CHAPTER III

RESEARCH METHODOLOGY

3.1 Research Questions

3.1.1 Primary research question

Can administering etoricoxib 120 mg or flavoxate 200 mg or both preoperatively effectively reduce the first 24 hours postoperative morphine consumption by 30% compared to the control group in patients undergoing transurethral prostatectomy?

3.2.2 Secondary research question

3.1.2.1 Can preoperatively administering etoricoxib 120 mg or flavoxate 200 mg or both effectively reduce the first 24 hours postoperative pain in patients undergoing transurethral prostatectomy?

3.1.2.2 Are there any differences in serious adverse effects (i.e., sedation, respiratory depression, pruritus, nausea and vomiting) between patients receiving etoricoxib 120 mg or flavoxate 200 mg or both compared to those receiving placebo?

3.1.1.3 Are there any differences in cost-effectiveness of the 4 treatment groups?

3.2 Research Objectives

3.2.1 Primary objective

To determine if patients who preoperatively receive etoricoxib 120 mg or flavoxate 200 mg or both will consume 30% less morphine during the first 24 hours than patients who receive placebo.

3.2.2 Secondary objective

3.2.2.1 To determine the analgesic efficacy of etoricoxib 120 mg or flavoxate 200 mg or both after transurethral prostatectomy compared to a placebo.

3.2.2.2 To evaluate the proportion of serious adverse effects, such as respiratory depression, over sedation, pruritus, nausea and vomiting, in the 4 treatment groups

3.2.2.3 To compare the cost-effectiveness between the 4 treatment groups.

3.3 Hypothesis

3.3.1 Research hypothesis

There is a difference in postoperative morphine consumption in the first 24 hours after transurethral prostatectomy between patients receiving etoricoxib or flavoxate or both compared to a placebo.

3.3.2 Statistical hypotheses

Null hypothesis

There is no difference in mean postoperative morphine consumption in the first 24 hours after transurethral prostatectomy between patients receiving only etoricoxib, only flavoxate, both etoricoxib and flavoxate and a placebo.

$$H_o: \ \mu_1 = \mu_2 = \mu_3 = \mu_4$$

Alternative hypothesis

There is at least one inequality in mean postoperative morphine consumption in the first 24 hours after transurethral prostectomy between patients receiving only etoricoxib, only flavoxate, both etoricoxib and flavoxate, and a placebo.
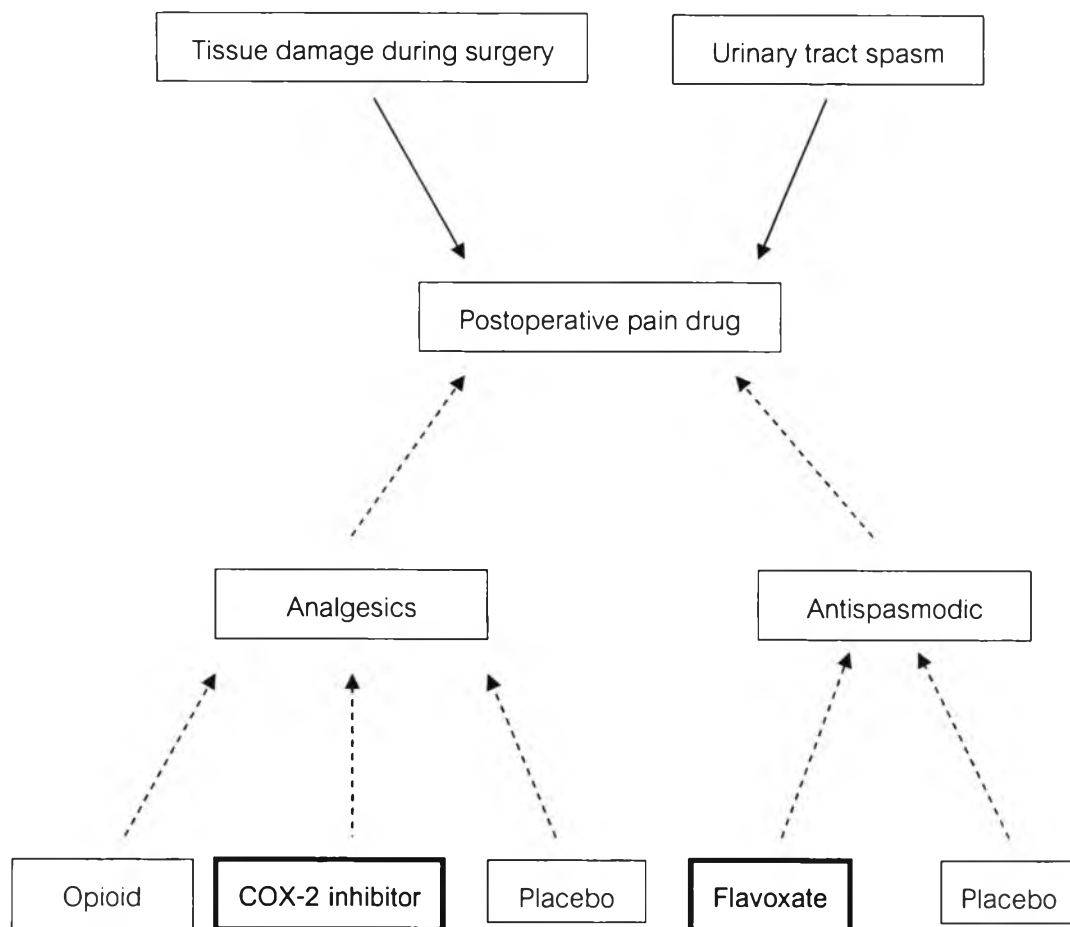
$$H_1: \ \mu_1 \neq \mu_2, \text{ or } \mu_1 \neq \mu_3 \text{ or } \mu_1 \neq \mu_4 \text{ or } \mu_2 \neq \mu_3, \text{ or } \mu_2 \neq \mu_4 \text{ or } \mu_3 \neq \mu_{4)}$$

