CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research question

Does senna compound have the same efficacy as oral sodium phosphate solution in bowel preparation before colonoscopy in adult Thai people?

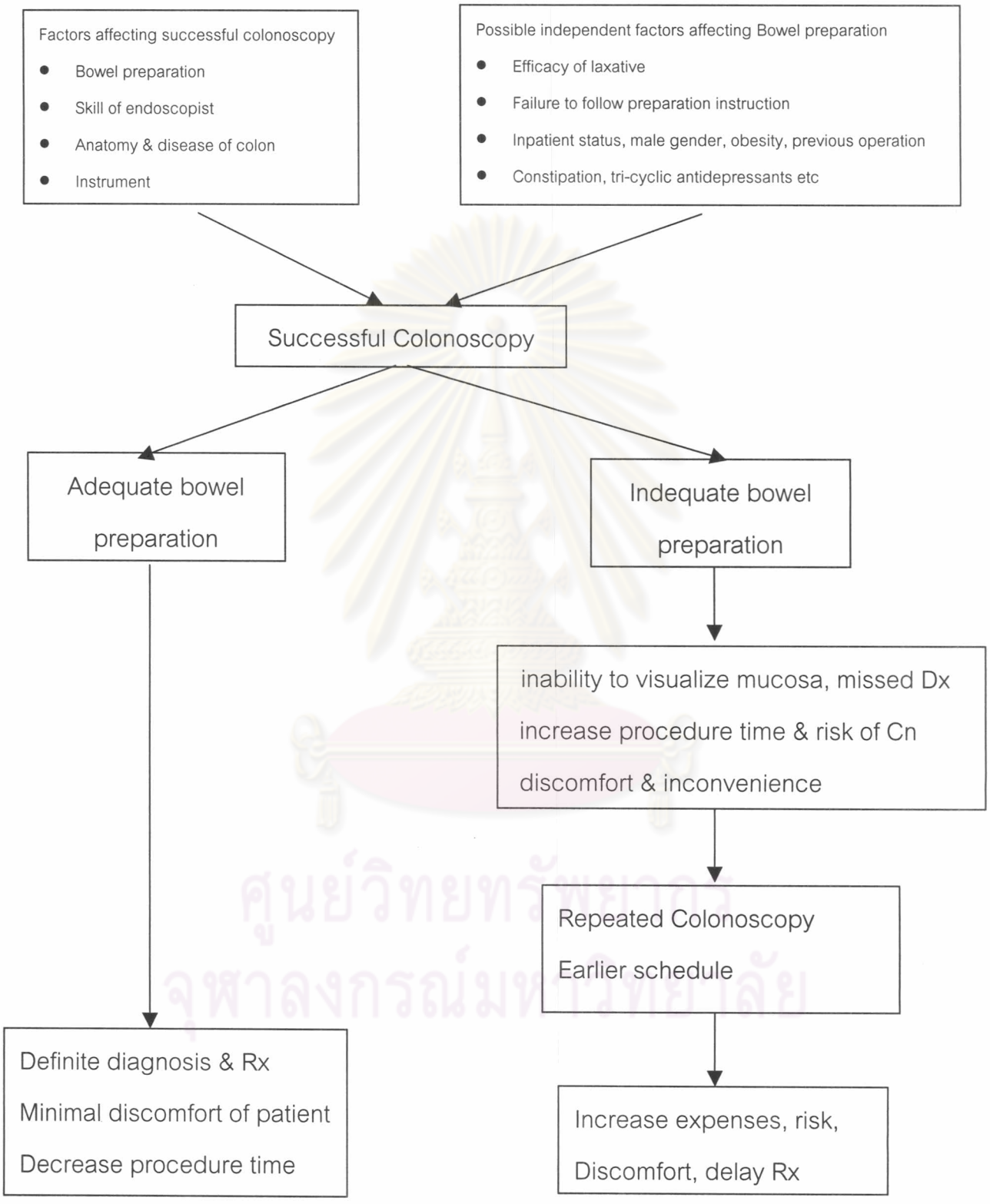
3.2 Research objective

To find the effective laxative that is cheaper, easier to administer and less side effect for bowel preparation before colonoscopy.

3.3 Hypothesis

Senna compound is effective and safe in bowel preparation before colonoscopy in adult Thai people.

3.4 Conceptual framework



3.5 Keywords

Bowel preparation, bowel cleansing, gut irrigation, large bowel preparation, colonic lavage, senna, colonoscopy , equivalence trial

3.6 Operational definition

Bowel preparation (or bowel cleansing) : is the method to empty the colon of all solid and some liquid feces to facilitate the process of colonoscopy. Bowel preparation may consist of low residual diet intake before colonoscopy, laxative drug(s) and/or enema.

