CHAPTER 4

RESULTS

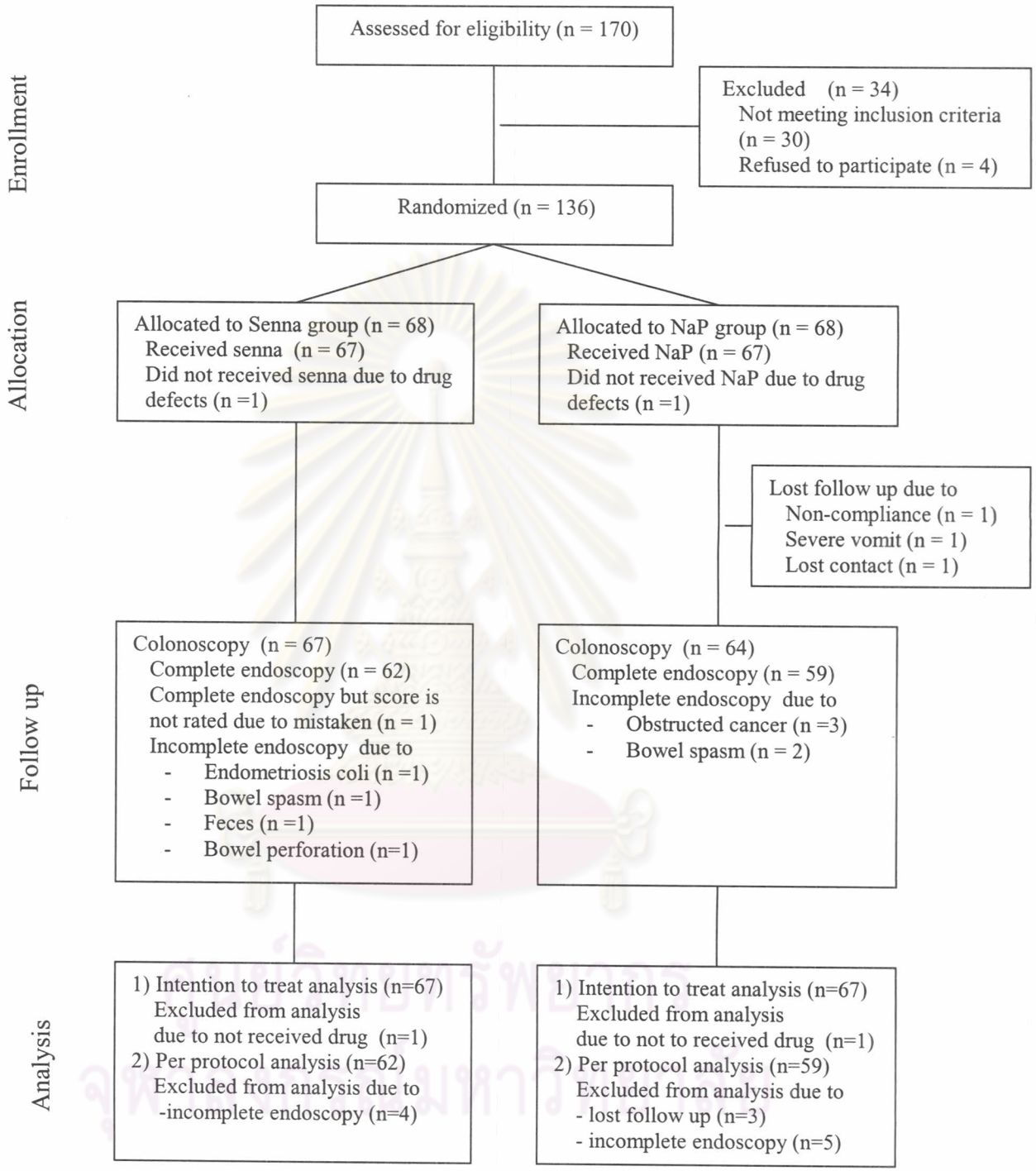
4.1 Participant flow and recruitment

From June to November 2002, one hundred and seventy patients are referred for colonoscopy at Department of Surgery, Ramathibodi hospital (Figure3)[39]. Thirty patients are excluded because they do not meet inclusion criteria such as previous colonic resection, massive bleeding, obstruction and unfit for study. Four patients refuse to participate because of economic reason and fear of complication from colonoscopy.

One hundred and thirty six patients are randomly allocated to senna group (experimental group) and sodium phosphate group (controlled group). Two patients (1.5%) were deviated from allocation because they did not receive laxatives due to error in drug packing. Three patients (2.2%) in controlled group do not attend colonoscopy. Among patients who attend colonoscopy, nine patients (7.3%) have missing data due to incomplete colonoscopy and one patient has missing data due to mistaken in data recording. No false inclusion is occurred in this trial.

At the end of the study, one hundred and thirty four patients are analyzed as intention-to-treat analysis and 121 patients are analyzed as per protocol analysis.

Figure 3 : