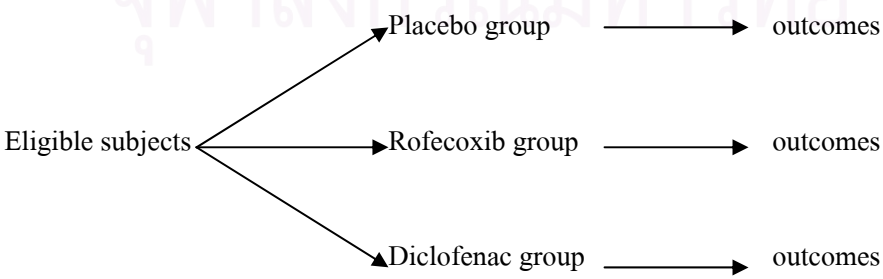
3.2 Conceptual Framework



3.3 Research Design

This study was carried out as a randomized (1:1:1) double-blinded, placebo controlled, parallel group clinical trial

3.3.1 Research Design Model



3.4 The Sample

3.4.1 Target Population

Patients who underwent major orthopaedic surgery.

3.4.2 Sample Population

Patients, who were in eligible criteria, schedule for major orthopedic surgery in King Chulalongkorn Memorial hospital.

3.4.2.1 Inclusion Criteria

1.Patient scheduled to undergo major orthopedic surgery including lumbar discectomy, laminectomy, long bone fracture fixation, ligament reconstruction, total knee arthroplasty, total hip arthroplasty, osteotomy etc.

2.Age between 18 – 65 years.

3.ASA physical status 1 or 2 (Appendix 1)

4.Women who were in postmenopausal period, surgically sterilized, or using an accepted form of birth control and had a negative result on a pregnancy test on study entry.

5.No prior NSAIDs or COX-2 inhibitor within 3 days before surgery.

3.4.2.2 Exclusion criteria

1.Contraindication for NSAIDs or COX-2 inhibitor.

2.Manifestation to respiratory, cardiac, hepatic or renal insufficiency.

3.History of hemorrhagic diathesis, hematemesis or anticoagulant therapy.

4.Allergy to morphine, aspirin, diclofinac or other prostaglandin inhibiting compounds.

5.History of peptic ulceration, upper GI bleeding or peptic perforation.

6.Patients refused to participate or continue the study.

3.4.3 Randomization Procedure

Simple randomization was conducted in this study. The patients who meet the selection criteria were randomly assigned to one of the three treatment groups. The treatment medications were kept in opaque encoded envelopes, which were distributed to the patients in the admission ward prior to surgery. Serial number and code were kept unbroken in the research office until the patients were discharged and all data were collected or in case of side effects and necessary interim analysis.

3.5 Experimental Maneuver

3.5.1 Pre-operative period

Patients in placebo treatment group received oral placebo 1 hour before anesthesia, intramuscular placebo injection immediately after operation, and another placebo injection 12 hours later.

Patients in rofecoxib treatment group received oral rofecoxib 50 mg 1 hour before anesthesia, intramuscular placebo injection immediately after operation, and another placebo injection 12 hours later.

Patients in diclofenac treatment group received oral placebo 1 hour before anesthesia, intramuscular diclofenac 75 mg immediately after completion of surgery, and intramuscular diclofenac 75 mg 12 hour later.

3.5.2 Operative period

All patients were operated with either general anesthesia or spinal anesthesia. The spinal anesthesia was performed using 0.5% heavy marcaine, volume as determined by anesthesiologist. The general anesthesia was performed by standardized general anesthesia as follows:

- Intravenous Fentanyl 1-2 μg/kg before induction of anesthesia
- Induction with Thiopental 3-5 mg/kg
- Intubation by either depolarizing or non-depolarizing muscle relaxant
- Maintenance with Nitrous oxide, Oxygen, Isoflurane and morphine 0.1-0.2 mg/kg
- Muscle relaxation with Vecuronium or Atracurium or Pancuronium
- Reversal with Atropine 0.02mg/kg and Neostigmine 0.05 mg/kg

3.5.3 Post-operative period

All patients were connected to a PCA pump on arrival to the post-anesthesia care unit. The PCA solution contained morphine 1 mg/mL; lockout interval, 6 min and 4-h limit. The maximum limit was 30 mg within 4 hours.

Patients were withdrawn from the study when they met these following criteria:

-Operation longer than 4 hours.

-Patients, who had complication during surgery, which affect the clinical evaluation and data collection.

3.5.4 Blindness

Since this study was a double-blind study, the patients and investigators who assessed patient's pain did not know which treatment each patient received. All patients received similar tablets before the operation and two injections after operation. Registered nurses who gave the injection and those who assessed the patient's pain were different individuals. The research coordinator who collected the PCA morphine data also did not know the treatment each patient received.

3.5.5 Intervention Agents

All investigational medications were packed in similar solid envelopes. All medications were divided in to three package types according to treatment groups i.e., placebo package contained two tablets of placebo and two ampoules of placebo, rofecoxib package contained two tablets of rofecoxib 25 mg, and diclofenac package contained two tablets of placebo and two ampoules of diclofenac sodium 75 mg for injection. Computer generated random numbers were generated and gave treatment code according to the following criteria: discarded random digit 0, assigned random digit 1-3 to placebo, 4-6 to rofecoxib and 7-9 to diclofenac respectively. One hundred and two serial numbers were placed on each envelope and the treatment medications were prepared according to the random numbers. Treatment codes were kept secret by principle investigator in enclosed envelope.

3.6 Measurement

3.6.1 Demographic Variables

- Age (years)
- Gender
- Type of surgery (Total knee replacement, Total hip replacement, Ligament reconstruction, Fracture repair, spinal surgery, others)
- Baseline pain intensity (verbal numerical pain score)
- Type of anesthesia (General, Spinal)
- Operative time (minutes)

3.6.2 Outcome Variables

-Total PCA morphine consumption diring 24 hours (mg)

-Cumulative morphine consumption at 4, 8, 12, 16, 20 and 24 hours post-operatively. (mg)

-Verbal numerical pain score at 4, 8, 12, 16, 20, 24 hours (score 0-10 : no pain – the worst imaginable pain)

-Patient satisfaction at 24 hours (Likert scale : not satisfy at all, not satisfy, satisfy, very satisfy, most satisfy)

-Side effects : Vomitting, hypotension, respiratory complication, upper abdominal pain

3.7 Sample Size Estimation

The primary efficacy outcome of the study was the total consumption of PCA morphine during 24 hours postoperative period. Therefore the null and alternative hypothesis were as follows:

H_0: $\mu_1 = \mu_2 = \mu_3$

H_A: At least one inequality

($\mu_1 \neq \mu_2$, or $\mu_1 \neq \mu_3$, or $\mu_2 \neq \mu_3$)

where μ_1, μ_2, μ_3 = mean total consumption of morphine 24 hour postoperatively in patients received rofecoxib, diclofenac and placebo respectively

Sample size estimation was based on a comparison of 2 independent means according to the following formula. Since there were 3 pairwise comparisons, sample size for each comparison was determined with no adjustment to type I error due to multiple comparisons.

$$\text{N/group} = \frac{2\sigma^2 [Z_\alpha + Z_\beta]^2}{[\mu_1 - \mu_2]^2}$$

where α = type I error (2-tailed) = 0.05

β = type II error = 0.1

σ = common standard deviation of total 24 hour morphine consumption in each treatment group

$Z_{0.025} = 1.96$ $Z_{0.1} = 1.28$

	μ_1	μ_2	μ_3	Pooled σ^2	N/group
Compare μ_1 and μ_3 [15]	71		117	109	1.08
Compare μ_2 and μ_3 [29]		38	59	634	30.18
Compare μ_1 and μ_2 Estimate 15% difference	71	71$\pm$10.65		109	20.17

To be conservative, the largest sample size among three pairwise comparisons was used. Thus sample size in each treatment arm was 31. With the anticipated 10% dropout, the estimated sample size became 34 per group.

3.8 Data Collection

The data was collected in a data collection form. The amount of morphine used and verbal numeric pain scale were collected every 4 hours for 24 hours by coordinating nurses blinded to intervention agents. Side effects were also recorded until patients discharged from the hospital.

3.9 Data Analysis

3.9.1 Demographic and Baseline Variables

All data was analyzed as intention-to-treat basis. The demographic and baseline data were presented as mean and standard deviation and proportions as appropriate.

3.9.2 Outcome Variables

For the primary efficacy endpoint of total amount of PCA morphine used during 24-hour postoperatively, Kruskal Wallis 1-way by ranks was employed to compare three treatment groups due to non-normally distributed data.

The secondary efficacy endpoint of verbal numerical pain score at 4, 8, 12, 16, 20 and 24 hours postoperatively was analyzed by Kruskal Wallis 1-way by ranks. Regarding patient satisfaction on treatment assessed at 24 hours postoperatively using five score Likert scale, Kruskal Wallis aqnd chi-square test was employed to compare three treatments. With regard to side effects e.g., vomiting, hypotension, respiratory complication, proportion of the complication was performed.

All statistical analyses were performed using SPSS/PC Version 10. A 2-sided significance level of 0.05 was used for all analyses.

3.10 Ethical Consideration

All eligible patients received detail of the study protocol and research assistants explained the protocol thoroughly to the patients. All patients gave written inform consent before randomization.

Rofecoxib and intramuscular diclofenac sodium were registered by Thai FDA to be used for the indication of post-operative pain. All medications had been use widely for post-operative pain

indication. If the trial medications failed to reduce the post-operative pain, all patients also received the self-monitor morphine treatment, which was very potent for postoperative pain. The trial medications reduced the use of morphine then this trial gave more benefit than harm to the patients.

3.11 Limitation and Obstacles

Using of Patient Control Analgesia system, the patients need to understand how to use the machine clearly. Therefore the patients were informed and educated how to use it after inclusion into the study.

3.12 Expected Benefit and Application

The information obtained from this study will be one of the information to create clinical practice guideline in the treatment of post-operative orthopedic pain in King Chulalongkorn Memorial Hospital.

CHAPTER 4

RESULTS

4.1 Basic Characteristics of Patients

During July 2002 to December 2002, a total of 102 patients were randomized to receive study medication, of whom 96 completed the study. Six patients were excluded from the study since the primary outcome could not be obtained. Among these excluded patients, 3, 2 and 1 were from the placebo, rofecoxib and diclofenac group respectively, resulting 31, 32 and 33 subjects in the placebo, rofecoxib and diclofenac group respectively (figure 1). The baseline characteristics were shown in Table 1. Patient's age range from 18 to 65 years with the mean age of 47.7, 44.3 and 38.9 in the placebo, rofecoxib and diclofenac group respectively. The ratio of female to male patients in each group was about one. Most of the patients recruited in this study had baseline numerical pain score of 2-3. The major orthopedic surgery in this study was classified into six types: knee arthroplasty, hip arthroplasty, ligament reconstruction, fracture fixation, spinal surgery and other surgery. The type of surgical procedure in each treatment group was shown in Table 1. The duration of each surgical procedure was less than 4 hours and the average duration in each group was from 130 to 150 minutes.

Figure 1 Disposition of major orthopedic postoperative pain study

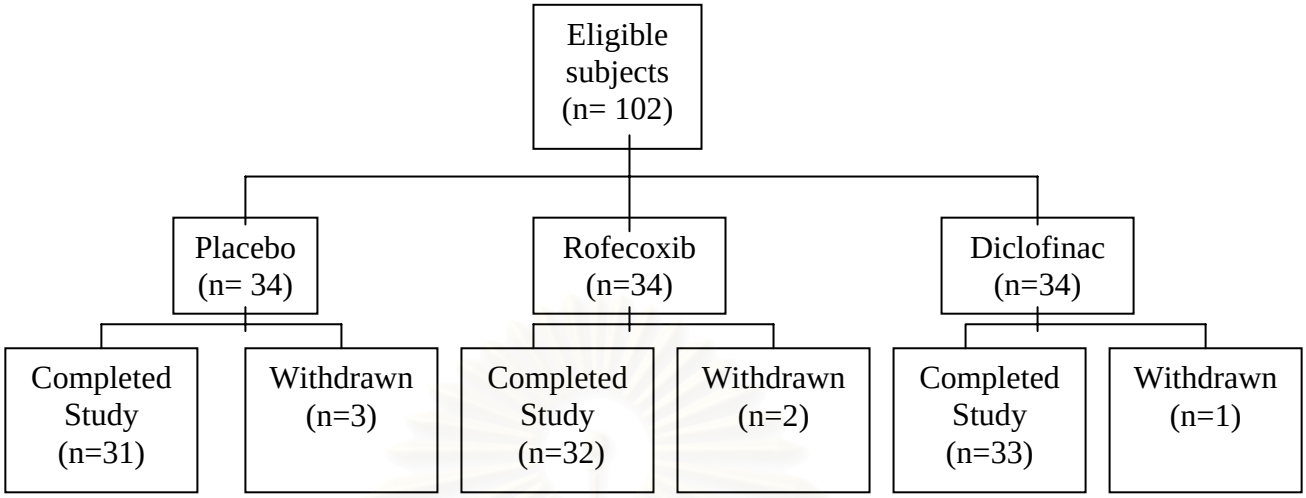


Table1 Patients' demographic and baseline characteristics (Mean ± SD)

	Placebo (n=31)	Rofecoxib (n=32)	Diclofinac (n=33)
Age (yrs)	47.7±14.5	44.3±14.6	38.9±16.2
Gender n (% female)	15 (48.4%)	16 (50.0%)	19 (57.6%)
Baseline pain	3.2 ± 2.4	2.6 ± 1.8	2.9 ± 2.1
Type of Surgery:			
Knee arthroplasty	11 (35.5%)	5 (15.6%)	7 (21.2%)
Hip arthroplasty	5 (16.1%)	5 (15.6%)	2 (6.1%)
Ligament recon.	1 (3.2%)	6 (18.8%)	5 (15.2%)
Fixation fracture	9 (29%)	8 (25%)	13 (39.4%)
Spinal surgery	5 (16.1%)	7 (21.9%)	4 (12.1%)
Others	0	1 (3.1%)	2 (6.1%)
Type of anest. n (% regional)	18 (58.1%)	19 (59.4%)	12 (46.4%)
Duration of surgery (minute)	147.6 ± 45.4	130.8± 51.1	135.8± 48.0

4.2 Primary Outcome Analysis

4.2.1 PCA morphine consumption

After completion of the surgical procedure, assistance nurse connected PCA morphine to the patients at the recovery room. The research coordinator recorded the amount of morphine used and numerical pain score every four hours for the first 24 hours.

There was a very high variation in the amount of PCA morphine used between patients in each groups. Some patients require very little morphine during the first 24 hours whereas some required self-administered maximum amount of PCA morphine from very early postoperative period. Nevertheless, the highest mean amount of morphine used in each time period occured in the placebo treatment group, while the lowest was in the diclofenac treatment group. The mean cumulative amount of morphine used, median and standard deviation in each treatment group were displayed in Table 2. Histogram and test of normality by Kolmogorov-Smirnov showed that amount of morphine used in each treatment period was not normally distributed. Therefore, non-parametric tests i.e., Kruskal-Wallis and Mann-Whitney tests are used to compare amount of morphine used between three and two treatment group respectively.

Table 2 PCA morphine used (±SD)

	PCA morphine used : Mean ± SD, Median					
	MO 4 hr	MO 8 hr	MO 12 hr	MO 16 hr	MO 20 hr	MO 24 hr
Placebo	9.4±7.6 8	14.8±9.7 13	19.1±11.0 16	23.3±12.1 21	28.4±13.7 30	32.6±15.7 35
Rofecoxib	5.9±3.8 6	9.7±5.9 8	13.0±8.0 12	15.3±9.2 14.5	18.4±11.0 16	20.3±11.7 17.5
Diclofenac	5.3±4.5 4	8.5±5.5 7	11.6±8.5 11	13.9±6.4 14	16.4±7.4 17	18.6±8.7 20
p-value	0.057	0.016*	0.018*	0.003*	0.001*	0.001*

