CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study objective

The objective of this study is to assess the equivalence of analgesic effect between 0.0625 % bupivacaine plus fentanyl 3 μg/ml and 0.15 % ropivacaine delivered by PCEA for 48 hours via a lumbar epidural catheter after unilateral total knee replacement (TKR) surgery.

3.2 Research questions

3.2.1 Primary research question

Primary question: Is patient-controlled epidural analgesia (PCEA) with 0.0625 % bupivacaine plus fentanyl 3 μg/ml as effective as PCEA with 0.15 % ropivacaine alone for 48 hour-postoperative analgesia after total knee replacement procedure assessed by 48 hour overall pain score on movement?

3.2.2 Secondary research question

Secondary question: Are there any differences in the incidences of untoward effects (motor block, vomiting, pruritus, respiratory and cardiovascular

complications), total consumed volume of study solution, total rescue analgesic drug, compared between these two regimens?

3.3 Research hypothesis

PCEA with 0.15 % ropivacaine is as effective as PCEA with 0.0625 % bupivacaine plus fentanyl for postoperative analgesia after TKR surgery.

Statistical hypothesis for equivalence study

Null hypothesis :

$H_O: \mu_R - \mu_{BF} \geq \Delta$ (inequivalence)

Alternative hypothesis :

$H_A: \mu_R - \mu_{BF} < \Delta$ (equivalence)

μ_R , μ_B = overall mean pain score on movement over 48 h

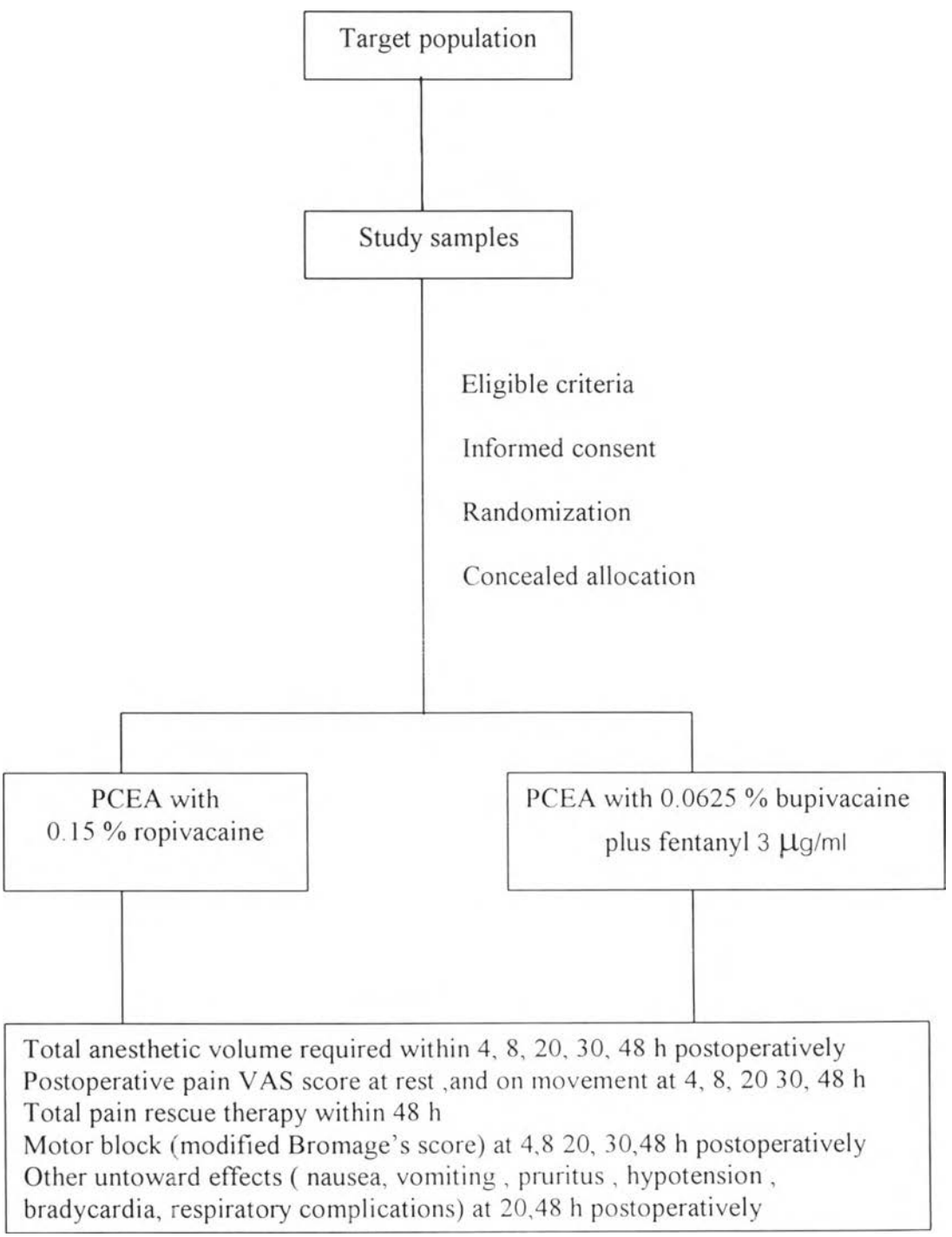
(R = ropivacaine group ; BF = bupivacaine plus fentanyl group)