3.4 Conceptual framework

3.5 Keywords

Transurethral prostatectomy, cox-2 inhibitors, factorial design, antispasmodic, postoperative pain

3.6 Operational definitions

3.6.1 ASA physical status

Patients were classified preoperatively according to the American Society of Anesthesiologists physical status classification (59).

Class1 Healthy patient

Class 2 Mild systemic disease-no functional limitation

Class 3 Severe systemic disease-definite functional limitation

Class 4 Severe systemic disease that is a constant threat to life

Class 5 Moribund patient unlikely to survive 24 h with or without operation

3.6.2 Pain (International Association for the study of pain)

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (60).

3.6.3 Hypotension during the operation

Hypotension is defined as systolic blood pressure less than 100 mmHg or a decrease of more than 20% of the control blood pressure.

3.6.3 Patient-controlled analgesia (PCA) device.

A self-administer device that allows patients to adjust their analgesic requirement by pushing the button. The device will be programmed by the physician in order to give a proper dose of analgesic drug at each button push. Meanwhile the device will be locked between each dose of the drug which is called lockout interval. The maximal dose of drugs can be controlled too.

3.6.4 Numeric rating scale (NRS)

An 11-point numerical rating scale with 0 = no pain to 10 = worst pain imaginable (61).

Normally pain can be assessed by various pain scales. The 3 commonly used scales are visual analogue scale (VAS), numeric rating scale (NRS) and verbal rating scale (VRS). They are simple and efficient. Visual analogue scale is a 10-cm line that requires patients to place a mark on in order to represent their pain. Verbal rating scale comprises a list of adjectives used to indicate pain intensities. The most common words used being: no pain; mild pain; moderate pain and severe pain (62,63). In this study NRS was used to assess pain because most of the patients were elderly which

might had problem with their sights. So it might be difficult for them to put the mark on the line when VAS was used. Besides that DeLoach LJ et al. (64) had demonstrated that VAS correlated well with an 11-point numerical rating scale.

3.6.5 Respiratory depression

Patients' respiratory rate $\leq$ 10 breaths / min.