* significant difference at 0.05

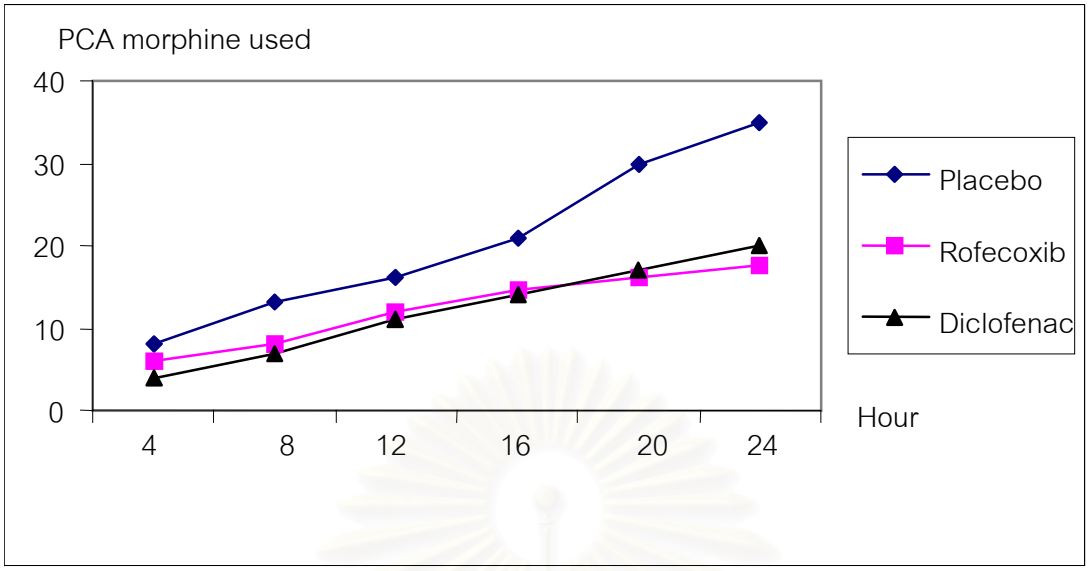


Figure 2 Median amount of morphine used

Patients in placebo group self-administered a significant greater amount of morphine compared to rofecoxib or diclofenac groups in every time that amount of PCA morphine had been measured (Table 2, Figure 2) except at 4 hours post-operatively compared to rofecoxib treatment group. The median cumulative amount of PCA morphine used by placebo patients within 24 hours was 35 mg compared with 17.5 mg in rofecoxib and 20 mg in diclofenac treatment groups. Within 24 hours after surgery, patients treated with pre-operative rofecoxib 50 mg consumed 50% less morphine and patients treated with post-operative diclofinac injection consumed 42.8% less morphine than the placebo treatment group. From table 2, the morphine sparing effect of rofecoxib 50 mg and diclofinac injection every 12 hours started 4 hours after surgery and continue to the end of 24 hours study period. Using median value, rofecoxib treatment group used less morphine at 20 and 24 hours post-operatively compared to diclofenac treatment group but no statistical significant was detected.

The Kruskal –Wallis analysis revealed statistically difference in PCA morphine used 8, 12, 16, 20 and 24 hours post-operatively (Table 2). Pair wise comparison using Mann-Whitney U test revealed no significance different of the amount of morphine used between rofecoxib treatment group and diclofenac treatment group in each time period during the first 24 hours while there were significant difference between placebo group compared to rofecoxib and diclofinac groups (Table 3).

Table 3 PCA morphine Used Mann-Whitney U test analysis (p-value)

	MO 4 hr	MO 8 hr	MO 12 hr	MO 16 hr	MO 20 hr	MO 24 hr
Placebo and Rofecoxib	0.097	0.047	0.032	0.006*	0.003*	0.003*
Placebo and Diclofenac	0.026	0.006*	0.007*	0.002*	<0.001*	<0.001*
Rofecoxib and Diclofenac	0.343	0.364	0.664	0.813	0.728	0.762

* significant difference at 0..05/3 = 0.0167

4.3 Secondary Outcome Analysis

4.3.1 Verbal Numeric Rating Scale

During 24 hours after operation, patients were asked to report their pain verbally every four hours. The pain score range from 0 to 10 where 0 and 10 indicate no pain at all and the most imaginable pain respectively. Table 4 showed mean, median and SD of pain score at each time period. Histogram and Kolmogorov-Smirnov revealed non-normality nature of pain score. Between three groups comparison was calculated by using non-parametric analysis, Kruskal –Wallis (Table 4) and pair wise comparison using Mann-Whitney tests (Table 5).

Table 4 Numerical Verbal Pain Score (±SD)

	Verbal numerical Pain Score: Mean ±SD, Median					
	VNP 4 hr	VNP 8 hr	VNP 12 hr	VNP 16 hr	VNP 20 hr	VNP 24 hr
Placebo	5.5±2.5 5	4.8±2.3 5	4.4±2.3 4	4.5±2.5 4	3.9±2.8 3	3.0±2.5 3
Rofecoxib	4.0±2.9 3.5	4.3±2.2 4.5	3.6±2.5 3	3.8±2.4 4	3.5±2.2 3	2.8±2.3 2.5
Diclofenac	3.3±2.8 2	4.2±2.6 5	3.6±2.3 4	2.9±2.0 3	2.9±2.3 3	2.8±2.3 3
P-value	0.009*	0.547	0.314	0.083	0.435	0.980

* significant difference at 0.05

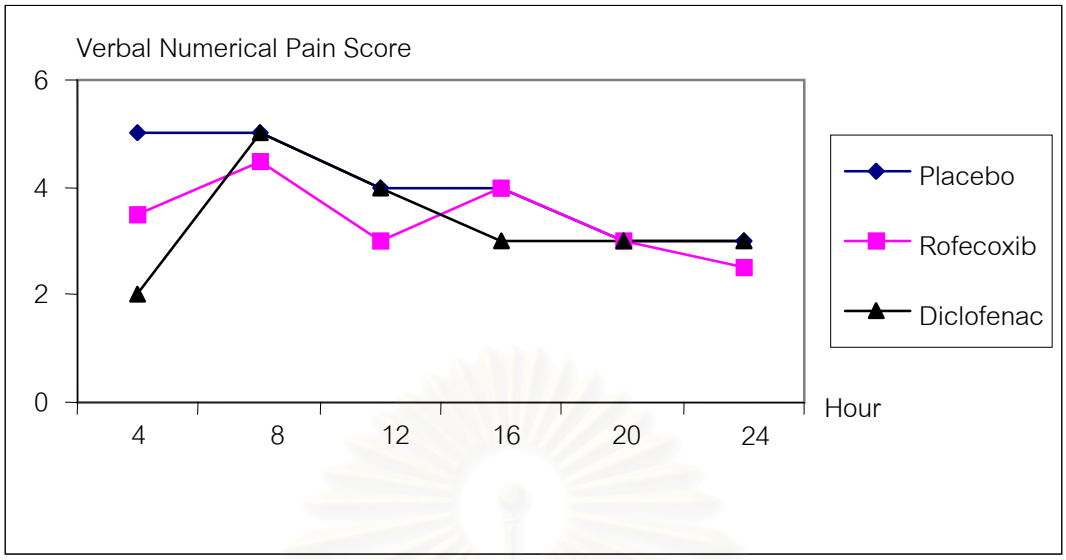


Figure 3 Median Verbal Numerical Pain Score

At 4 hour after operation, verbal numerical pain score was higher in placebo group compared with rofecoxib and diclofenac groups and verbal numerical pain score in rofecoxib group was higher than diclofinac group. Verbal numerical pain in the placebo group reduced gradually from 5 at 4 hours postoperatively to 3 after 24 hours. Verbal numerical pain score in the rofecoxib group, which took rofecoxib 50 mg single dose 30 minute before operation, started at 3.5 and rose up to 4.5 and then reduced gradually to 2.5. Verbal numerical pain score in the diclofenac group, who had diclofenac 75 mg intramuscularly at immediate postoperatively, started at 2 and increased to 5 at 8 hour. Then at 16 hour after second dose of intramuscular diclofinac injection verbal numerical pain score reduced to 3 and maintained at 3 until 24 hour. At 24 hour, pain score in rofecoxib group was the lowest at 2.5 scores. Graphic characteristic of median value of verbal numerical pain score of the three studied groups was shown in Figure 3. Kruskal-Wallis between three groups comparison showed a significant difference at 4 hours post-operatively and pairwise comparison (Mann-Whitney test) showed significant pain score between diclofenac group and placebo group at 4 hours postoperative period only (Table 5).

Table 5 Verbal Numerical Verbal Pain Score pairwisecomparison Mann-Whitney test p-value

	Verbal Numerical Pain Score					
	4 hr	8 hr	12 hr	16 hr	20 hr	24 hr
Placebo and Rofecoxib	0.044	0.306	0.140	0.270	0.592	0.950
Placebo and Diclofenac	0.003*	0.377	0.257	0.036	0.211	0.859
Rofecoxib and Diclofenac	0.284	0.936	0.832	0.174	0.428	0.873

*significant difference at 0.05/3 = 0.0167

4.3.2 Satisfaction

Satisfaction of the patients were evaluated using 5 score Likert scale i.e., “not satisfy at all”, “not satisfy”, “satisfy”, “very satisfy” and “most satisfy”. Most of the patients reported their satisfaction after 24 hour of treatment to be “satisfy” and “very satisfy”. There were two patients reported “not satisfy”, one in placebo treatment group and another one in rofecoxib treatment group. The percentages of satisfactory scores in each treatment group were shown in Table 6. In placebo group, there were 3% not satisfy, 52% satisfy, 39% very satisfy and 6% most satisfy. In rofecoxib group, there were 3% not satisfy, 56% satisfy, 25% very satisfy and 16% most satisfy. In diclofenac group, there were 42% satisfy, 52% very satisfy and 6% most satisfy.