Colonoscopy : is the way to examine directly the colonic lesion. Endoscope is inserted via anus into the lumen of colon up to cecum or terminal ileum. Therapeutic procedure of colonoscopy includes polypectomy, hemostasis, dilatation with or without stent placement, tumor ablation etc.

3.7 Research design

The study will be carried out as a randomized, controlled (equivalent) trial which the influence of confounding variables is well controlled. The randomization process will ensure that the allocation of treatment is independent of the characteristics of the patients. The blind process is applied to investigators, patients and outcome assessors.

3.8 Research Method

Target population

Adult patient who need elective colonoscopy and fulfill the inclusion and exclusion criteria.

Study population

Adult patients who attend General Surgery Clinic at Ramathibodi Hospital and agreed to participate and giving informed consent.

Inclusion criteria

1. Age of 15 or older
2. Patients who have symptoms of chronic diarrhea, mucus bloody stool, bowel habit change, lower gastro-intestinal hemorrhage, abdominal pain, cancer surveillance and abnormal findings from barium enema.
3. Patient who has given written informed consent prior to participation in the trial and who undertake to comply with protocol.
4. If female, patient is not pregnant or is not of childbearing potential but using approved method of contraception.
5. Patient who is not judged by the investigator as unfit for admission into the study due to physical or other factors.

Exclusion criteria

1. Patient who are contraindicated for colonoscopy for example, peritonitis, acute colonic obstruction and severe ascites etc.
2. Patient who ever had colonic resection before.
3. Emergency colonoscopy
4. Known allergy to senna, sodium phosphate solution
5. Presence of severe metabolic, renal and cardiac conditions
6. Bed-ridden patient and psychotic patient
7. Patient is taking laxative within 1 week prior to enrollment.

3.9 Sample size

The main outcome variable is the cleanliness of colon (no solid or liquid feces in the lumen of colon) which is recorded as Visual Analog Scale.

We assume that subjects are randomized into two treatment groups of equal size n, the groups being denoted by R (reference treatment or sodium phosphate group) and T (test treatment or senna group). Let μR and μT denoted the expected mean values of the normally distributed observations for group R and T, respectively, and let s^2 be a variance of the observations, assumed the same in the two groups.

The sample size calculation is based on testing equivalence of two treatments. The null hypothesis is that the standard treatment is more effective than the experimental treatment by at least some specified amount (range of equivalence or equivalence margin = $-\delta$ and $+\delta$). Rohmel[36] stated that equivalence margin (1) cannot be zero (2) has to be determined in advanced of the study and must not be a *post hoc* decision (3) should be smallest as possible (4) in contrast to bioequivalence study, there are no generally accepted margins for equivalence. In this study the equivalence margin equal to -1 and +1 are chosen because this margin value did not have clinically significant.

When the confidence interval approach is used to assess equivalence, two sorts of mistake can occur: we can decide that the treatments are equivalent when they are not (the type I error) or we can decide that the treatments are not equivalent when they are (the type II error).

The sample size for a 95% two-sided interval is as followed

The Null hypothesis is H_0 : $\mu R - \mu T \geq \delta, \delta > 0$ (Difference)

The alternative hypothesis H_a : $-\delta < \mu R - \mu T < \delta$) (Equivalence)

δ = difference to claim equivalence (=1)

α = (1-0.95)/2 ; Z(1- α) = Z(0.975) = 1.96

power = 0.8 ; Z(1-β/2) = Z(0.90) = 1.28

N/group = $2s^2 / \delta^2 (Z(1-\alpha) + Z(1-\beta/2))^2$ [37]

From our pilot study which NaP solution are used as laxative, the variance of VAS score in rectum of 10 patients is 2.93

N/group = $2*(2.93)^2 / (1)^2 (1.96+1.28)^2$

= 61 patients => 68 patients (Dropout 10 %)

3.10 Randomization

In this trial, the patients are allocated into two group :

Experimental group: Senokot® 300 mg. (12 capsules)

Control group: Sodium phosphate solution (90 ml.)

Sodium phosphate solution, senna compound and dummy are supplied from the pharmaceutical company. Drug and dummy in each group are enclosed in sealed package and send to statistician for allocation using software STATA-7. The statistician allocated drug into group A or B, sealed the package with running number and kept the controlled sheet until the end of the study. A data manager at a secretariat office of the Department of Surgery keeps drugs.

After the participants signed the consent, the research assistant telephoned to the secretariat office and asked for package of drug. The drug will consecutively dispense on running number. The assistant investigator record the name, study number of new participants and other baseline characteristics in part I of case record form.

