CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research question

3.1.1 Primary research question

Do patients administering ginger preoperatively have different postoperative nausea and vomiting after intrathecal morphine for lower extremity surgery from placebo?

3.1.2 Secondary research question

1. Do patients administering ginger preoperatively have different postoperative nausea and vomiting at different period : intraoperative period , 0-6 h , 6-24 h after intrathecal morphine for lower extremity surgery from placebo?
2. Do patients administering ginger preoperatively have different severity of nausea, requirement of rescue anti-emetic, and time to first rescue anti-emetic after intrathecal morphine for lower extremity surgery from placebo?
3. Do patients administering ginger preoperatively have different pain intensity and requirement of analgesic after intrathecal morphine for lower extremity surgery from placebo?
4. Do patients administering ginger preoperatively have different pruritus and requirement of anti-pruritus after intrathecal morphine for lower extremity surgery from placebo?
5. Are there any differences in adverse event ?

3.2 Objective

1. To compare the efficacy of ginger administered preoperatively in prevention of postoperative nausea and vomiting after intrathecal morphine for lower extremity surgery to placebo ; in the term of incidence of PONV, severity of nausea , requirement of anti-emetic , and time to first rescue anti-emetic

2. To evaluate the effect of ginger on pain and pruritus after intrathecal morphine for lower extremity surgery

3. To compare adverse events between patients who received oral ginger and placebo

3.3 Hypothesis

3.3.1 Research hypothesis

There is difference between the efficacy of oral ginger and placebo in prevention of postoperative nausea and vomiting after intrathecal morphine for lower extremity surgery

3.3.2 Statistical hypothesis

Null hypothesis

There is no significant difference in the proportion of postoperative nausea and vomiting (PONV) after intrathecal morphine for lower extremity surgery between ginger and placebo group

Alternative hypothesis

There is significant difference in the proportion of postoperative nausea and vomiting (PONV) after intrathecal morphine for lower extremity surgery between ginger and placebo group

