CHAPTER III

RESEARCH METHODOLOGY

3.1 Research question

3.1.1 Primary research question

Can intravenous parecoxib sodium decrease 24 -hour postoperative morphine consumption following total knee arthroplasty by 25% compared with placebo?

3.1.2 Secondary research question

What are the incidences of adverse effects of morphine and parecoxib sodium?

3.2 Objective

1. To assess the efficacy of intravenous parecoxib sodium in decreasing morphine consumption for acute postoperative pain following total knee arthroplasty.
2. To determine the side effects of morphine and parecoxib sodium.

3.3 Statistical hypothesis

Null hypothesis

There is no significant difference in the 24 hour morphine consumption after total knee arthroplasty in patients who received parecoxib sodium and placebo group.

Alternative hypothesis

There is 25% difference in the 24 hour morphine consumption after total knee arthroplasty in patients who received parecoxib sodium and placebo group.

$$Ho : \quad \mu_1 = \mu_2$$

$$Ha : \quad \mu_1 \neq \mu_2$$

Where μ_1 = mean of 24 h morphine consumption after total knee arthroplasty in patients who received placebo

μ_2 = mean of 24 hour morphine consumption after total knee arthroplasty in patients who received parecoxib sodium.

3.4 Conceptual framework

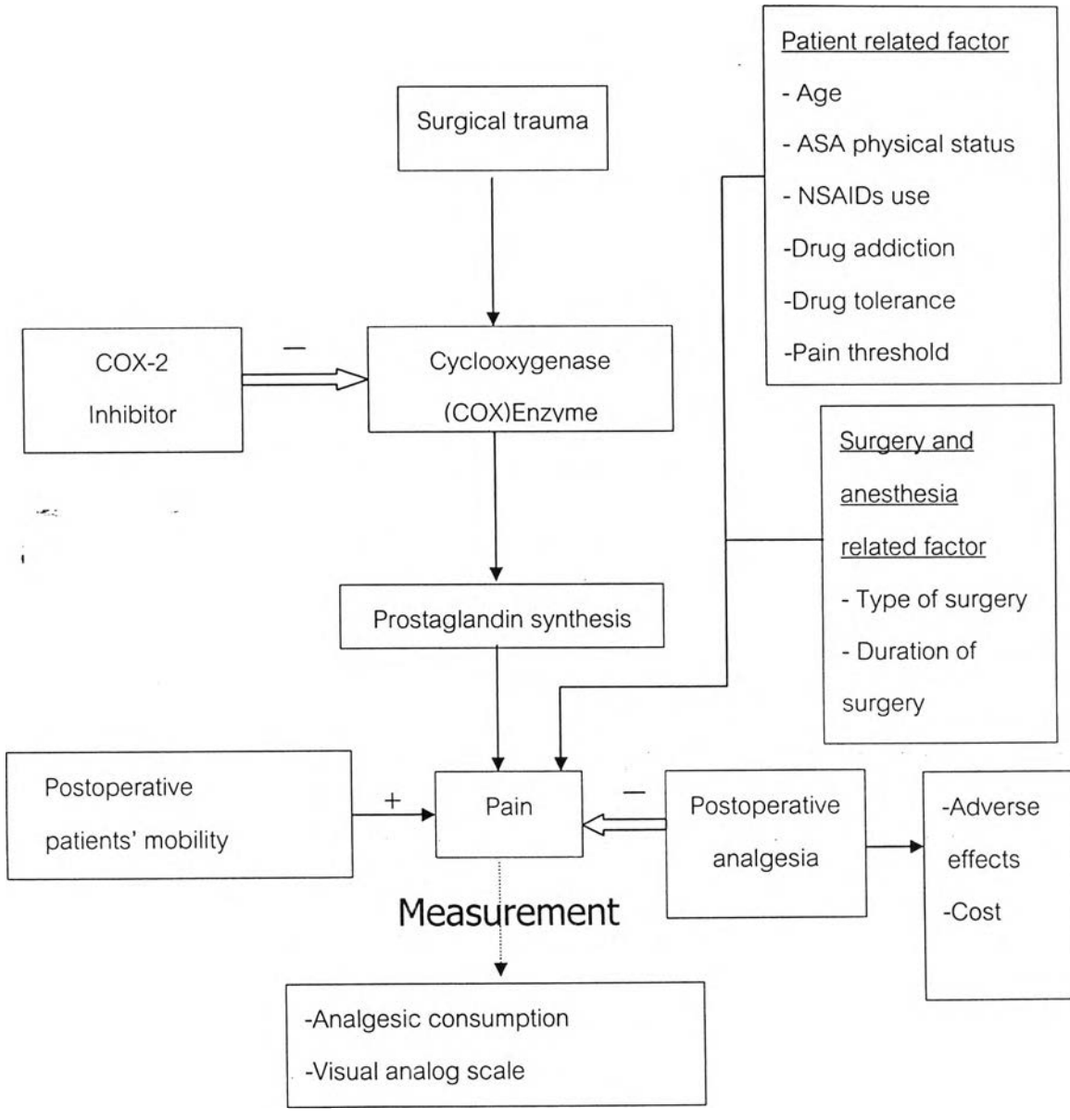


Figure 1 Conceptual framework

3.5 Keyword

Parecoxib sodium,

Post-operative pain,

PCA-morphine,

Total knee arthroplasty

3.6 Operational definition

Visual analog scale (VAS)

The VAS is a 100 mm or 10 cm horizontal line labeled "no pain" at one end and "worst pain imaginable" on the other end. The patient is asked to mark on this line where the intensity of the pain lies. The distance from "No pain" to the patient's mark numerically quantities the pain.

Patient-controlled analgesia (PCA) device

Patient-controlled analgesia (PCA) device is a device that allows the patient to self-administer precise dose of analgesic by pushing a button. The physician programs the infusion pump to deliver a specific dose (incremental dose), the minimum interval between doses (lock out interval) and the maximum amount of analgesic that can be given in a given period (usually 1 or 4 hours)

3.7 Research design

The study was conducted as a prospective randomized double-blind controlled trial. The patients undergoing unilateral total knee arthroplasty who met eligible criteria and already presented in postanesthetic care unit were randomized by the data manager (simple randomization; 24 balls for intervention and 24 balls for placebo). The allocation (two set of parecoxib sodium or placebo) was prepared in sequentially numbered, opaque, sealed envelopes. Envelopes are opened sequentially only after participant details are written on envelope.

The allocation concealment was performed under an opaque sealed envelope to reduce allocation bias. In addition, the randomization can avoid allocation bias, tends to produce comparable groups and assures the validity of statistical tests of significance.

