CHAPTER 5

DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 Discussion

The aim of this trial is to show the therapeutic equivalence of senna (experimental) and sodium phosphate (controlled) as laxative of bowel preparation before colonoscopy. The rational for study is base on the problems in clinical practice. Sodium phosphate, a standard and high efficacy laxative, has disadvantages in poor taste, poor compliance and electrolyte imbalance while senna has advantage in better taste and lower cost. In addition, it is unethical to compare between senna and placebo.

There are two features, which distinguish equivalence trials from comparative trials. The first feature relates to the statistical methods used for analysis and the consequences for determining the required number of patients. In a comparative trial, the standard analysis uses statistical significances tests to determine whether the null hypothesis of "no difference" may be rejected, together with confidence limits to place bounds on the possible size of the difference between the treatments. In an equivalence trial, the conventional significance test has little relevance. Failure to detect a difference does not imply equivalence; a difference, which is detected, may not have any clinical relevance and may respond to practical equivalence. The confidence interval defines a range for the possible true difference between the treatments but have no clinical importance then the treatments may be considered equivalent. In this study, we have predefined a range of equivalence as interval from -1 to +1 and then we check whether the confidence interval of the mean difference, measured by colon-cleanliness score, lies entirely between -1 and +1 in all segments of colon. Most of the previous studies rated the cleanliness of colon as the whole segment; in

contrast, we rated the five segments of colon to get the more detail information since the feces are distributed unequally in each segment of colon.

The second feature affecting the equivalence trial is the lack of internal check on its validity. The finding in a trial that two treatments are equivalent does not require that both treatments are effective. Therefore, it is pre-specified that the mean score should lie above seven to assure that both laxatives are effective.

The most difficult issue relating to the analysis of an equivalence trial concerns which patients and which data from these patients to include. The most common approaches to the analysis of randomized trials are "intention to treat" and "per protocol" analyses.

Intention to treat analysis is the practice of attributing all participants to the group to which they were randomized, regardless of what subsequently occulted. It avoids the problems created by omitting dropouts and noncompliant patients, which can negate randomization, introduce bias, and overestimate clinical effectiveness.

The purpose of using different ways of analysis, whatever its name is to answer different research questions or different clinical situations.

In per protocol analysis, the efficacy of both laxatives is evaluated in ideal clinical settings that compliance is perfect, both laxatives have no side effects and colonoscopy could be passed completely up to cecum.

In per-protocol analysis (Table 6.1), the confidence interval for the differences of all segments of colon are lie entirely within the equivalence margin (-1 to +1) so that equivalence between two laxatives may be concluded with only a small probability of error.

In Intention-to-treat analysis, we excluded two patients who did not receive laxatives because the timing of allocation is started when the patients take laxatives and this situation could not happen in real clinical practice. In this study, the missing data in both groups are occurred because of lost follow-up in three patients, incomplete colonoscopy in 9 patients and score is not rated in one patient. No consensus exists about how missing responses should be handled. Sally[41] suggested different approaches for different situation. For

patients who lost follow-up or did not attend colonoscopy we assign zero score in all segments of colon while patients who had incomplete colonoscopy we assign score of unrated segments (segments that colonoscope could not passed up to) in different ways as follow:

1.) ITT-1 analysis, we assign average score of unrated proximal segment in both groups. (Table 6.2 - "carry forward" analysis), assuming that the unrated proximal segments have the same colon-cleanliness score as the rated distal segments.

2) ITT-2 analysis, we assign zero score of unrated proximal segment in both groups (Table 6.3 – "moderate case" analysis), assuming that the unrated proximal segment have lower colon-cleanliness score than rated distal segments.

3) ITT-3 analysis, we assign zero score of unrated proximal segments in experimental group, average score of unrated proximal segments in controlled group (Table 6.4 – "extreme case" analysis)

Table 6.2 show that the confidence interval of difference are lie within the equivalence range in three segments of colon (rectum, transverse and ascending colon) but it did not in other two segments of colon. However, in Table 6.3 and Table 6.4, the confidence intervals are lie within equivalence margin in two and one segment of colon respectively. Not all segments of colon that the confidence interval of difference is within equivalence margin whatever the situations or type of ITT analysis are. Therefore, we believed that differences of efficacy remain a real possibility and equivalence cannot safely be concluded. When the confidence interval of difference are determined, the efficacy of senna tend to be lower than sodium phosphate solution but the mean value in both groups are above 7. We concluded that senna have no immediate advantage but should be considered to be alternative or second line laxatives for bowel preparation in colonoscopy.

It was noticed that the colon cleanliness score in the cecum segment of experimental group appear to be better than the controlled group. This phenomenon may be cause by the timing of laxative intake. Church[42] stated that patients who take laxatives five hours before

colonoscopy had better result than patients who take laxative one day before colonoscopy. In our study, the patients take laxative one day before colonoscopy and the action of senna may be longer than sodium phosphate solution.

Another problem arises from this equivalence trial. How "small" the magnitude of equivalence margin should be? Greene[43] stated that there is no "gold standard" criterion for what should be the smallest margin but they propose the differences can be standardized as an "effect size". It is calculated as the direct increment between groups divided by the standard deviation in the control group. In addition, an effect size less than 0.2 has often been considered small, 0.5 has been considered moderate, and 0.8 has been considered large.

Table 9 : The effect size of equivalence margin from Intention to treat analysis

Segment of Colon	ITT-1 analysis	ITT-2 analysis	ITT-3 analysis
Rectum	0.13	0.13	0.13
Sigmoid Colon	0.16	0.09	0.16
Descending Colon	0.1	0.06	0.28
Transverse Colon	0.08	0.10	0.13
Ascending Colon & Cecum	0.41	0.40	0.18

Table 9 demonstrated that most of the effect size is less than 0.2 that is considered small. It was assured that the selected equivalence margin of this trial (-1 to +1) are small enough for statistical purpose. Besides the direct quantitative comparison of numbers, decision about importance involves considerations of clinical severity impact.

In this trial, the risk of complication or adverse event (Table 7), detection rate for any disease (34.3% experimental group VS 35.8% controlled group), colonoscopy time and rate

of incomplete colonoscopy (Table3) are not different. We judged that these equivalence margins are small enough for clinical purpose.

From Table 7, the VAS score of taste, likeliness and nausea &vomiting symptom in experimental group are significantly different from controlled group. This confirm our rational background that senna is more palatability but less side effect than sodium phosphate solution. In testing the difference, we use P value because we did not pre-specified the boundary limit for confidence interval and this outcome variables are not the primary outcome. Four patients had adverse events that are not related to laxatives.

5.2 Conclusion

There is no strong evidence to confirm that senna has the same efficacy as oral sodium phosphate solution in bowel preparation before colonoscopy in Thai people although senna has fewer side effect and better compliance.

5.3 Recommendation

Senna has no immediate advantage but it should be consider the alternative or second line laxatives for bowel preparation in colonoscopy.