CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study aim

The objective of this study was to determine whether the intravenous morphine administered before surgical incision results in decreasing the severity of postoperative pain when compared with the same dose of morphine administered after surgical incision.

3.2 Research questions

3.2.1 Primary research question

In major abdominal surgery, does the preincisional morphine administration decrease the postoperative analgesic requirement by 30% when compared with postincisional morphine ?

3.2.2 Secondary research questions

1. Is the length of pain-free period after surgery longer in patients receiving preincisional morphine than those receiving postincisional morphine ?

2. What is the rate of adverse effects associated with pre- and postincisional intravenous morphine ?

3.3 Hypothesis

That in randomized controlled trial of preincisional versus postincisional morphine, those patients having preincisional morphine will require at least 30% less analgesia within the first 48 hours postoperatively compared to patients having routine postincisional morphine.

3.4 Research design

A double-blind randomized controlled trial was undertaken to compare the effectiveness of preincisional morphine (experimental) and

postincisional morphine (control) in term of analgesic requirement during the first 48 hours postoperatively.

3.5 Research methods

3.5.1 Population

Reference population included all the surgical patients of 20-65 years of age who were scheduled to have major abdominal surgery. Sample group recruited any surgical patients at Chulalongkorn University Hospital (tertiary care center) who met the following inclusion criteria.

3.5.2 Inclusion criteria

1. Surgical patients of physical status 1 or 2 according to the American Society of Anesthesiologists. (Appendix 1)
2. Age 20-65 years
3. Anticipating an elective abdominal operation under general anesthesia.

4. Agree to participate (by giving free informed consent)
5. Able to understand how to use patient-controlled analgesia (PCA) machine which will be the important tool used to record the amount of analgesic consumption.
6. Expected duration of surgery 2-3 hours (The important reason to define the duration of surgery was to equalize the degree of surgical trauma in each study group)

3.5.3 Exclusion criteria

1. Pregnant women
2. Patients who assigned to have regional anesthesia for some specific indications
3. Known hypersensitivity to morphine
4. History of bronchial asthma
5. History of chronic use of opioids or narcotic addiction (confirmed by urine opiate test)
6. Patients who undergoing an emergency operation

3.5.4 Stratification and randomization procedure

Patients meeting the selection criteria were stratified according to gender and site of surgery (which were considered to be the two most important factors affecting the outcome). The site of surgery was stratified as upper, lower and combined upper and lower abdomen using the umbilicus as the landmark. There were altogether 6 strata. After stratifying, the patients in each stratum were allocated into the experimental and the control group by block randomization using a block size of 4 to avoid having unequal numbers of subjects assigned to each group. The randomization, therefore, should remove allocation bias, tends to produce more comparable study groups and also helps to control for both known and unknown confounders.

The randomized scheme had been prepared by an anesthesiologist not involved in the study and kept in a sealed envelope before starting the recruitment period. As soon as an eligible patient decided to participate in the study the nurse anesthetist who kept the envelope was informed of which stratum that patient belonged to. The nurse anesthetist then opened the randomized scheme and prepared the study drugs according to the assignment in the scheme. The study drugs were freshly

prepared at the anesthetic office outside the operating room and were sent to the operating room just before the scheduled time of surgery. Each study drug was coded and contained in identical syringes so that the patient and investigator were unaware of the nature of drug being administered.

3.5.5 Intervention

1. Premedication

During the preoperative visit, the patients who agreed to enter the study were provided with the following information : the purpose and details of study protocol, how to estimate pain intensity by Numeric Rating Scale (NRS)[30] and how to operate the PCA machine. They were also informed that no premedication would be given except for some night-time sedation if indicated.

2. Morphine injection

The experimental group received the standard dose of 0.15mg/kg of intravenous morphine 15 minutes before surgical incision (just prior to anesthetic induction) followed by the same amount of normal saline 15

minutes after surgical incision. The control group was given normal saline 15 minutes before surgical incision followed by morphine 15 minutes after incision. Both morphine and normal saline were prepared identically to maintain double-blind nature as mentioned. In some occasions, it was not easy to blind the anesthesiologist since he or she would be able to tell if the patient had received morphine especially those patients who developed urticarial rash along the injection site. In order to solve this problem, we asked the nurse anesthetist in acute pain service to evaluate pain intensity and collect the data. The nurse anesthetist and personnels in acute pain service had already been trained to interview the patient and to evaluate pain intensity score. However, they were not directly involved in the study protocol.

3. Anesthetic intervention

All of the patients recruited in this study received general anesthesia by the same standard protocol. The technique is classified as balanced anesthesia. The list of drugs used is shown in Appendix 2. No additional narcotic or other analgesic drugs were given either intraoperatively or postoperatively to assure that the cointervention had been avoided.

4. Postoperative analgesia

Postoperative analgesia was provided by patient- controlled analgesia (PCA) pump, which is an electronically controlled infusion pump with a timing device. When patients experience pain, they can trigger the device by pressing a button on a cord that extends from the machine. A preset amount of analgesic agent (usually 1 mg. of morphine) was, then, delivered into the patient's intravenous catheter. A timer was programmed to prevent administration of additional doses until a predetermined interval had elapsed. This period is sometimes refered to as the"lockout"period. The purpose of this control is to prevent administration of a second dose until after the first dose has a chance to exert its maximal analgesic effect. PCA prescription is listed in Appendix 3.