Δ = prespecified acceptable difference as equivalence

(expert opinion = 10 mm of pain VAS score)

3.4 Research design

This will be a hospital – based, randomized, allocation – concealed, double blind clinical equivalence trial.



3.5 Research methods

3.5.1 Population

Target population: All adult undergoing unilateral total knee replacement (TKR) patients who require postoperative pain therapy via epidural catheter.

Study samples : All adult undergoing unilateral TKR patients at Siriraj hospital who require postoperative pain therapy via epidural catheter and fulfill the eligible criteria.

3.5.2 Eligible criteria:

Inclusion criteria

All orthopedic patients aged 45-80 years, ASA physical status I, II, and stable III (Appendix 1) underwent elective unilateral TKR who

1. has epidural catheter inserted preoperatively for providing regional anesthesia during operation.
2. can speak Thai and understand how to use PCEA device and how to assess pain with VAS score after being educated.

Exclusion criteria

1. Any patients who has contraindication for epidural catheter insertion or in whom that epidural catheter can not be inserted properly.
2. Any patients who are allergic to local anesthetics and / or fentanyl
3. Any patients who are narcotic dependence
4. Any patients who undergo re-operation of TKR
5. Any patients who or their relatives do not want to participate in this study

3.5.3 Sample size determination

Based on the primary efficacy variable: the overall 48 hour pain VAS score on movement

For a one sided confidence interval approach of the equivalence study according to Jones B et al. [28], the corresponding formula is :

$$n = \frac{2 s^2}{\Delta^2} [Z_{(1-\alpha)} + Z_{(1-\beta)}]^2$$

n = number of study samples per group

s^2 = an estimate of the variance of the pilot study

= 257.25 mm^2

α = 0.05 (one sided); $Z_{(1-\alpha)} = 1.64$

β = 0.2; $Z_{(1-\beta)} = 0.84$

Δ = pre-specified acceptable pain VAS score difference on movement as equivalence by expert opinion = 10 mm pain VAS score

$$n = \frac{2\,(257.25)(1.64+0.84)^2}{(10)^2}$$

$$= 31.64 = 32 \text{ patients}$$

Estimated protocol violation is around 10 %

compensated number of patients / group = 36 patients

total number of study samples = 72 patients

3.5.4 Allocation of the study population

A random allocation of the study population is assigned using random permutation table by blocks of 16 and 20 to divide the patients into two groups receiving either PCEA with 0.0625 % bupivacaine plus fentanyl 3 μg (BF) or 0.15 % ropivacaine (R). The allocation for each patient is concealed by placing the patients' assignments in the envelopes that are drawn in ascending consecutive order. Both patient and evaluator are blinded to treatment groups.