The satisfactions were compared between groups using Kruskal-Wallis test. There was no statistically different satisfaction between three groups of treatment (p=0.625).

Table 6 Percentage of satisfaction

Satisfactory Score	**Placebo**	**Rofecoxib**	**Diclofinac**	**Total**
Not Satisfy at all	0%	0%	0%	0%
Not Satisfy	3%	3%	0%	2%
Satisfy	52%	56%	42%	50%
Very Satisfy	39%	25%	52%	39%
Most Satisfy	6%	16%	6%	9%

4.3.3 Side Effects

During the 24 hour studying period, patients were monitored for side effect and complaint. Side effects of the surgery and morphine were recorded. The common side effects included; nausea vomiting, hypotension, pruritus, dizziness. Other complaints were also recorded (Table 13). There were 2 patients in each group reported nausea and vomiting. Two patients reported hypotension, one was in rofecoxib group and another in diclofenac group. There was one patient with dyspepsia in the placebo treatment group.

Table 7: Side Effects

Side Effect	Placebo	Rofecoxib	Diclofinac
Vomiting	2	2	2
Hypotension	-	1	1
Pruritus	-	-	1
Dizziness	1	-	-
Others: Dyspepsia	1	-	-
Total	4(12.9%)	3 (9.4%)	4 (12.1%)

4.4 Summary of Result

The total of 102 patients were included for this study while 96 patients were completed. Baseline data included; age, sex, baseline pain, type of operation, type of anesthesia and duration of the operation.

The primary outcome of this study, which were the amount of morphine used during first 24 hours. There were statistical difference in the amount of morphine used between placebo and the two medication treatment groups. At 24 hours, diclofinac treatment used 42.8% less morphine than the placebo group, where as the rofecoxib treatment group used 50% less morphine than the placebo treatment group. There was no statistical significant different of the amount of morphine used between rofecoxib and diclofinac groups.

The secondary outcomes were verbal numerical pain score and patient satisfaction. The verbal numerical pain score were reduced gradually after operation. Most of the patients report verbal numerical pain scores between 2 to 4 points. The patient in placebo group reported pain score of 5 at 4 hours after operation, and then reduced gradually to score of 3. The statistical significant different pain score were found between placebo and diclofinac group at 4 hours after operation. Eighty nine

percent of the patients reported satisfaction scores to be “satisfy” and “very satisfy”. Two patients reported, “not satisfy at all” and nine patients reported, “most satisfy”. There was no significant difference satisfactory score between those three groups.

There was no serious adverse event occurred. There were 11% of patients who reported side effects such as; nausea, vomiting and hypotension. There was no complication of the studied medication.

CHAPTER 5

DISCUSSION

The new trend toward orthopedic surgery, nowadays, is to minimize the post-operative pain, early mobilization of the patient, bring the patient back to their activity of daily living and create patient satisfaction. Post surgical pain pathway and mechanism especially peripheral and central sensitization were studied extensively[39,40,41] . The researches showed effect of multiple drugs on reducing post-operative pain which acting on different sites of pain pathway. The used of multimodality in the management of peri and post operative pain could minimize pain and other untoward effects[42]. Modification of the technique in orthopedic surgery could also reduce the surgical trauma, reduce the operation time and preserve more functional tissue unit resulting in reduction of post-operatve pain. Although, opioid is the best medication for post-operative pain, patients who took opiod might not be able to leave the bed to start rehabilitation program and start their activity of daily living soon due to opioid side effects such as; sedation, dizziness, nausea vomiting, pruritus and etc. One concern in the treatment of post-operative orthopedic pain is to reduce the amount of opioid used.

This study was aim to compare the efficacy of a classical NSAIDs, diclofenac injection, to a new selectiveCOX-2 inhibitor, oral rofecoxib, and placebo in the amount of PCA morphine used 24 post-operatively and compare post-operative pain score as well as side effects. The hypothesis for this study was that, there were difference between the effect of diclofenac, rofecoxib and placebo. This study could not show statistical difference between the efficacy of oral rofecoxib and intramuscular diclofenac injection in the amount of morphine used, post-operative numerical pain score and side effect. However, there were statistical difference between the amount of PCA morphine used, between rofecoxib group and placebo group, as well as, diclofenac group and placebo group. This study also showed the efficacy of an oral selective COX-2 inhibitor, rofecoxib, and classical NSAIDs, diclofenac sodium injection, in large amount of opioid used reduction by 50% and 43% in the first 24 hours compare to placebo.

The amount of morphine used and numerical pain score data obtained from this study showed not normal distribution. Both data distributions were skewed to the right. Some patients administered

maximum amount of morphine intravenously at the beginning of postoperative period but some patients were reluctant to push the PCA button to obtain morphine. Some patients like morphine not only for reduction of pain but the sedative effect and euphoric effect. Some patient did not like morphine due to the side effect and afraid of addiction. The measurement of pain by using morphine as an indicator could be measured in to continuous variable but there were some subjective factors as mention earlier, which may affect the outcome. However, the nonparametric analysis was applied to analysis of these sets of morphine used data.

Reuben[15] (2000) studied the amount of PCA morphine used in patients underwent spinal fusion surgery who received placobo or rofecoxib or celecoxib pre-operatively. His studied revealed that patients who received rofecoxib used PCA morphine by the mean of 71 mg, while patients who received celecoxib used PCA morphine 107 mg and patients who had placebo used PCA morphine 117 mg. That study had higher amount of 24 hours PCA morphine used in both placebo and rofecoxib treatment group compare to our study and rofecoxib showed 39% opioid sparing effect, which comparable to our study. Laitinen and Nuutinen (1992) [18] studied the post-operative opioid sparing efficacy of intravenous diclofenac sodium 75 mg intravenous loaded and 5 mg/hr infusion compare to placebo in patients underwent total hip replacement. That studied revealed 39.8% fentanyl reduction in the group of patients who received diclofenac sodium. In that study, patients who received diclofenac had significant less pain (0.75 VS 2.4) and no different rate of complications. Hodsman et al[29] studied the opioid sparing effect of intramuscular 75 mg diclofenac sodium every 12 hours following abdominal surgery, and found that diclofenac sodium could reduce PCA morphine used by 35.5% (38 mg VS 59 mg) after 24 hours post-operatively. In our study, diclofenac intramuscular injection could reduce 43% morphine used compare to placebo, which was comparable to Hodsman study.

Silvanto et al (2002) [43] compared the efficacy of ketoprofen, diclofenac and placebo after total knee arthroplasty. They found that patients who received intravenous diclofenac sodium 75 mg followed by oral diclofenac 150 mg/day could spare intravenous oxycodone by 25.9%, 51.1% and 57.8% compare to placebo while ketoprofen 100 mg intravenous followed by 300 mg orally could reduce intravenous oxycodone by 28.9%, 18.3% and 39.6% for three days post-operatively. During administration of diclofenac on days 1-3 and ketoprofen on day 2, the mean pain scores (VAS) were lower than in the placebo group ($P < 0.05$).

Paracetamol was another medication that was used to control post-operative pain. Hernandez-Palazon et al (2001) [17] studied the efficacy of intravenous propacetamol 2g injection every 6 hours

following spinal laminectomy compare to placebo. After 72 hours, patients in propacetamol treatment group required 46.25% less PCA morphine compare to placebo treatment group (60.3 +/- 20.5 vs 112.2 +/- 39.1 mg; $P < 0.001$). However, pain intensity scores were smaller than 3 in both groups.

Camu et al (2002) [44] studied the opioid sparing efficacy of another new oral COX-2 inhibitor, valdecoxib, following total hip arthroplasty and found that single dose 20 mg and 40 mg valdecoxib could reduce the amount of PCA morphine used by 40% compare to placebo. Reynolds et al (2003)[45] studied the efficacy of valdecoxib following total knee replacement. Patients who received valdecoxib 40 mg or 80 mg daily reduced the amount of PCA morphine used by 17.3% and 24.2% after 48 hours post-operatively. Patients receiving valdecoxib 40 mg and 80 mg daily experienced significantly lower maximum pain intensity on Day 2 ($P < 0.05$), and rated their study medication significantly higher than patients receiving morphine alone.

Comparing the 24 hour opioid sparing effect of rofecoxib and diclofenac in this study to other studies, rofecoxib and diclofenac sodium injection had comparable opioid sparing effect to other NSAIDs. There was no report of the superior efficacy of opioid sparing effect of COX-2 inhibitor over classical NSAIDs. Most reports showed no statistical difference between NSAIDs and selectiveCOX-2 inhibitor as also was shown in this study. In this study, diclofenac injection showed significant superior efficacy to placebo in the amount of morphine used at 8, 12, 16, 20 and 24 hours pos-operatively, while, rofecoxib showed superior efficacy to placebo at 16, 20 and 24 hours only. The nature of multiple administration of diclofenac injection every 12 hours may contribute to this difference.