3.5.6 Outcome measurement

The outcome variables being measured were as follows:

1. Primary outcome variables

Postoperative analgesic requirement

Analgesic consumption during the postoperative period was assessed by recording the total amount of morphine consumed within the first 48 hours. However, the amount of morphine delivered during 6, 12, 24 hours were also recorded to determine trend of response.

Pain intensity

Pain intensity was assessed at 6, 24 and 48 hours postoperatively using Numeric Rating Scale (NRS) which was introduced by Downie et al.[30] This scale allows the patient to classify the severity of pain from 0 to 10 ; a score of 0 means no pain and a score of 10 means the most excruciating pain one can imagine. NRS is an 11-point numerical scale which is simpler and more understandable than Visual Analog Scale. It also gives consistent and reproducible measurements and allows for interpatient assessment and the changes within a patient during treatment.[31,32] Assessment of pain intensity was carried out to monitor the adequacy of analgesic consumption which is the major outcome in this study. However, NRS at 12 hours after surgery was not assessed since this time was likely to be the sleeping period of the patients.

2. Secondary outcome variables

Pain-free period after surgery

Time measured in minutes from the end of surgery to first requirement of analgesia was recorded as time to first analgesic (TFA) and represented the pain-free period after surgery. This can also be defined as time until the first dose of analgesic was given.

Side effects

The major side effects of morphine are nausea, vomiting and respiratory depression. Respiratory depression was defined as having a respiratory rate less than 8 breaths/minute. All of these side effects were determined by a nurse anesthetist while patients were observed in the recovery room during the first two-hour period postoperatively.

3.6 Data analysis

All the data was processed and computed by computer software program SPSS-PC and SAS.

3.6.1 Test for distribution of data

The distribution of data was 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.

3.6.2 Describing of data

Demographic and baseline data were compared between the experiment and control group. For age, duration of surgery, time interval between first injection of morphine/placebo and incision making which were quantitative data, mean and standard deviation were demonstrated and the Student's t-test was used to compare the difference between groups. For gender and site of surgery, the frequency distribution was described and chi-squared test was used to compare between the experiment and control groups.

3.6.3 Significance tests

The outcome variables were described and compared between the experiment and control group using the appropriate inferential statistics. (Table 3.1)

Table 3.1 Inferential statistics used to compare outcome variables.

Variables	Inferential statistics
1. Postoperative analgesic consumption in 48 hours	Student's t-test
2. NRS	Mann-Whitney "U" test
3. Time to first analgesic	Survival analysis
4. Side effect events	Chi-squared test or Fisher's exact test

3.6.4 Proposed analysis for each hypothesis

1. That in a RCT of preincisional versus postincisional morphine, those patients having preincisional morphine will require 30 % less analgesia within the first 48 hours postoperatively compared to patients having routine postincisional morphine.

The mean amount of morphine used within the first 48 hours in both groups were compared by unpaired t-test.

In addition, since the amount of analgesic consumption was measured at 6, 12, 24 and 48 hours the repeated measure analysis was also used to determine the interaction between time and analgesic consumption.

2. The length of pain-free period after surgery in preincisional morphine group is longer than that in the postincisional group.

The time to first analgesic was measured and survival analysis was performed. The median survival times of both groups was also compared.

3. The side effect events such as nausea, vomiting and respiratory depression in both groups are equal.

The side effect events in both groups were counted and compared by Chi-squared or Fisher's exact test when appropriate.

3.7 Sample size estimation

Since the primary outcome is the mean value of total postoperative analgesic requirement, sample size formula for comparing two means of two independent groups was used.[33]

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

where $\alpha = 0.05$

$Z_\alpha = 1.96$ (two-tailed)

$Z_\beta = 0.84$ (Power = 0.80)

Based on the previous study by Richmond et al,[26] using the same outcome measure, estimates of the effect size and variance from their

study were used to calculate the sample size. The difference in mean morphine consumption in each group was about 10, while the variance from their study was 18.42.

Therefore,

$$\text{N/group} = \frac{2\,(1.96 + 0.84)^2\,(18.42)^2}{(10)^2}$$

$$= 53.20$$

The total number of patients needed in this study was 108.

3.8 Ethical consideration

The study protocol had been thoroughly explained to the patient before enrolling in the study and the free informed consent was obtained. Moreover, the intervention should provide more benefit than harm and postoperative analgesia will be ready as soon as it is required. Therefore, the ethical issue should not be a problem.

3.9 Limitation and obstacle

The study was carried out in the surgical patients who were undergoing major abdominal operation, it might not be generalized to the patients having different type of surgery.

Pain sensation is the subjective symptom which can not be easily measured since it may be influenced by many factors including psychological backgrounds and personal experiences. To alleviate this problem we used the NRS as the assessment tool to ensure the adequacy of postoperative analgesia and used the amount of analgesic consumption as the main outcome.

3.10 Expected benefit and application

The efficacy of pre-emptive treatment will be confirmed and will result in effective treatment of pain after surgery. Reduction of pain and analgesic consumption in postoperative period would certainly lead to reduction in the incidence of certain complication, number of days spent in hospital and total hospital costs.