3.6.6 Sedation score

0 = fully awake

1 = somnolence, responds to call

2 = somnolence, responds to tactile stimulation

3 = asleep, responds to painful stimulation

3.6.7 Creatinine clearance (65)

Creatinine clearance = [[140-age (yr)] X weight (kg)] / [72 X serum Cr (mg/dL)] (multiply by 0.85 for woman)

3.7 Research design

This study was conducted as a randomized (1:1:1:1), double-blind, placebo controlled, 2x2 factorial design to compare four treatments i.e., placebo, only etoricoxib, only flavoxate, and etoricoxib plus flavoxate (see below). The patients, anesthesiologists and nurses who gave treatment and evaluated the outcome were blinded to the treatment.

		Flavoxate (B)		Total
		Yes	No	
Etoricoxib (A)	Yes	Etoricoxib & Flavoxate (AB)	Etoricoxib alone (AO)	All A (AO & AB)
	No	Flavoxate alone (OB)	None (OO)	All non-A (OO & OB)
Total		All B (BO & AB)	All non-B (OO & AO)	

3.8 Research methodology

3.8.1 Population and sample

Target population:

Male patients who were scheduled for transurethral prostatectomy.

Sample population:

Male patients who were admitted to the Urology Division, Department of Surgery, Siriraj Hospital, Faculty of Medicine, Mahidol University. The patients met the following eligibility criteria.

3.8.2 Inclusion criteria

1. Male patient, ASA physical status I-III.

2. Scheduled for an elective TURP.

3. Body weight $\geq$ 50 kg

4. Can operate a patient-controlled analgesia (PCA) device.

3.8.3 Exclusion criteria

1. History of asthma, angioneurotic edema or urticaria following the administration of aspirin or other NSAIDs.

2. Known hypersensitivity to morphine.

3. History of severe hepatic dysfunction.

4. Creatinine clearance < 30ml/min.

5. History of bleeding tendency.

6. History of gastrointestinal bleeding or active peptic ulcer.

7. Known case of inflammatory bowel disease.

8. Severe heart failure.

9. History of coronary artery disease or cerebrovascular disease.

3.8.4 Sample size calculation

The primary outcome of the study was the total amount of morphine patients received in the first 24 hours postoperative period. As there were 4 treatment groups (i.e., 4 independent means), the sample size estimation was based on 1-way Analysis of Variances (ANOVA) using the effect size as shown below (66).

$$f \; = \text{Effect size} \; = \; (\delta/\,S) \times factor$$

$$\delta \; = \; \text{Difference between the highest and the lowest mean}$$

$$S \; = \; \text{Common SD within each treatment group}$$

The *factor* depends on distribution of k means (k = number of treatments), for example (Figure 1).

Minimal dispersion: $\qquad factor = \sqrt{\dfrac{1}{2k}}$

Intermediate dispersion: $\qquad factor = \dfrac{1}{2}\sqrt{\dfrac{(k+1)}{3(k-1)}}$

Maximal dispersion (k=odd): $\qquad factor = \sqrt{\dfrac{(k^2-1)}{2k}}$

Maximal dispersion (k=even): $\quad factor = 1$

A Minimum

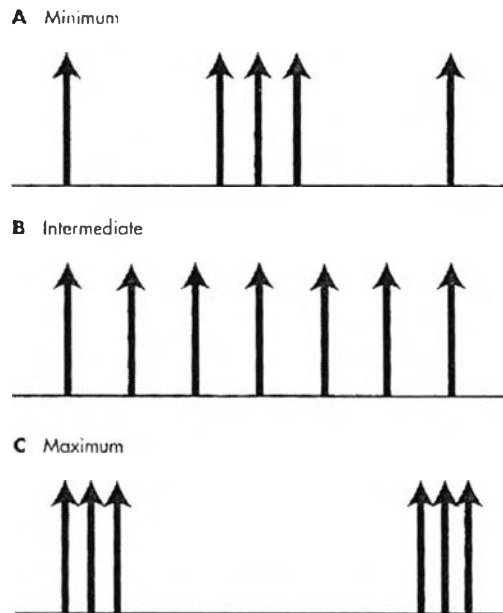**B** Intermediate

C Maximum

Figure 1 Some possible distribution of means in a one-way ANOVA

According to a pilot study in 40 patients (10 patients in each of 4 treatment groups), the mean ± SD of 24-hour morphine consumption (mg) were as follows: placebo 7 ± 4.497 mg, etoricoxib 5.4 ± 4.926 mg, flavoxate 11.8 ± 10.675 mg, combined 2.9 ± 2.601 mg respectively. These means seemed to follow the intermediate distribution (Figure 1). The Pooled SD was calculated from shown formula.

$$\text{Pooled Variance} = (SD_1^2 + SD_2^2 + SD_3^2 + SD_4^2) / 4$$

$$= (4.497^2 + 4.926^2 + 10.675^2 + 2.601^2) / 4$$

$$= 41.3023$$

$$\text{Pooled SD} = 6.4267$$

Then the required sample size was calculated as shown below.