Postsurgical pain is often undertreated. Opioids are frequently used in peri-operative analgesia. Some patients had opioid side effect and received inadequate dose for pain relief. The administrations of NSAIDs in peri-operative period showed the efficacy to reduce the amount of opipoid used and pain score. The use of balanced analgesia as combination of opioids, NSAIDs, and local anesthesia or utilizing agents from other classes (eg, ketamine, clonidine) improves the efficacy of pain relief and decreases risk of side effects. Non-selective NSAIDs may not cause side effects of opioids, but may cause bleeding as a result of their inhibitory effects on COX-1. For this reason, COX-2-selective inhibitors (coxibs) were attractive opioid-sparing analgesic options in the perioperative setting[46]. Factors in addition to side effects such as time to onset of action, duration of action, maximum pain relief, use of rescue medication, and other factors relevant to a given pain model are important in determining overall analgesic efficacy. Clinical studies show that COX-2-selective inhibitors are effective for the treatment of preoperative and postoperative pain and reduce

postsurgical requirements for opioids. This evidence supports a role for COX-2-derived prostaglandins as key mediators of nociceptive pain and peripheral sensitization (hyperalgesia).

The administration of rofecoxib in this study was single dose 50 mg orally 1 hour before surgery, while diclofinac sodium 75mg was given intramuscularly at immediately post-operative period and another 75mg intramuscularly at 12 hours later. The mechanism of action of both rofecoxib and diclofinac sodium were to reduce the production of prostaglandin by inhibition of cyclo-oxygenase enzyme[47,48,49]. The site of action may occur at site of trauma, where tissue injury occurred. The action of classical NSAIDs and selectve COX-2 inhibitor contributed to peripheral sensitization of the neuro-transmission, which pain sensory was transmitted[50,51]. There was some evidence that the COX-2 inhibitor may reduce pain through central sensitization, which pain was modulation and perceived in the central nervous system, by reduction of central prostaglandin[52,53,54] or serotonin in the brain[55]. This mechanism may explain the phenomenon of pre-emptive analgesia, which analgesic drug was given before tissue injury[56,57,58,59]. In this study, rofecoxib which was given prior to operation and reduce the amount of opioid used significantly, may exhibit the pre-emptive property which were shown in other studies[15,20,23,60,61].

Another question for this study was whether there was difference between the efficacies of rofecoxib, diclofenac and placebo in pain score given by patients in each group. The secondary outcome for this question was verbal numerical pain score. All patients in this study received self-administered morphine, which was a very effective pain treatment modality. Mean and median numerical pain scores were not significantly different between rofecoxib and diclofenac groups. If numerical pain score may classify to be four categories, which were no pain (0-1), mild pain (2-4), moderate pain (5-7), and severe pain (>7), most of patient reported mild pain, while patient in placebo group reported moderate pain at 4 and 8 hour post-operatively. At 4 hour, diclofinac treatment group had lower pain compare to placebo significantly, which may due to the surged of drug level after injection. Most of the time when pain was measured, pain score between rofecoxib group, diclofenac group and placebo group were not significantly difference, which may be due to the effect of PCA morphine each patient received as baseline pain treatment throughout 24 hour post-operative period.

Chang et al studied the efficacy of single dose rofecoxib 50 mg compare to enteric-coated diclofenac 50 mg three time daily for post dental extraction and found that rofecoxib gave earlier onset, lower amount of pain and longer duration of action[62]. At the end of 24 hours, all patients reported pain level lower than other time point significantly. Claeys[30] compared postoperative pain after major orthopedic surgery between diclofenac infusion and placebo and found that patients in

diclofenac treatment group had less numerical pain score (3 VS 3-4). Other studies that used PCA morphine had numerical pain score at 24 hours between 2-4 (mild pain). This study showed similar efficacy for post-operative numerical pain score to other NSAIDs and other modality.

Another secondary outcome for this study was patient satisfaction. Ninety-eight percent of all patients reported "satisfy" to "most satisfy", whereas patients in rofecoxib treatment group reported highest percentage of "most satisfy" to be 16% compare to 6% in placebo group and 6% in diclofinac treatment group. In a systematical review[38], patient controlled analgesia (PCA) yielded the most satisfaction pain treatment modality. The satisfaction in this study may due to multiple factors including; PCA morphine used, rofecoxib and diclofenac used, explanation on pain treatment, frequent question on pain for the research project etc.

There were no serious adverse event and significant side effect occurred in this study. Common side effects were nausea and vomiting which may contribute to the used of morphine for post-operative pain rather than due to the studied medications. Morphine is a very strong medication to reduce pain but contribute to many side effects such as nausea, vomiting, hypotension, drowsiness and respiratory depression. The used of morphine may not allow patient to start rehabilitation early. However, rate of adverse events in those three-studied group considered being low.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently discontinued before elective total knee arthroplasty (TKA) because of the increased incidence of perioperative bleeding[3,5]. Rofecoxib, a selective cyclooxygenase 2 inhibitor, does not interfere with the coagulation system and may be a safer NSAID for patients undergoing TKA. Reuben et al (2002) [20] evaluated safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. In that study, 100 patients undergoing elective TKA discontinued their use of NSAIDs 10 days before surgery and were assigned randomly to receive either placebo (n = 50) or rofecoxib (n = 50), 25 mg daily for 5 consecutive days starting 3 days before surgery. The administration of rofecoxib resulted in improved preoperative pain scores and no significant increase in the incidence of perioperative bleeding or international normalized ratio compared with placebo. Rofecoxib does not need to be discontinued before elective TKA.

Post-operative bleeding is one of major concern for the used of NSAIDs. Classical NSAIDs inhibit thromboxane[61] and caused peri-operative bleeding[13,64,65]. Patient had to stop using NSAIDs at least two week prior to operation. These patients may suffer from pain due to the orthopedic condition that required surgical treatment. Patient with inadequately treated painful condition would suffer more pain post-operatively. Selective COX-2 inhibitor such as rofecoxib does not inhibit thromboxane and

does not cause post-operative bleeding[15]. Patients can take rofecoxib to reduce painful condition until time of surgery. Patient with lower pain prior to surgery would have lower pain post-operatively and would be more satisfy.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Oral single dose pre-operative rofecoxib is as efficacious as intramuscular diclofinac injection 12 hourly in term of opioid sparing effect, numerical pain score, and patient's satisfaction. Rofecoxib and diclofinac could significantly reduce the amount of morphine used during 24 hours post-operatively. There was no serious adverse event occurred and side effect of the studied medications in 24 hours post-operatively was minimal. Single dose pre-operative oral rofecoxib should be recommended to patients undergoing major orthopedic surgery if there is no contra-indication for the used of selective COX-2 inhibitor.

6.2 Recommendation

Selective COX-2 inhibitor showed good efficacy in the treatment of post-operative pain with less complication and better compliance. There should be more clinical researches to compare efficacy between new selective COX-2 inhibitors or the injection form, which will be registered and use in Thailand very soon. The study design for future research should be the efficacy of COX-2 inhibitor in same type of surgery such as total knee arthroplasty or total hip arthroplasty. Other efficacy for post-operative pain such as pre-emptive efficacy should also be investigated. There should be monitoring for post-marketing complication and side effect.

REFERENCES

1. CoderreTJ, Melzack R. The contribution of excitatory aminoacids to central sensitization and persistent nociception after formalin induced tissue injury. *J Neurosci* 1992;12:3665-670.
2. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anesthesiol Scand* 1997;41:94.
3. Cashman J, McAnulty G. Nonsteroidal anti-inflammatory drugs in perisurgical pain management: mechanisms of action and rationale for obtimum use. *Drugs* 1995;49:51-70.
4. Cashman JN. The mechanism of action of NSAIDs in analgesia. *Drugs* 1993;52(suppl 5):13-23.
5. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: Rational for use in severe postoperative pain. *Br J Anaesth* 1991;66:703-712.
6. Jadad AR, McQuay HJ (1993) The measurement of pain. In: Pynsent P, Fairbank J, Carr A (eds). *Outcome measures in Orthopaedics*. Oxford: Butterworth-Heinemann.
7. Yeomans SG (2000) Assessment of pain. In: Yeomans SG (eds). *The clinical application of outcome assessment.* Stamford: Appleton&Lange.
8. Seibert K, Masferer JL. Role of inducible cyclooxygenase (COX-2) in inflammation. *Receptor* 1994;4:17-23.
9. Smith TJ. Cyclooxygenase as the principle target for the action of NSAIDs. Rheum *Dis Clin NorthAm* 1998;24:501-523.
10. DeWitt D. Prostoglandin endoperoxide synthase: regulation of enzyme expression. *Biochem Biophys Acta* 1991;1083:121-134.
11. Meade EA, Smith WL, deWitt DL. Differntial inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozyme by aspirin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* 1993;268:6610-6614.
12. McCormack K. Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain* 1994;59:9-43.
13. Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. *Anesth Analg* 1994;79:1178-90.