Figure 2 Process of Randomization

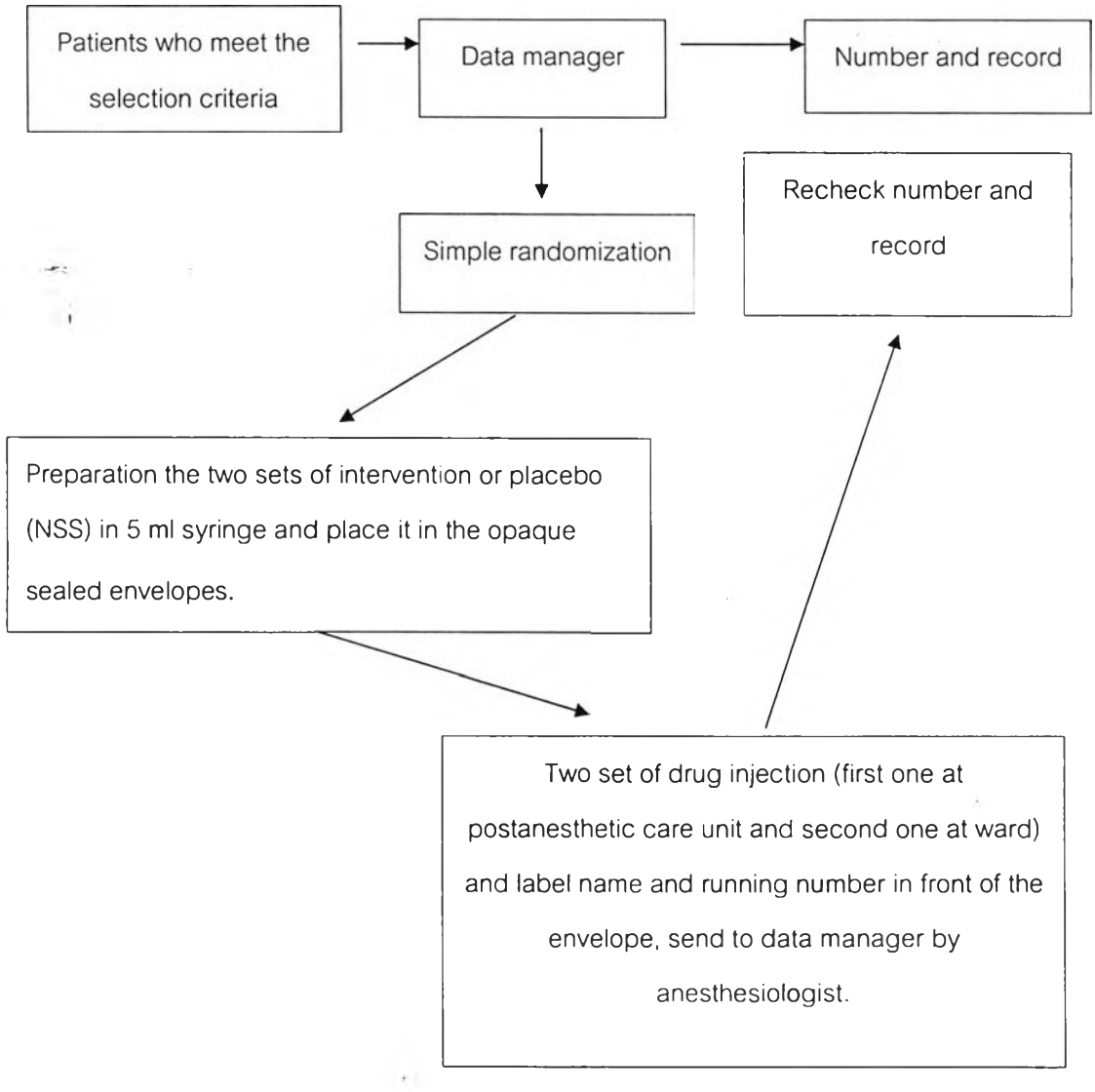
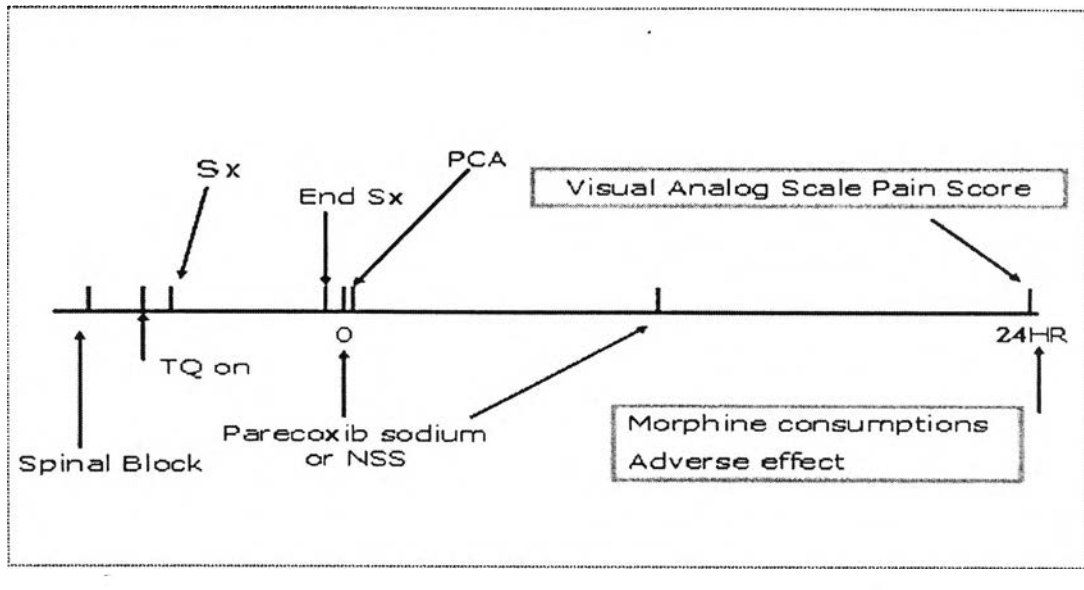