$$Ho : \quad \pi_1 = \pi_2$$

$$Ha : \quad \pi_1 \neq \pi_2$$

π_1 = proportion of postoperative nausea and vomiting (PONV) in ginger group

π_2 = proportion of postoperative nausea and vomiting (PONV) in placebo group

3.4 Conceptual framework

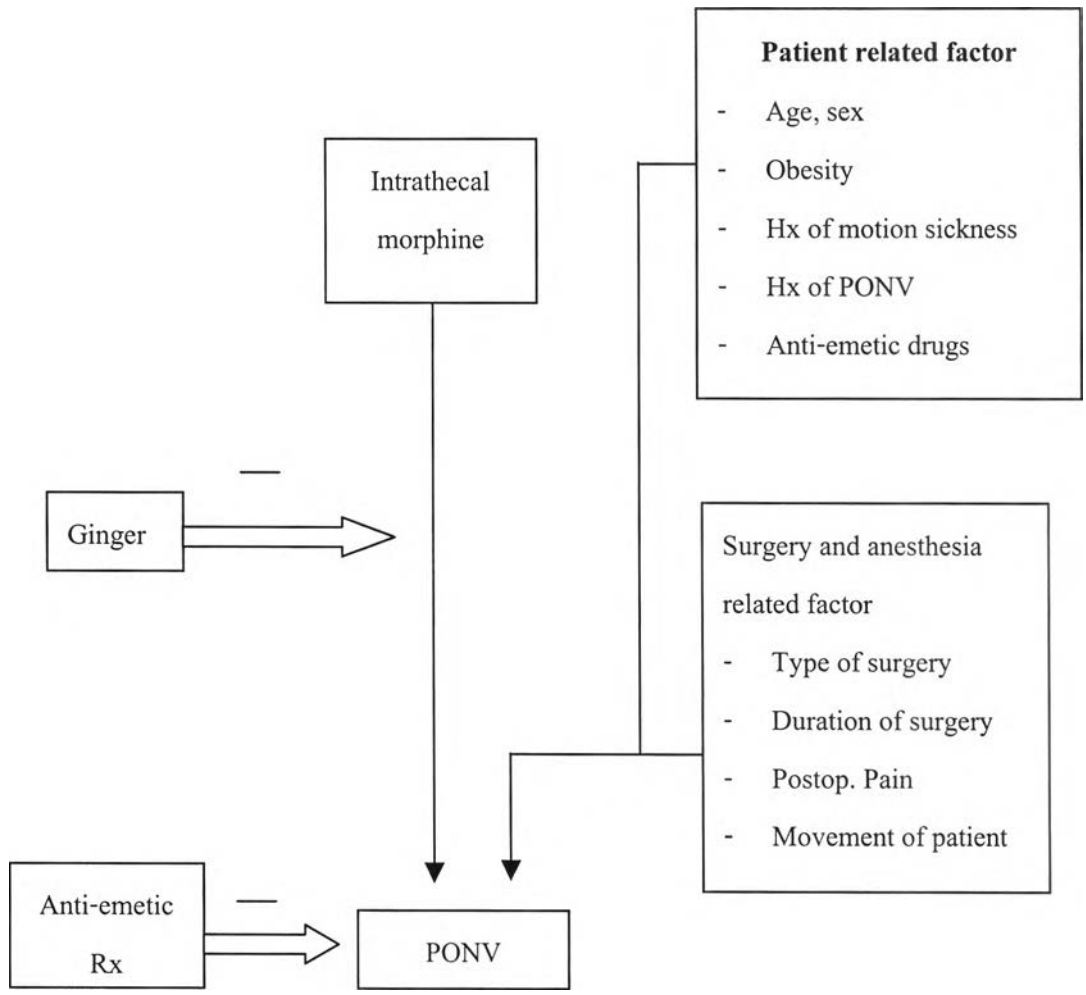


Figure 3 Conceptual framework

PONV is a common side effect of intrathecal morphine. The physiology and neuropharmacology of opioid-induced nausea and vomiting are complex as figure I (6). The factors associated with PONV consist of patient related factors and surgery and anesthesia related factors(53). PONV is likely to be lowest in infants less than 12 months of age, maximum in school age children then may decrease with age.

The incidence of PONV in adults does not much vary with age. Women have higher incidence of PONV than men. The patients with history of motion sickness or PONV , obesity may have higher incidence of PONV. Other factors involved in PONV include pain and opiate use to treat it , some types of surgery and movement.

Anti-nausea and anti-emetic activities of ginger may be on CNS and direct gastrointestinal system , possibly as antiHT_3(13-16). Therefore, ginger should prevent PONV when administering preoperatively. However, the patients who have PONV can be received anti-emetic drug for the treatment.

3.5 Keyword

Intrathecal morphine

Postoperative nausea and vomiting

Ginger

3.6 Operational definition

PONV is defined as presence of emetic episode and/or nausea throughout the observation period .

NO PONV is defined as absence of any emetic episode and no nausea throughout the observation period .

Nausea is the subjective sensation of a desire to vomit.

Vomiting is defined as forceful expulsion of gastrointestinal contents through the mouth. Regurgitation is not considered vomiting.