14. Rosenow DE, Albrechsen M, Stolke D. A comparison of patient-controlled analgesia with Lornoxicam versus Morphine in patients undergoing lumbar disk surgery. *Anesth Analg* 1998;86:1045-50.

15. Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. *Anesth Analg* 2000;91:1221-5.

16. Rosenow DE, Krieken F, Stolke D, Kursten FW. Intravenous administration of lornoxicam, a new NSAID, and Pethidine for postoperative pain. A placebo-controlled pilot study. *Clin Drug Invest* 1996;11(1):11-19.

17. Hernandez-Palazon J, Tortosa JA, Martinez-Lang JF, Perez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. *Anesth Analg* 2001 Jun;92(6):1473-6.

18. Laitinen J, Nuutinen L. Intravenous diclofinac coupled with PCA fentanyl for pain relief after total hip replacement. *Anesthesiology* 1992;76:194-198.

19. Reuben SS, Sklar J, El-Mansouri M. The preemptive analgesic effect of intraarticular bupivacaine and morphine after ambulatory arthrocopic knee surgery. *Anesth Analg* 2001 Apr;92(4):923-6.

20. Reuben SS, Fingeroth R, Krushell R, Maciolek H. Evaluation of safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. *J Arthroplasty* 2002; 17(1): 26-31.

21. Eggers KA, Jenkins BJ, Power I. Effect of oral and i.v. tenoxicam in postoperative pain after total knee replacement. *Btrit J Anesth* 1999;86(3):876-81.

22. Gimbel JS, Brugger A, Zhao W, Verberg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocordone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Therapeutics* 2001;23(2):228-41.

23. Reuben SS, Bhopatkar S, Maciolek H, Joshi W, Sklar J. The preemptive analgesic effect of rofecoxib after arthroscopic knee surgery. *Anesth Analg* 2002;94:55-9.

24. Reicin A, Brown J, Jove M, et al. Efficacy of single-dose and multidose rofecoxib in the treatment of post-orthopaedic surgery pain. *Am J of Orthop* 2001;Jan:40-48.

25. Pang WW, Hsu TC, Hung CP, Chang DP, Huang MH. Is total knee replacement more painful than total hip replacement? *Acta Anesthesiol Sin* 2000 Sep;38(3): 143-8.

26. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rational for use in severe postoperative pain. *Br J Anaesth* 1991; 66:703-12.

27. Kehlet H, Dahl JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. *Anesth Analg* 1993;77:1048-56.

28. Task Force on Pain Management, Acute Pain Section. Practice guidelines for acute pain management in the perioperative setting. *Anesthesiology* 1995;82:1071-81.

29. Hodsman NBA, Burns J, Blyth A, et al. The morphine sparing effect of diclofinac sodium following abdominal surgery. *Anaesthesia* 1987;42:1005-8.

30. Claeys MA, Camu F, Maes V. Prophylactic diclofinac infusions in major orthopaedic surgery: effect on analgesia and acute phase proteins. *Acta Anaesthesiol Scand* 1992;36:270-275.

31. Haekey CJ. COX-2 inhibitors. *Lancet* 1999;353:307-14.

32. Crofford LJ, Lipsky PE, Brooks P, et al. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. *Arthritis Rheum* 2000;43:4-13.

33. Ehrich EW, Dallob A, de Lepeleire I, et al. Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999;65:336-347.

34. Morrison BW, Christensen S, Yuan W, et al. Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: randomized, controlled trial. *Clin Ther* 1999;21:943-953.

35. Morrison BW, Daniel SE, Kotey P, et al. Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol* 1999;94:504-508.

36. Laine L, Harper S, Simon T, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase-2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucasa of patient with osteoarthritis. *Gastroenterology* 1999; 117:776-783.

37. Langman M, Jensen D, Watson D, et al. Incidence of upper gastrointestinal perforations, symptomatic ulces, and bleeding: rofecoxib compare with NSAIDs. *JAMA* 282(20):1929-1933.

38. WalderB, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand* 2001; 45: 795-804.

39. Raja SN, Meyer RA, Campbell JN. Peripheral mechanism of somatic pain. *Anesthesiology* 1988; 68:571-90.

40. Woofe CJ. Evidence of central component of post-injury pain hypersensitivity. *Nature* 1983; 306:686-8.

41. Petersen KL, Brennum J, Dahl JB. Experimental evaluation of the analgesic effect of ibuprofen on primary and secondary hyperalgesia. *Pain* 1997 Apr;70(2-3):167-74.

42. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993 Nov;77(5):1048-56.

43. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. *Acta Anaesthesiol Scand* 2002 Mar;46(3):322-8.

44. Camu F, Beecher T, Recker DP, Verburg KM. Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. *Am J Ther* 2002 Jan-Feb;9(1):43-51.

45. Reynolds LW, Hoo RK, Brill RJ, North J, Recker DP, Verburg KM. The COX-2 Specific Inhibitor, Valdecoxib, Is An Effective, Opioid-Sparing Analgesic in Patients Undergoing Total Knee Arthroplasty. *J Pain Symptom Manage* 2003 Feb;25(2):133-41.

46. Katz WA. Cyclooxygenase-2-selective inhibitors in the management of acute and perioperative pain. Cleve *Clin J Med* 2002;69 Suppl 1:SI65-75.

47. Ogilvie-Harris DJ, Bauer M, Corey P. Prostaglandin inhibition and the rate of recovery after arthroscopic menisectomy: a randomized double-blind prospective study. *J Bone Joint Surg* 1985; 67: 567-71.

48. Vander-Schilden JL. Improvements in rehabilitation of the post menisectomized or meniscal repair patient. *Clin Orthop* 1990; 252: 73-9.

49. Pederson P, Nielsen KD, Jensen PE. The efficacy of Na-naproxen after diagnostic and therapeutic arthroscopy of the knee joint. *Arthroscopy* 1993; 9: 170-3.

50. Vane JR, Botting RM. Mechanism of action of non-steroidal anti-inflammatory drugs. *Am J Med* 1998;104[suppli 3]: 2S-8S.

51. Romsing J, Moiniche S, Ostergaard D, Dahl JB. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand* 2000 Jul;44(6):672-83.

52. Woolf CJ, Chong MS. Preemptive analgesia: treating post-operative pain by preventing the establishment of central sensitization. *Anest Analg* 1993; 77:362-79.

53. Samad TA, Moore KA, Sapristein A, et al Interleukin-1B-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 2001; 410:471-5.

54. Dirks J, Moiniche S, Hilsted KL, Dahl JB. Mechanisms of postoperative pain: clinical indications for a contribution of central neuronal sensitization. *Anesthesiology* 2002 Dec;97(6):1591-6.

55. Sandrini M, Vitale G, Pini LA. Effect of rofecoxib on nociception and the serotonin system in the rat brain. *Inflamm Res* 2002 Mar;51(3):154-9.

56. Katz J. Preemptive analgesia: importance of timing. *Can J Anaesth* 2001; 48:105-14.

57. Colbert ST, O'Hanlon DM, McDonnell C et al. Analgesia in day case breast biopsy: the value of pre-emptive tenoxicam. *Can J Anaesth* 1998; 45: 217-22.

58. O'Hanlon DM, Thambipillai T, Colbert ST, et al. Timing of pre-emptive tenoxicam is important for post-operative analgesia. *Can J Anaesth* 2001; 48:162-6.

59. Gottchalk A, Smith DS. New concept in acute pain therapy: preemptive analgesia. *Am Fam Physician* 2001; 63(10):1979-1984.

60. Reuben SS, Bhopatkar S, Maciolek H, Joshi W, Sklar J. The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. *Anesth Analg* 2002; 94: 55-9.

61. Bekker AS, Cooper PR, Frempong-Boadu, Babu R, Ericco T, Lebovits A. Evaluation of Preoperative administration of the cyclo-oxygenase-2 inhibitor rofecoxib for the treatment of post-operative pain after lumbar disc surgery. *Neurosurgery* 2002; 50(5): 1053-58.

62. Chang DJ, Desjardins PJ, Chen E, Polis AB, McAvoy M, Mockoviak SH, Geba GP. Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: a randomized, placebo-controlled clinical trial. *Clin Ther* 2002 Apr; 24(4):490-503.