Figure 3 Study Protocol



3.8 Research method

3.8.1 Population

Target population

All patients of 50-75 years of age who are scheduled for total knee arthroplasty

Sampled population

All of patients who underwent total knee arthroplasty at Phramongkutklao hospital during July 2005 – March 2006 and meet the following eligible criteria.

3.8.2 Eligible criteria

Inclusion criteria

1. ASA physical status 1, 2 and 3 (Appendix A)
2. Age 50-75 years
3. Anticipated in elective unilateral total knee arthroplasty under spinal anesthesia and already presented in post anesthetic care unit.
4. Agreed to participate and give informed consent for the study (Patient's free inform consent)
5. Able to understand how to use a patient-controlled analgesia (PCA) device

Exclusion criteria

For safety, the following exclusion criteria were used.

1. Patients who have known hypersensitivity, or contraindication to morphine, sulfa drugs or any NSAIDs
2. Patients who have preoperative hepatic and renal dysfunction.
3. Patients who have serious cardiac and respiratory diseases.
4. Patients who have history of peptic ulcer
5. Patients who have coagulopathy (congenital or acquired)

For prevention confounding factors, the following exclusion criteria were used.

1. Patients who are drug addiction.
2. Non-steroidal anti-inflammatory medication was continued at least 24 hours before surgery.

3.9 Sample size calculation

The primary outcome was the mean value of 24 hours morphine consumption; sample size formula for comparing two means of two independent groups was used.

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

Where N1, N2 = sample size for group 1 and 2 respectively (Assume N1=N2=N)

α = 0.05

Z_{α} = 1.96 (two-tailed test)

Z_{β} = 0.84 (power = 0.80)

Base on previous similar research[1] ,amount of morphine consumed during the first 24 hours in the control group (n=15) = 45±13 mg. Assuming that the amount of 24 hours morphine in the intervention group will be decreased 25%, then

μ_2 = 45 - (45 X 25%)

= 45 – 11.25 = 33.75

The difference of μ_1 and μ_2 = 45 - 33.75 = 11.25

n / group = $\frac{2\,(13)^2(1.96+0.84)^2}{(11.25)^2}$

= 20.9 = 21

Estimated drop out = 10%

N / group after correct dropout= 21 / 0.9 = 23.3 = 24

The total number of patients needed in this study = 48

3.10 Randomization

Simple randomization was used by choosing one of 48 balls in concealed box (24 balls for parecoxib sodium group and 24 balls for placebo group) without replacement. A data manager centrally assigned treatment on telephone verification of the correctness of inclusion criteria. The data manager prepared two set of intervention (parecoxib sodium) or placebo (NSS) in sequentially numbered, opaque, sealed envelopes. Envelopes were opened sequentially only after participant details were written on the envelope.

3.11 Intervention

3.11.1 Premedication

During the preoperative visit, the patient was explained about the detail of the protocol. No premedication was given except for some night time sedation if indicated.

3.11.2 Study drug

The subjects received two injections of either the parecoxib sodium 40 mg or an

equivalent volume of normal saline intravenously when they first presented in post anesthetic care unit and 12 hours later. Both subject and investigator were blinded as mentioned earlier.

3.11.3 Anesthetic drugs

Spinal anesthesia was administered by standard technique used at Phramongkutklao hospital by one anesthesiologist. The subjects were monitored with non-invasive blood pressure; pulse oximetry and continuous monitoring of electrocardiography. They were received 10 mg/kg of balance salt solution (acetar) before conduct spinal anesthesia with 0.5%Bupivacaine 3-3.5cc. During surgery, patients were received 5 cc kg^{-1} for compensation of insensible fluid loss. Then the subjects were given those 2 mg of midazolam and 25 mg of pethidine intravenous for sedation. If blood pressure decreased more than 20% of baseline, the patients were given 6 mg of ephedrine or 0.5 mg of metaraminol intravenously.