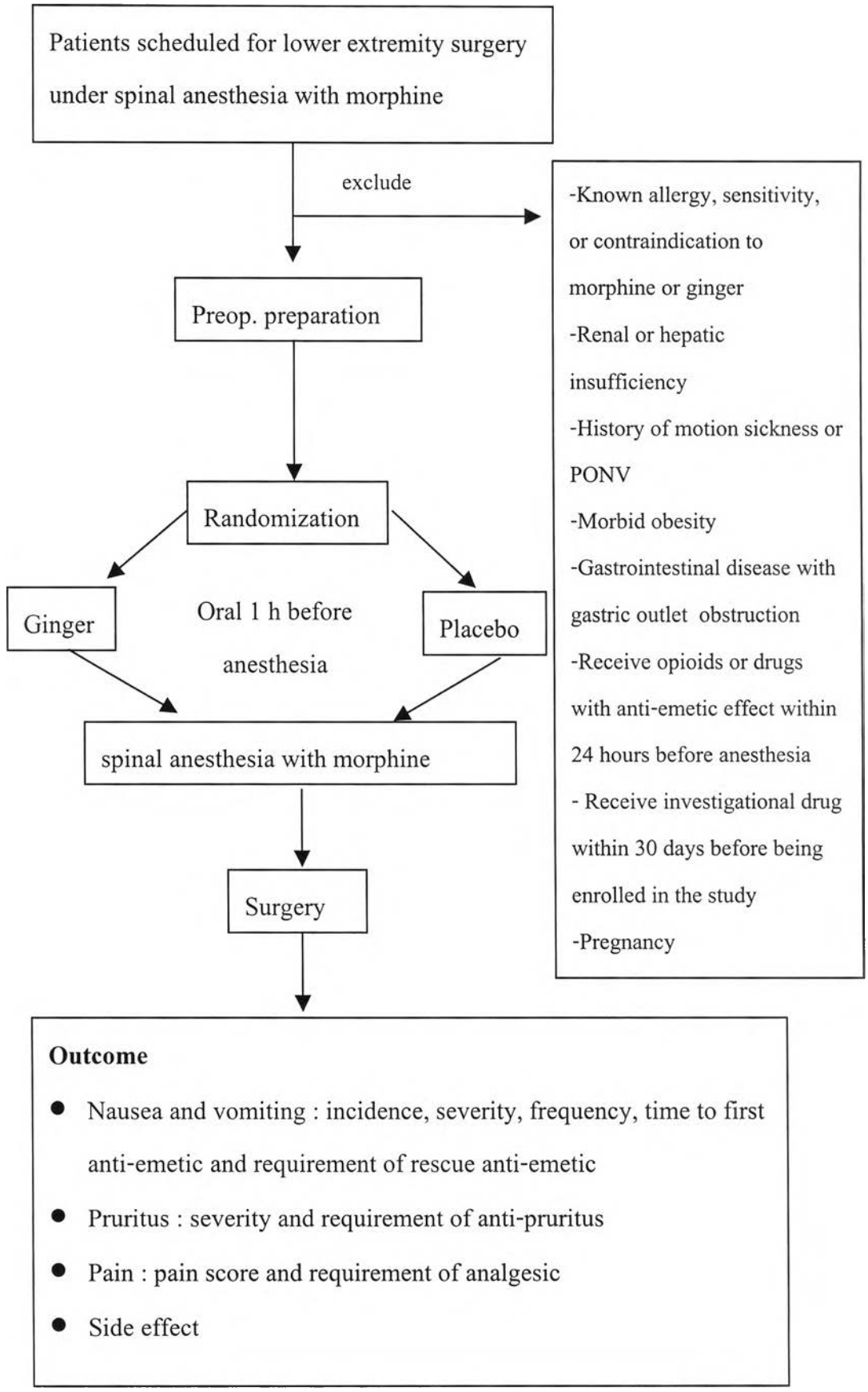
Retching is defined as vomiting movements without expulsion of gastric content.

Hypotension is defined as a decrease of the systolic blood pressure by 20% of baseline.

3.7 Research design

The study was conducted as a prospective randomized double-blind controlled trial. The patients, the investigators, the caregivers, the anesthesiologists, and the assessors were blinded to the treatment allocation in order to prevent outcome assessment bias. The patients were enrolled into the trial by an inclusion criteria. All recruited patients were received a similar protocol of anesthetic and post-anesthetic care in order to avoid a possibility of contamination and co-intervention. The eligible patients were randomly assigned into two groups. 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 4 Study protocol



3.8 Research method

3.8.1 Population

Target population

- Patients scheduled for lower extremity surgery under spinal anesthesia with morphine

Sampled population

- All of the patients at BMA general hospital who met the following inclusion criteria were recruited in this study.