63. Schafer AI. Effects of non steroidal anti-inflammatory therapy on platelets. *Am J Med* 1999; 106: 25S-35S.

64. Connelly CS, Panush RS. Should non-steroidal anti-inflammatory drugs be stopped before elective surgery? *Arch Intern Med* 1991; 151: 1963-6.

65. Moiniche S, Romsing J, Dahl JB, Tramer MR. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg* 2003Jan;96(1):68-77.

APPENDICES

Appendix A: ASA Physical Status Classification

ASA I: A normal healthy patient

ASA II: A patient with mild systemic disease (mild diabetes, controlled hypertension, chronic brochitis, morbid obesity)

ASA III: A patient with a severe systemic disease that limits activity (angina, obstructive pulmonary disease, prior myocardial infarction)

ASA IV: A patient with an incapacitating disease, life threatening (heart failure, renal failure)

ASAV: A moribund patient not expected to survive 24 hours (ruptured aneurysm, head trauma with increase intracranial pressure)

For emergency operation, add the letter E before classification)

Appendix B: Data Collection Form

Case Record Form

Title: A randomized, controlled trial to compare the efficacy of oral rofecoxib and intra-muscular diclofinac sodium for the treatment of post-operative pain after major orthopedic surgery.

Principle Investigator: Pongsak Yuktanandana MD.

---

1. Data Entry No……...

Date:……/……/…….

Patient's name……Hospital number……..Ward……

Address…….

Baseline data

2. Age……year

3. Body weight……..kg

4. Height……cm

5. Sex ☐ Male ☐ Female

6. Pre-operative Diagnosis……

7. Type of surgery ☐ Laminectomy ☐ Discectomy
☐ TKA ☐ THA
☐ Fracture Fixation
☐ Ligament Reconstruction
☐ Osteotomy
☐ other (specify)…….

8. Type of anesthesia ☐ General Anesthesia
☐ Regional anesthesia
☐ Subarachnoid ☐ Epidural

9. Operation time……..hours…….minutes

10. Morphine used during operation……..mg

11. Baseline numeric pain score (1-10) ……..

(0=no pain and 10 is equal to the worst imaginable pain)

Outcome

12. Cumulative PCA Morphine consumption (mg)

4 hour(mg)	8 hour(mg)	12 hour(mg)	16 hour(mg)	20 hour(mg)	24 hour(mg)

13. Verbal numerical pain score (1-10) at 4, 8, 12, 16, 20, 24 h

4 hour	8 hour	12 hour	16 hour	20 hour	24 hour

14. Patient satisfaction on the treatment of postoperative pain

☐ not satisfy at all ☐ not satisfy ☐ satisfy ☐ very satisfy ☐ most satisfy

Side effect

15. Post-operative bleeding(24 hour)…….ML

16. Untoward effect

☐ Vomitting ☐ Hypotension ☐ Respiratory complication

☐ Priritus ☐ Bradycardia

Selection of Subjects

Inclusion Criteria

Each subject must fulfill all of the following criteria for entrance into study.

Criteria	yes	no
1. Schedule for major orthopedic surgery	☐	☐
2. Age between 18 – 65 years	☐	☐
3. ASA physical status 1 or 2	☐	☐
4. Women: postmenopausal, sterilized, birth control, or preg test –ve	☐	☐
5. No prior NSAIDs or COX-2 inhibitor within 3 days before surgery	☐	☐

Note: A “No” for any inclusion criteria is sufficient to exclude the subject from the study.

Exclusion criteria

1. Contraindication for NSAIDs or COX-2 inhibitor	☐	☐
2. Respiratory, cardiac, hepatic or renal insufficiency	☐	☐
3. History of hemorrhagic diathesis or anticoagulant therapy	☐	☐
4. Allergy to morphine, aspirin, diclofinac or other prostaglandin inhibiting compounds.	☐	☐
5. History of peptic ulceration, upper GI bleeding or peptic perforation.	☐	☐
6. Patients refuse to participate or continue the study	☐	☐

Note: A “Yes” for any exclusion criteria is sufficient to exclude the subject from the study.

ข้อมูลสำหรับผู้ป่วย

การศึกษาทางคลินิก: การประเมินผลของการใช้ยารับประทานโรฟีคอกซิบ 50 มก เทียบกับ ยาฉีดไดโคลฟีแนก 75 มก และยาหลอก ในการรักษาอาการปวดจากการผ่าตัดใหญ่ทางศัลยกรรมออร์โธปิดิกส์

เรียน ผู้ป่วยทุกท่าน

ท่านเป็นผู้ที่ได้รับเชิญจากแพทย์ ให้เข้าร่วมการศึกษาทางคลินิกเพื่อประเมินผลการใช้ยา ในการใช้ยารับประทานโรฟีคอกซิบ เทียบกับการใช้ยาฉีดเข้ากล้ามไดโคลฟีแนก และเทียบกับยาหลอกในการรักษาอาการปวดจากการผ่าตัดใหญ่ทางศัลยกรรมออร์โธปิดิกส์ ก่อนที่ท่านจะตกลงเข้าร่วมการศึกษาครั้งนี้ ขอเรียนชี้แจงเหตุผลและรายละเอียดในการศึกษาวิจัย ดังนี้

บทนำ

ผู้ป่วยที่ได้รับการผ่าตัดทางออร์โธปิดิกส์มักประสบอาการปวดจากการผ่าตัด อาการปวดดังกล่าวทำให้ได้รับความทุกข์ทรมาน และอาจทำให้ไม่ประสงค์จะขยับส่วนที่ได้รับการผ่าตัดอันอาจเป็นผลเสียหายต่อผลการผ่าตัดรักษาได้ ยาที่ใช้รักษาอาการปวดจากการผ่าตัดแบ่งเป็นหลายกลุ่ม กลุ่มมอร์ฟีนและอนุพันธ์ของมอร์ฟีนเป็นกลุ่มที่ได้ผลดีมาก ทำให้ลดอาการปวดและมีความสบายใจมากขึ้น แต่ยากลุ่มนี้หากได้รับปริมาณมากหรือเป็นระยะเวลานาน อาจทำให้เกิดผลข้างเคียง เช่น คลื่นไส้ อาเจียน ง่วงซึม กดการหายใจและเป็นยาเสพติด การใช้ยาแก้ปวดกลุ่มอื่นร่วมด้วยทำให้สามารถลดการใช้ยากลุ่มมอร์ฟีนลงได้

ยากลุ่มที่นิยมนำมาใช้รักษาอาการปวดจากการผ่าตัดเสมอๆ เป็นยากลุ่มต้านการอักเสบแบบดั้งเดิม ได้แก่ยาฉีดเข้ากล้ามไดโคลฟีแนก ยากลุ่มนี้ได้ผลลดอาการปวดได้ดีแต่หากใช้ติดต่อกัน อาจมีผลข้างเคียง เช่น ทำให้เกร็ดเลือดทำงานได้ลดลงและเลือดออกมากขึ้น รบกวนกระเพาะทำให้ปวดท้อง เป็นต้น ในปัจจุบันมียากลุ่มใหม่ เช่น โรฟีคอกซิบ พบว่าสามารถลดอาการปวดภายหลังผ่าตัดได้ดี ไม่มีผลข้างเคียงเกี่ยวกับการทำงานของเกร็ดเลือด และผลข้างเคียงในการรบกวนกระเพาะอาหารน้อยมาก ยาโรฟีคอกซิบจึงเป็นทางเลือกในการรักษาอาการปวดจากการผ่าตัดเพื่อลดการใช้ยากลุ่มมอร์ฟีนให้น้อยลง

วิธีการ

การศึกษาวิจัยครั้งนี้ผู้ป่วยที่เข้าหลักเกณฑ์และยินยอมเข้าร่วมการศึกษาวิจัยจะถูกแบ่งออกเป็น 3 กลุ่ม ได้แก่ กลุ่มรับยาโรฟีคอกซิบ กลุ่มรับยาไดโคลฟีแนก และกลุ่มยาหลอก ทั้งนี้การแบ่งกลุ่มใช้การสุ่ม ท่านจะไม่ทราบว่าท่านถูกจัดอยู่ในกลุ่มใดเพื่อไม่ให้เกิดอคติต่อการแปรผล ผู้ป่วยทุกกลุ่มจะได้รับยาแก้

ปวดมอร์ฟินซึ่งจะให้ผ่านทางสายน้ำเกลือโดยท่านควบคุมจำนวนยาที่ท่านต้องการเองตามความเจ็บปวดแต่ทั้งนี้อุปกรณ์จะจำกัดจำนวนยาเพื่อไม่ให่ท่านได้รับยาเกินขนาดโดยอัตโนมัติ