3.11.4 Surgical technique

To prevent intraoperative blood loss, a pneumatic tourniquet will be placed around the thigh and inflated to a pressure of 350-400mmHg after exsanguinizations. The surgeon performed the cemented knee prosthesis in all patients. One or two high-vacuum intra-articular drain was used. The tourniquet was released at the end of surgery when a compressive dressing was applied and the blood drainage system functioned correctly.

3.11.5 Postoperative analgesia

Patients were connected to a PCA device on arrival in the post anesthesia care unit. The PCA solution contained morphine 0.5 mg/ml. Initial settings were as follows: incremental dose 2 ml. (1mg.), lockout interval 4 min and 4-h limit 50 ml. (25 mg).

3.12 Outcome measurement

Baseline variables

Demographic data: age, gender, weight, height, ASA physical status, duration

of surgery and duration of tourniquet time.

Primary outcome variable

- Postoperative analgesic requirement

The 24 h morphine consumptions (24 hours from starting intravenous parecoxib sodium) was recorded and summarized in mean and SD.

Secondary outcome variables

- Pain intensity

Patients were asked to quantify their pain on 100 mm visual analog scale (VAS), where 0 mm = no pain and 100 mm = the worst imaginable pain at 24 h later

- Adverse effects

The major side effects of morphine such as nausea, vomiting and respiratory depression were recorded.

3.13 Data collection and analysis

The demographic data and baseline data was recorded in case record form by the investigator. During the surgery, the following variables were recorded: time when study drug was administered, time when tourniquet is applied, time when the incision was made, and duration of surgery. The morphine consumption (recorded by PCA device) at 24 hours in each group sodium was recorded. Mean VAS pain scored at 24 hours was also recorded. The investigator also assessed the side effects as mentioned earlier.

Data analysis

All patients who had enrolled in the study were included in the analysis.

- Demographic and baseline data

Variables	Type of variables	Descriptive statistics
1. Age	Continuous	Range, mean and SD
2. Sex (male/female)	Categorical	Percent
3. Body weight (kg)	Continuous	Range, mean and SD
4. Height (cm)	Continuous	Range, mean and SD
5. ASA status (1/2)	Categorical	Percent
6. Duration of Surgery	Continuous	Range, mean and SD

- Outcome variables

Inferential statistics were used to analyze the data according to research questions and type of outcome variables.

Variables	Inferential statistics
1. Postoperative morphine consumptions	Unpaired t-test (Mann-Whitney U test)
2. Visual Analog Scale Pain Scores	Unpaired t-test (Mann-Whitney U test)
3. Side effects	Chi-squared test (Fisher exact)

The primary outcome was the mean of 24 hours morphine consumption, which was a continuous variable. Because morphine consumption in each group was normally distributed, unpaired t-test was used to assess the difference between the treated and control group.

The secondary outcome was the mean of visual analog scale pain score, which was a continuous variable. Because visual analog scale pain score in each group was normally distributed, unpaired t-test was used to assess the difference between the treated and control group.

3.14 Limitation

The study had been carried out in the surgical patients who underwent total knee arthroplasty; some factors that affect pain such as patient threshold, psychological condition, and drug tolerance could not be controlled. Cooperation of the patients may affect the outcome, since Visual Analog Scale was the subjective outcome. In addition, patients had been explained and reassured to control postoperative pain using patient controlled analgesia (PCA) device. Moreover, funding had been limited for this study due to costs of parecoxib and PCA device. Due to time constraint, this study was unable to recruit 48 subjects according to sample size calculation. There were only thirty-six patients enrolled in this study, eventually.

3.15 Ethical consideration

The study protocol was thoroughly explained to the subjects before enrolling in the study. The study was approved by Ethic Committee of Royal Thai Army Medical Department. The informed consent document contained a statement defining that the consent was freely given and had to be signed for every participated subject. The patient was aware of risks and benefits of entering the study, and the patient was free to withdraw from the study at any time. All the data was used for study purpose only and was confidential. Any adverse effects, that occured, were treated until recovery.