For intermediate dispersion: *factor* $= \dfrac{1}{2}\sqrt{\dfrac{(4+1)}{3(4-1)}} = 0.372677$

f = effect size $= [(11.8-2.9)/\,6.4267] \times 0.372677$

$$= 0.5161$$

Using the effect size of 0.5161 and from the Cohen's table (67) at 2-sided α= 0.01, β = 0.1, k = 4, sample size per group was then 21. With the probable 10% dropout, the estimated sample size became 24 per group.

3.8.5 Randomization and allocation concealment

To randomly allocate the treatment, block (of size 8) randomization was applied using a computer. The treatment allocation was concealed in separate well-sealed opaque envelopes by the nurse.

3.8.6 Intervention

The patients who met the eligibility criteria were randomized into either group as shown in Table 1. During the preoperative visit, the patient was informed about the PCA usage. The study drugs were packed in an individual opaque plastic bag and each was labeled with the code for each patient who was enrolled in the study.

Table 1 Treatment protocol in each group.

Group	1 hour preoperative	Postoperative	
		6 hour	12 hour
Placebo	2 Placebos	Placebo	Placebo
Etoricoxib	Etoricoxib & placebo	Placebo	Placebo
Flavoxate	Flavoxate & placebo	Flavoxate	Flavoxate
Combined	Etoricoxib & flavoxate	Flavoxate	Flavoxate

All patients received a standard anesthetic technique. Oral diazepam or midazolam was given together with the study drug one hour preoperatively. After arriving in the operative theater, an intravenous catheter was placed and standard monitoring was applied to the patients including noninvasive blood pressure monitoring, pulse oximeter, electrocardiography. Spinal anesthesia was then given with 0.5% heavy bupivacaine 1.8-3.0 ml in order to get the analgesic level at T_8-T_{10} dermatome. After receiving spinal anesthesia, the analgesic level was tested every minute for 5 minutes.

If the target analgesic level was reached then the patient was laid in a lithotomy position. If the target analgesic level was not reached, the patient was then placed in a 20° Trendelenberg's position and retested every minute until the target analgesic level was reached or for 15 minutes. Supplemental oxygen was given via an oxygen mask with oxygen flow of 5 liters/minute. The upper part of the patient's body was kept warm with a warmer blanket (Bier Hugger®). Hypotension was treated with incremental dose of 4 microgram of norepinephrine intravenously.

After arriving in the postanesthesia care unit (PACU), a PCA device was connected to the patient. The PCA solution contained morphine 1 mg/ml. Initial settings were: incremental dose 1 ml, lockout interval 5 minutes and 4-hour limit to 30 mg. The total morphine consumption and the first time the patient triggered the PCA were recorded in the PCA device. In the ward, patients received flavoxate 200 mg or a placebo every 6 hours in a total of 2 dosages.

Patients were asked to give their pain score using a numeric rating scale (0-10) at 5, 7 and 24 hours postoperative. The patients were evaluated by the evaluators who were blinded to the patients' assigned.

3.8.7 Outcome measurement
3.8.7.1 Demographic variables
- Age (yrs)
- Body weight (kg)
- Height (cm)
- ASA physical status
- Anesthetic time (minutes)
- Surgical time (minutes)
- Level of analgesia

3.8.7.2 Outcome variables
3.8.7.2.1 Primary outcome variable
- Total amount of morphine (mg) the patient received in the first 24 hours

3.8.7.2.2 Secondary outcome variables

- Numeric rating scale (NRS) (score 0-10; where 0 is no pain and 10 is the worst imaginable pain) at 3, 5 and 24 hours
- Time (minutes) from receiving anesthesia to the first trigger of the PCA machine of each patient
- The proportion of respiratory depression, over sedation, pruritus, nausea and vomiting and any other possible side effects.