3.5.5 Operational definition

1 Pain VAS score : 100 mm pain visual analogue scale score ;

0 = no pain , 100 = worst pain ever

2. Pain at rest : stable pain without movement

3. Pain on movement : pain evoked by active dorsi-flexion of ankle joint on operated leg simultaneous with passively flex hip to an angle of 60 ^{o}

4. Motor block : assessed by using the modified Bromage's scale,

0 = no motor block;

1 = inability to raise the extended leg (hip blocked);

2 = inability to flex knee (knee blocked);

3 = inability to flex ankle (hip, knee and ankle blocked)

5. Sedation assessed by 4 point scales

1 = awake & alert

2 = mildly sedated, easily to wake up with call

3 = moderately sedated, easily to wake up with touch or slight shake

4 = deeply sedated & difficult to wake up

6. Respiratory complication :

Respiratory depression : defined as respiratory rate < 10 bpm and / or SpO_2 < 90 % (breathing room air)

Major respiratory depression: defined as respiratory depression plus deep sedation (sedation scale 4)

7. Hypotension : defined as a systolic blood pressure less than 100 mmHg that persists for 10 min or more.

8. Bradycardia : a heart rate less than 45 bpm

9. Nausea : a feeling of sickness or disgust

10. Vomiting : a violent ejection of food or gastric juice through the mouth

11. Pruritus : a feeling of irritation on the skin, causing a desire to scratch

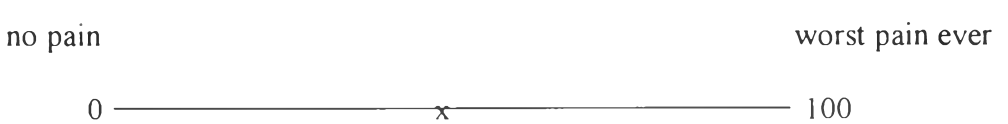
3.5.6 Observation and outcome measurement

Patients were routinely observed and recorded of vital signs every hour for the first 6 hours then every four hours until the end of the study.

Two evaluators were trained for assessment of all outcome variables. These variables were assessed at 4, 8, 20, 30, and 48 hours postoperatively except for the episodes of untoward side effects. Number and severity of untoward episodes were recorded by asking the patients and by reviewing nurse record at 20, 48 hours.

Total consumed volume of study solutions (0.0625% bupivacaine and fentanyl or 0.15 % ropivacaine) at 4, 8, 20, 30, and 48 hours postoperatively were reviewed from computerized volume record of PCA device
(Abbott Pain Management Provider ^{TM}).

Pain score was assessed by pain visual analogue scale (VAS) score which is a 100 mm line starting from 0 (no pain) to 100 (worst pain ever). Patient made a cross mark on the line that corresponded to his or her pain



The distance from 0 to a cross mark was measured by a blind evaluator.

The pain VAS score at rest was assessed first and after performed an active

dorsi-flexion of ankle joint simultaneously with passive movement up and down on the operated leg for 4 times within 1 min ,then the pain score after that manipulation was noted as pain on movement and was recorded on another pain VAS chart.

Motor block assessment by 4 point scale of modified Bromage scales (0-3) were recorded. This scale is well accepted for qualitative motor block evaluation during regional anesthesia.

Sedation also was assessed by 4 point scale as stated earlier.

Number and severity of untoward effects were recorded at 20 and 48 h. The severity of side effects was assessed as 0 = none; 1= yes; but not require treatment; 2 = yes; that require and relief by treatment; 3= yes; but not relief by treatment.

Total rescue analgesic drug required during 48 hours postoperatively will be recorded.

At the end of the study, patients were asked to assess their satisfaction on overall pain management by 4 point scales.

Excellent = Patients satisfied with this pain therapy and are happy to have this type of therapy in the future without any change.