The code will be broken in the following situations:

1. When there are serious adverse effects or side effects of the laxative that is judged by investigator.
2. When there are serious complications of colonoscopy causing by inadequate bowel preparation.
3. in the end of the study

3.11 Intervention

Before enrollment, the patients are informed about the risk and benefit of colonoscopy and laxatives. After the patients signed the consent, they are advised about bowel preparation process. All patients are asked to have low residue diet for 2 days before colonoscopy. The day before colonoscopy, the patients take laxatives at 2.00 p.m. and 4.00 p.m.; drink water or electrolyte solution at least 1 liter, then fast after-midnight.

All patients are interrogated before each colonoscopy by assistant investigator who is blind to treatment. They are questioned about such side effects, compliance, acceptance and adverse effects of laxatives. Then the clinician will take physical examination and laboratory assessment before colonoscopy. Colonoscopy is performed under intravenous anesthesia or conscious sedation up to patient or clinician preference. During colonoscopy, polypectomy or biopsy may be done according to clinical indication. Colonoscopic procedure will be recorded with videotape for re-assess if necessary.

After colonoscopy, the patients are kept in recovery room for two hours. They are assessed about complication or any adverse reaction. The end of this trial is the time when they were discharged home.

3.12 Outcome measurement

To evaluate the efficacy of laxatives for bowel preparation before colonoscopy, most previous studies use the categorical scale as judged by single colonoscopist as follow:

- 1 (Excellent) negligible amounts of liquid stools, little suction required
- 2 (Good) moderate amounts of liquid stools but easily cleared by suction
- 3 (Fair) large amounts of liquid stools and/or small amounts of solid stools, limited to cecum and ascending colon
- 4 (Poor) solid stools beyond the cecum and ascending colon

Grade 1 and 2 are summarized as adequacy of bowel preparation while grade 3 and 4 are summarized as inadequacy of bowel preparation. This categorical model is not appropriate for level of measurement because the cleanliness is a matter of degree and no clear dividing line. There are more problem concerning about categorical model such as (1) potential loss of information and a corresponding reduction in reliability (2) loss of efficiency of the instrument.[38]

To minimize the error of measurement, our research study develops a new method of measurement using adjectival scales. This scale with continuous responses bears close resemblance to the VAS (visual analog scale), with the adjective descriptions as figure 1 below:

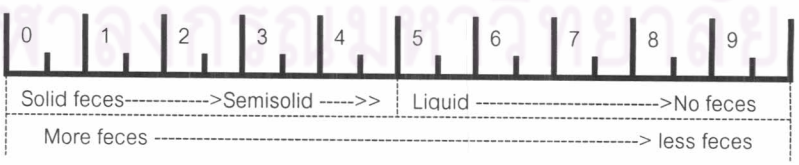


Figure 1: VAS colon-cleanliness score

Since colon & rectum could be divided in 5 parts (cecum & ascending colon, transverse colon, descending colon, sigmoid colon and rectum) in which feces could be dispersed unequally in each particular segment of colon. The solid feces usually occupied in the rectum and sigmoid colon and it is the cause of incomplete colonoscopy, while the liquid feces occupied the cecum. The transverse colon and descending colon did not have many feces or did have small amount of liquid feces.

Using this scale, all of the segments of colon `will be rated and scored by two observers (investigator and assistant) during procedure. Score of each segment will be used later for statistical test. Score over seven is clinically judged as adequacy (or efficacy) of bowel preparation. To estimate the degree of agreement between two raters, we judged that two raters should not rated 2 points far apart. Also we expect most of the difference will lie between $di - 2s$ and $di + 2s$, where di is mean difference and s is standard deviation of the differences.

From our pilot study, the variance score of rectum was 2.93. We use the variance of the rectum because this part of colon is clinically important which determined the successfulness of the procedure. The other reason is that it is the highest value compare with other segment, so the sample size is maximized.

The following variables are measured:

3.12.1 Dermographic and baseline variables

Sex, age, gender, body weight, smoking habit, alcohol drinkers, tea and coffee drinkers, constipation habit, laxative users, previous obstretic-gynaecologic surgery, previous colonoscopy, underlying diabetes , indication for colonoscopy and colonoscopic diagnosis.

3.12.2 Outcome variables

- Colon cleanliness score

- Time to reach cecum , colonoscopy time, proportion of complete colonoscopy
- VAS score of acceptance and side effects of laxatives
- Proportion of complication or adverse events

3.13 Data collection

The case record form (Appendix 1) comprised of two parts:

Visit I: Research assistant and clinician at entry site fill demographic data, past history, concomitant medication, vital sign and physical examination. The label number of the medications is filled in the form after the patient received laxatives. Then the patient is scheduled for colonoscopy.