3.8.8 Data collection

Patient's data were recorded in case record form (Tables 2, 3).

3.8.8.1 Demographic data

Table 2 Patient's baseline characteristics by treatment group.

	Placebo	Etoricoxib	Flavoxate	Combined
Age (yrs)				
Body weight (kg)				
Height (cm)				
ASA physical status				
Anesthetic time (minutes)				
Surgical time (minutes)				
Level of analgesia				

3.8.8.2 Outcomes

Table 3 Outcomes by treatment group

	Placebo	Etoricoxib	Flavoxate	Combined
24-hour total morphine consumption (mg)				
Time to first PCA trigger (min)				

	Placebo	Etoricoxib	Flavoxate	Combined
Numeric rating scale (0-10)				
Respiratory depression (%)				
Over sedation (%)				
Pruritus (%)				
Nausea and vomiting (%)				
Other side effects:				
1. (%)				
2. (%)				

3.8.8.3 Cost

Table4 Data collection of costs

Cost (baht) of drug therapy	Placebo	Etoricoxib	Flavoxate	Combined
PCA cost				
Cost of etoricoxib				
Cost of flavoxate				
Cost of treating side effects:				
Cost of ondansetron (IV)				
Cost of diphenhydramine (IV)				
Cost of diphenhydramine syrup				
Labor cost of drug preparation and administration				
Labor cost of cleaning vomitus				
Total cost				

3.8.9 Data analysis

Quantitative variables i.e., demographic, baseline variables, cumulative morphine usage at 3-, 5-, 24- hour postoperative, numeric rating scale at 3-, 5-, 24- hour postoperative and time to first PCA trigger were presented as mean, median, standard deviation and (minimum, maximum) as appropriate. According to sample size estimation and due to non-normal distribution of 24-hour morphine consumption, morphine consumption in the four treatment groups was compared using the Kruskal-Wallis test. A Mann-Whitney test was then used for pairwise comparisons. Since the four treatments could also be considered as treatment combinations from a 2x2 factorial design, 2-way ANOVA was also performed as a supporting analysis using a log10 transformed 24-hour morphine dose.

Regarding the pain score (0-10) via NRS, a Kruskal-Wallis test was performed to compare four treatment groups due to the ordinal and subjective nature of the pain score. For the time of first triggering of the PCA machine for morphine, a Kruskal-Wallis test was applied to compare the triggering time between the four treatment groups among patients who required morphine. In case some patients did not require any morphine during 24 hours (i.e., censored observation), a Kaplan-Meier survival curve for painfree time was applied. A Logrank test was then carried out to test the difference in the survival curve between four treatment groups.

Categorical data i.e., side effects were presented as number and percentages and chi-square test was used to assess the difference between four treatments.

All statistical data analyses were performed using SPSS version 10.0. A 2-sided p-value of ≤ 0.05 was considered of statistical significance. The analysis was done on the basis of intention-to-treat.

3.9.10 Ethical consideration

The proposal was submitted for approval by the institutional ethics committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University and the

Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University. Patient's informed consent was obtained in every case. Patients could freely refuse to continue in the study at any time during the study period without interference with the standard treatment. All data were kept confidential and used for the purpose of the study only.

Every patient received PCA morphine for postoperative analgesia which was a standard treatment. All resuscitation equipment was prepared during the study period. The adverse effects were treated until recovery.

3.9.11 Limitation

Patients' pain threshold was different due to their background. So these might affect the primary outcome. The amount of morphine consumption may vary in each group. These might also have affect to the NRS pain intensity outcome. The cost of PCA devices may need to be funded.

3.9.12 Implication

If the analgesic effect of valdecoxib and flavoxate was good, then this intervention could be generalized for patients having TURP done. The usage of an opioid drug for postoperative analgesia in this group of patients may decrease, which reduces the adverse effects of these drugs. So a better pain control could be achieved with fewer side effects.

3.9.13 Obstacle

The maximal number of cases that could be included in the study was only 3 cases per day. This was due to the limited number of PCA machines available for research.