Good = Patients satisfied with this pain therapy and are happy to have this type of therapy in the future with minor change.

Fair = Patients accepted this pain therapy but still request some other

type of pain therapy

Poor = Patients did not accept this pain therapy

3.5.7 Study intervention

1. A day before the operation, one of the investigators visited all eligible patients to explain thoroughly the study protocol and allowed patients to comfortably make a decision whether or not to enter into the study. After receiving a written informed consent, the details on how to use the PCA device and how to assess pain with VAS score were explained.

2. All patients were premedicated with midazolam 5 - 7.5 mg orally approximately 1 hour before surgery.

3. All patients received combined epidural and general anesthesia with spontaneous ventilation via laryngeal mask airway (LMA) for TKR procedure (Appendix 2).

4. In the recovery room, the patients were randomly assigned (sealed envelope method) to two treatment groups, receiving PCEA of blinded study solution (0.15% ropivacaine or 0.0625% bupivacaine plus fentanyl 3 μg /ml) for 48 hours postoperatively. (Blinded study solution according to allocation concealment was prepared by one of our investigator who did not involve in the evaluation of the patient)

PCEA was set at basal infusion of 5 ml/h and a bolus (PCA) dose of 3 ml, with a lockout interval of 15 min, and no 4 hour-limit.

5. All patients were monitored for routine vital signs every hour for the first 6 hours then every 4 hours until study ended.

6. All patients were assessed for pain VAS score at rest and on movement, and motor block at 4,8,20,30,48 hours postoperatively.

7. All patients were asked for episodes and severity of untoward effects (nausea, vomiting, pruritus). Patients' charts will be also reviewed for episodes of cardiovascular and respiratory complications include the treatment for those episodes

8. Side effects were treated with :

Metoclopramide 5-10 mg intravenously every 4-6 h for nausea and vomiting when requested.

Diphenhydramine 25-50 mg orally every 6 h for pruritus when requested.

200 ml of balanced salt solution given intravenously within 20 min for systolic blood pressure less than 100 mmHg that persists for 10 min or more when no other definite causes expected. If the patient did not improve or response to that therapy, one of investigators would be notified.

Oxygen nasal cannula 3 lpm, for $SpO_2 < 90\%$ or RR <10 bpm, then notified investigator team.

Naloxone 0.1 mg intravenously every 5 min, for a maximum of 3 doses for major respiratory depression then notified investigator team.

Tramadol 50-100 mg given intramuscularly every 6 h as rescue analgesic, if patient requested for additional pain therapy

3.6 Ethical consideration

This study was approved by The Institutional Review Board on Human Research of Siriraj hospital.

The detail of the study include any potential untoward effects was explained

clearly to the patients and written informed consent was signed before study commenced. The patients had a right to withdraw of the study at any time whenever they wanted and will not interfere with their routine management. Since pain management with this technique and drugs are well accepted and patients have to be monitored closely as hospital basis, we do not expect any serious complications or any harm to the patients.

3.7 Data analysis

All data were processed and computed by computer software programme SPSS and SAS systems. The distribution of data were tested by Kolmogorov Smirnov goodness of fit test. The parametric statistic test was used for the normal distributed data. For the skewed data the equivalent non-parametric test was used instead. Data were presented as numbers, medians and ranges, or as mean (SD). Comparison of pain VAS score at the different measurement times and consumed PCEA volume between groups were performed by using independent t test. Correction for multiple comparison was made by using the Bonferroni method to preserve the overall significant level as $P< 0.05$. Categorical data were examined by Chi-square and Fisher's exact test, if applicable. Chi-square for trend was used for comparing of the ordinal data. A mixed model for repeated measurement with unequal intervals (overall pain VAS score over 48 hour postoperative period) was used and one sided of confidence interval approach was addressed for an equivalence. All P values but overall pain VAS score over 48 hour postoperative period were two tailed, and $P < 0.05$ was considered significant.