ท่านจะได้รับยาที่จะทำการประเมินผล 2 เม็ด ก่อนการผ่าตัด 1 ชั่วโมง หลังผ่าตัดในขณะที่ท่านยังไม่รู้สึก ท่านจะได้รับยาชนิดฉีดเข้ากล้าม 1 เข็ม และ หลังผ่าตัด 12 ชั่วโมง ท่านจะได้รับยาฉีดเข้ากล้ามอีก 1 เข็ม

การประเมินผล

ผู้ป่วยทุกท่านจะได้รับการประเมินความเจ็บปวดโดยการถามให้ท่านบอกความเจ็บปวดเป็นค่าตัวเลข 0 – 10 ทุก 4 ชั่วโมงหลังการผ่าตัด จนครบ 24 ชั่วโมง ปริมาณยามอร์ฟินที่ท่านใช้ตลอดระยะเวลา 24 ชั่วโมงจะถูกบันทึกเพื่อประเมินผล นอกจากนี้ความพึงพอใจของท่านต่อการรักษาอาการปวดหลังผ่าตัดจะได้รับการบันทึกเพื่อเปรียบเทียบผล ผลข้างเคียงของการใช้ยาจะได้รับการเฝ้าระวังและแก้ไขทันทีที่มีอาการ ภายหลัง 24 ชั่วโมง ท่านจะได้รับการดูแลอาการปวดหลังผ่าตัดต่อเนื่องต่อไป จนกระทั่งกลับบ้าน

ประโยชน์ที่จะได้รับ

หากท่านตกลงที่จะเข้าร่วมการศึกษาวิจัยนี้ ท่านจะได้รับการดูแลอาการปวดจากการผ่าตัดอย่างใกล้ชิดโดยไม่ต้องเสียค่าใช้จ่ายในการรักษาอาการปวดจากการผ่าตัด รวมทั้งค่ารักษาอาการข้างเคียงจากยาที่ทำการศึกษา หากมีอาการไม่พึงประสงค์เกิดขึ้น ข้อมูลที่ได้จะเป็นประโยชน์อย่างยิ่งในการดูแลผู้ป่วยต่อไป

จำนวนผู้เข้าร่วมโครงการ

จะมีผู้ป่วยเข้าร่วมโครงการทั้งสิ้น 102 ราย

คุณสมบัติของผู้เข้าร่วมโครงการวิจัย

เป็นผู้ป่วยชายหรือหญิง อายุ 18 – 65 ปี ที่รับไว้ในแผนกออร์โธปิดิกส์ โรงพยาบาลจุฬาลงกรณ์ เพื่อรับการผ่าตัดใหญ่ทางออรโธปิดิกส์ ได้แก่ การผ่าตัดกระดูกสันหลัง การผ่าตัดกระดูกขาหัก การผ่าตัดเปลี่ยนข้อเข่าหรือข้อสะโพก การผ่าตัดซ่อมสร้างเอ็นข้อเข่า การตัดกระดูกเพื่อรักษาภาวะความผิดปกติของแนวกระดูก เป็นต้น ไม่เคยมีประวัติแพ้ยากลุ่มต้านอาการอักเสบ เช่น แอสไพริน โวลทาเรน ไวอ๊อก ไม่มีประวัติแพ้ยากลุ่มมอร์ฟีน ไม่มีประวัติแผลในกระเพาะอาหาร เลือดออกในกระเพาะอาหาร ไม่มีประวัติโรคเรื้อรังของ ตับ และ ไต

การรักษาความลับ

ผลของการศึกษานี้ จะใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น ข้อมูลต่างๆเกี่ยวกับตัวท่านจะถูกเก็บเป็นความลับ การตีพิมพ์เผยแพร่ผลงานทางวิชาการจะไม่มีการระบุชื่อของผู้เข้าร่วมโครงการ คณะกรรมการจริยธรรมของการศึกษานี้และหน่วยงานที่มีหน้าที่รับผิดชอบอาจทบทวนบันทึกข้อมูลทางการแพทย์ของท่าน โดยมีวัตถุประสงค์เพื่อตรวจดูความถูกต้องของข้อมูลและวิธีการต่างๆของการศึกษาวิจัย และข้อมูลทางการแพทย์ของท่านอาจถูกนำไปจัดเก็บไว้ในคอมพิวเตอร์

จากการลงนามในเอกสารยินยอมเข้าร่วมโครงการวิจัย ท่านอนุญาตให้ดูแลบันทึก เก็บข้อมูลและโอนย้ายข้อมูลดังกล่าวข้างต้น

สิทธิผู้ป่วย

การเข้าร่วมการศึกษานี้เป็นไปโดยสมัครใจ ท่านอาจปฏิเสธที่จะเข้าร่วมโครงการ หรือถอนตัวจากการศึกษาได้ตลอดเวลา โดยไม่กระทบต่อการดูแลรักษาที่จะได้รับจากแพทย์

การลงนาม

เพื่อเข้าร่วมโครงการศึกษาวิจัย ท่านหรือผู้แทนโดยชอบด้วยกฎหมายต้องลงนามพร้อมวันที่ในใบยินยอมเข้าร่วมโครงการวิจัยที่แนบด้วยกันนี้

หากท่านมีปัญหาหรือข้อสงสัยประการใด กรุณาติดต่อ รศ.น.พ.พงศ์ศักดิ์ ยุกตะนันทน์ ภาควิชาออร์โธปิดิกส์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ตึกเจริญ-สมศรี ชั้น 2 โรพยาบาลจุฬาลงกรณ์

Appendix C: ใบยินยอมเข้าร่วมการศึกษาวิจัย (Cosent form)

เลขที่คนไข้..... ชื่อและนามสกุล.....
ข้าพเจ้าได้รับทราบจากแพทย์ผู้รักษา ซึ่งได้ลงนามด้านท้ายของหนังสือนี้ถึงวัตถุประสงค์ ลักษณะและแนวทางการศึกษาของยาโรฟีคอกซิบ และ ยาไดโคลฟีแนก รวมทั้งทราบถึงผลดีที่จะได้รับ ผลข้างเคียงและความเสี่ยงที่อาจเกิดขึ้น ข้าพเจ้าได้ซักถาม ทำความเข้าใจเกี่ยวกับการศึกษาดังกล่าวนี้ เป็นที่เรียบร้อยแล้ว

ข้าพเจ้ายินดีเข้าร่วมการศึกษาวิจัยนี้โดยสมัครใจ และอาจถอนตัวจากการเข้าร่วมการศึกษานี้เมื่อใดก็ได้ โดยไม่จำเป็นต้องแจ้งเหตุผล และยอมรับสิ่งไม่พึงประสงค์ที่อาจเกิดขึ้น และจะปฏิบัติตัวตามคำแนะนำของแพทย์ทุกประการ ผู้วิจัยรับรองว่าหากเกิดอันตรายใดๆ จากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็น ด้วยเหตุผลทางวิชาการเท่านั้น

ข้าพเจ้ายินดีให้ข้อมูลของข้าพเจ้าแก่คณะแพทย์ผู้รักษา เพื่อประโยชน์ในการศึกษาวิจัยครั้งนี้

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้วและมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

....
(ชื่อผู้ป่วย) (ลายเซ็น) (วันที่)

....
(ชื่อผู้ป่วย) (ลายเซ็น) (วันที่)

....
(ชื่อผู้ป่วย) (ลายเซ็น) (วันที่)

VITAE

Dr. Pongsak Yuktanandana was born on June 6, 1960 in Bangkok, Thailand. He graduated from Chulalongkorn University in 1985 after accomplishment of a six-year course and earned the degree of Bachelor of Science (B.Sc.) and Doctor of Medicine (M.D.). He completed one-year internship in a regional hospital at Chantaburi provice. He worked as a director and doctor in a district hospital in Uthaithani for 2 years. After completion of a three-year residency training in department of Orthopedic Surgery, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, he worked as an orthopedic surgeon in Chiengrai Regional hospital for 3 years. He started his career as an instructor in Department of Orthopedic Surgery, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University since May, 1993. He received the Takeda Foundation Scholarship to support his three months arthroscopy surgical training in Tokyo, Japan in 1995 and AO foundation scholarship for three months training in Germany in early 1996. He had been a sports medicine research fellow in the Center for Sports Medicine, University of Pittsburgh Medical Center, Pittsburgh, USA, during May 1996 to April 1997.

Since June 2001, he had been admitted in the Master Degree Program of Health Development in Faculty of Medicine Chulalongkorn University. He had principal research in postoperative orthopedic pain management.

Presently, he is an Assoc.Prof. in the department of Orthopedic Surgery, Faculty of Medicine, Chulalongkorn University.