3.8.2 Eligible criteria

Inclusion criteria

- Scheduled to have an elective surgery of lower extremity under spinal anesthesia with morphine
- Patients of ASA physical status I or II (Appendix 1)
- Age between 18-65 years
- Agree to participate in the study and sign the informed consent

Exclusion criteria

- Known allergy, sensitivity, or contraindication to morphine or ginger
- Renal or hepatic insufficiency
- History of motion sickness or PONV
- Morbid obesity
- Gastrointestinal disease with gastric outlet obstruction
- Receive investigational drug within 30 days before being enrolled in the study
- Receive opioid or drugs with anti-emetic effect within 24 hours before anesthesia
- Pregnancy

The enrolled patients included the patients who were scheduled to have a lower extremity surgery under spinal anesthesia with morphine. The patients must be healthy with ASA physical status I or II. The patients must be at least 18 years old because they could give the informed consent themselves legally. Moreover, the patients who younger than 18 and older than 65 years old were not good candidates for spinal anesthesia with morphine. All patients agreed to participate to the study and signed the informed consent according to the Helsinki declaration. The patients with conditions that could interfere the outcome such as history of motion sickness or PONV, morbid obesity, gastrointestinal disease with gastric outlet obstruction, and received investigational drugs with anti-emetic effect within 24 hours before anesthesia were excluded from the study. In addition, the patients who had known allergy, sensitivity, or contraindication to morphine or ginger, the major drugs in the study, were excluded as well.

3.9 Sample size calculation

Since the primary outcome is proportion of PONV in each group, the sample size formula for comparing two independent proportions was used(54)

$$n/\text{ group} = \frac{[Z_\alpha \sqrt{2\bar{P}(1-\bar{P})} + Z_\beta \sqrt{P_1(1-P_1)+P_2(1-P_2)}\ ]^2}{(P_1-P_2)^2}$$

where α= Probability of type I error = 0.05 Z_α (2 sided) = 1.96

β= Probability of type II error = 0.10 (90% power) Z_β= 1.28

P_1 = proportion of postoperative nausea and vomiting in ginger group

P_2 = proportion of postoperative nausea and vomiting in placebo group

From the pilot study of 10 patients in each group ;

P_1 = 0.2 P_2 = 0.5

$\bar{P} = (P_1+P_2)/2 = 0.35$

n/ group = $50.8 \approx 51$

5% drop out : $N = \frac{n}{(1-R)} = \frac{51}{(1-0.05)} \approx 54$

The total estimated sample size was 51 patients per group. To allow for an expected 5 % drop out rate, a total of 108 patients (54 per group) was randomized.

3.10 Randomization

The eligible patients were randomly allocated into 2 groups to receive single dose of either oral ginger or placebo preoperatively by using random numbers table with allocation concealment (consecutive opaque sealed envelope method) .The random number was written in sealed envelope. The number compatible with number in sealed envelope was on the package of intervention agent and placebo. The code was kept without broken until the patients were discharged and all data were collected or in case of severe side effects occur and interim analysis might be necessary.

3.11 Intervention

Preoperative period

The patient who met the criteria was explained about the detail of the protocol and how to rate nausea score and visual analogue scale. The routine preoperative preparation was done. The patient received 1 g ginger or placebo contained in identical dark-colored capsule orally 1 hour before induction of anesthesia

Intraoperative period

A similar standardized anesthetic technique was used. After being monitored with noninvasive blood pressure, electrocardiogram and pulse oximeter, all patients were placed in left lateral position and received spinal anesthesia consisting of 0.5 % bupivacaine with 0.2 mg morphine. Intravenous fluid and ephedrine were administered

as appropriate to maintain systolic blood pressure more than 80% of baseline. After testing for satisfactory sensory block, surgery was performed in the usual way.

Postoperative period

The patients were assessed by the nurse who had no knowledge of which treatment the patient had received. Metoclopramide 10 mg IM was given as rescue anti-emetic drug at the patient' s request. The occurrence of nausea and vomiting was observed at intraoperative period , 0-6 h and 6-24 h. Retching was considered vomiting but regurgitation was not. Severity of nausea was assessed by 4-point rating scale. Emetic episode per person, rescue anti-emetic requirement, time to first rescue anti-emetic, and any adverse effect were recorded.