Visit II: Assistant nurse collects Laboratory data, compliance & acceptance, side effects and adverse events of laxative before endoscopy. During colonoscopy, colonoscopist and assistant rated the colon-cleanliness score and other colonoscopic data. Videotape is recorded for re-evaluation if necessary. After colonoscopy, the patient is evaluated for complication of colonoscopy in the recovery room. If any serious adverse event occurred, detailed evaluation is done to identify the relationship with the laxative and severity assessment.

3.14 Data analysis method

Demographic and baseline variables are presented as mean, standard deviation or proportions as appropriate.

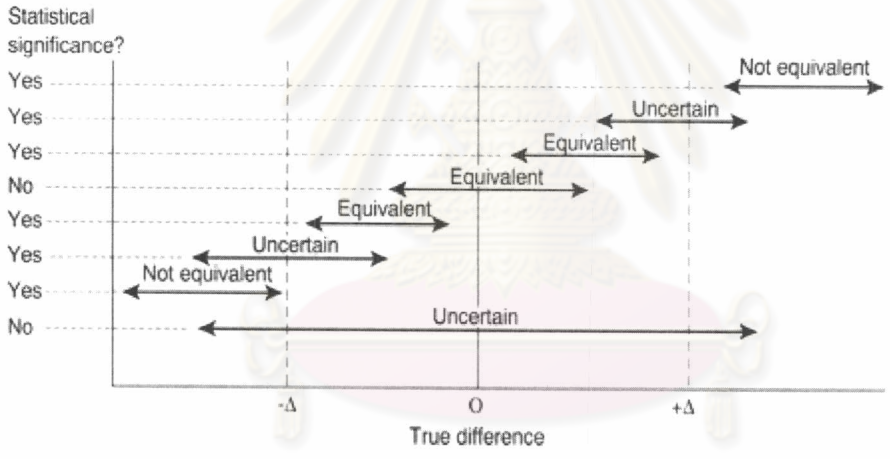
The primary outcome variables are presented as mean, standard deviation and mean difference with 95% confidence interval. The secondary outcome variables also are presented as mean of the VAS score and standard deviation.

Intention to treat analysis and per protocol analysis will be carry out and hope to show equivalence in either case.

The efficacy of laxative drugs for bowel preparation is the equivalent efficacy between senna and NaP solution. If 95 % confidence interval for the mean difference of the score lies entirely within $-\delta$ (-1) and + δ (+1), equivalence is demonstrated as figure 2. If it does not, there is stillroom for doubt. The 95% confidence interval for the true differences ranges from -1.96 SE(d) to +1.96 SE(d) where d denotes mean difference.

Figure 2 Example of Possible results of using the confidence interval approach:

$-\delta$ to $+\delta$ is the pre-specified range of equivalence; the horizontal lines correspond to possible trial outcomes expressed as confidence intervals



3.15 Ethical consideration

The research proposal was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

The potential complication of both laxative drugs and colonoscopy will be explained to the patients in detail before consent. The assistant investigator is available for telephone advice if required. If any complications occur during bowel preparation, they are advised to the hospital immediately. Patients who cancelled their appointment for colonoscopy will be contact by phone and may be reappointment and other bowel regimen is offered. The minor and major complication of colonoscopy will be managed with proper medical equipment and personnel.

As far as the ethical considerations are concerned, the patients will be fairly treated because

- Informed consent is a prerequisite to enter the study and the patients have the right to exit the study at any time.
- The treatment of interest and conventional treatment have no serious harmful effect.
- The treatment of interest has some evidence to be effective.
- Guideline and written instructions will be prepared to prevent and handle complications.
- If the outcome is not satisfactory, the procedure can be repeated with other conventional treatment.

3.16 Limitations

This study was first attempted to be a double-blinded randomized controlled but the laxative and placebo are similar in only external appearance. The taste of placebo solution could not be produce the same taste as sodium phosphate solution. If the patient ever had drink the real sodium phosphate solution before they can differentiate the placebo from the

real one. However most of the patients (118 patients or 88%) did not had colonoscopy before.

There are no standard criteria or score to measure the cleanliness of colon. In addition, there is no standard cut-off point to define the adequacy or efficacy of bowel preparation.

There are many confounding variables that could be affect bowel preparation such as diet, timing of colonscopy, constipation habit, socio-economic status but we assume that these factors may be contribute into both group by unbiased allocation to treatment. We do not perform subgroup analysis because of the sample size are not large enough. We also cannot extend the study or increase the number of patients due to limitation of period and budget.

3.17 Expected Benefit & Application

If the efficacy, compliance and safety of senna has been demonstrated. It may be use as the standard laxative for bowel preparation to reduce cost of colonoscopy. In Ramathibodi hospital, it is estimated that 1,000 colonoscopy are performed annually.

3.18 Obstacles

The assistant nurses are already having numerous workloads so they could not fully participate in this clinical trial. In addition, the floor space and the equipments of colonoscopy are not enough for workload.