The patients were evaluated of having pruritus by using 4-point rating scale and pain intensity using visual analogue scale. Chlorpheniramine 10 mg IM or Acetaminophen 1g orally were given when patient requested for pruritus or pain, respectively. Requirement of anti-pruritus and analgesic drug were also recorded.

3.12 Outcome measurement

Baseline variables

- Demographic data: age, sex, weight, height, ASA physical status
- Incidence of intraoperative hypotension
- Duration of surgery

Primary outcome variable

The primary outcome variable was the number of patients who had postoperative nausea and/or vomiting (PONV) in the first 24 hours. This was defined as presence either any emetic episode or nausea throughout the observation period.

Secondary outcome variables

- The incidence of nausea and vomiting separately at intraoperative period , 0-6 h, and 6-24 h to compare the incidence during early and late period.
- Severity of nausea (four- point rating scale)(23, 24)
  - 0= no nausea
  - 1= mild nausea
  - 2= moderate nausea
  - 3= severe nausea
- Emetic episode per patient was recorded as the number of episodes that the patient ,who suffered from vomiting , had vomited
- Requirement of rescue anti-emetic was recorded as the number of patients who required rescue anti-emetic
- Time to first rescue anti-emetic was recorded as the duration from the induction of anesthesia to the first time that the patient asked for the rescue anti-emetic
- Pain intensity using VAS
- Requirement of analgesic was recorded as the number of patients who required analgesic
- Pruritus score (four- point rating scale)(55)
  - 0= no pruritus
  - 1= mild pruritus
  - 2= moderate pruritus
  - 3= severe pruritus
- Requirement of anti-pruritus was recorded as the number of patients who required anti-pruritus
- Incidence of any adverse effects

Since there were some studies reported the analgesic and antihistamine effects of ginger, the data about pain and pruritus was also recorded.

3.13 Data collection and analysis

The data was collected in a data record form by a nurse who was blinded to investigational agents. All data was analyzed as intention-to-treat basis. Demographic and baseline continuous variables such as age, weight, height were presented as mean (SD). For categorical baseline variables such as sex, ASA physical status, incidence of intraoperative hypotension were presented as proportion. These aimed to compare if the two groups were similar regarding the baseline characteristics.

The primary outcome was proportion of subjects who had PONV. Comparison between two groups was performed using Z- test. Absolute risk reduction and number needed to treat with 95% CI were calculated. Secondary binary outcomes including the incidence of PONV, nausea, and vomiting separately at different period, requirement of anti-emetic, anti-pruritus, and analgesic were analyzed in a similar way as for the primary outcome. The secondary outcomes that were ordinal variables were compared between two groups by using chi-square test for trend. VAS, emetic episode per patient , which were continuous data , was presented as mean and SD , if they were normally distributed, if not , the median (range) was used, and evaluated with unpaired t-test or Mann-Whitney U test. Time to first anti-emetic was analyzed by survival analysis. P values < 0.05 was considered statistically significant . SPSS version 11.0 program was used for data analysis.

3.14 Limitation

1. Rating of pain intensity (VAS), severity of nausea and pruritus needs patient's cooperation and understanding. The patients were explained how to rate before the beginning of the study.

2. The quantity of active ingredients may be varied by geographic origin and degree of maturity when harvested. To minimize this problem, the ginger was harvested at the same origin, same time of harvesting and maturity . The sampled

ginger capsules were tested by the quantitative and qualitative analysis to make sure that they were nearly equal amounts of ingredients or in acceptable difference.

3.15 Ethical consideration

The proposal was reviewed by the ethical committee of BMA. The study was conducted after written consent from the committee and patients were obtained. The patients could withdraw from the study at any time without any interference on their further standard treatment. All the data was used for study purpose only and was confidential. During the study, all equipments for resuscitation were prepared. Any adverse effects that might occur was treated until recovery.

This study was designed to prevent the adverse effect. The intervention should provide benefit more than harm. The rescue anti-emetic was ready as soon as it was required. No evidence exists that treatment of established PONV is less efficacious than prevention. In addition, the gold standard anti-emetic intervention for PONV prophylaxis is yet unknown. Therefore, it should not be unethical to give placebo in the control group.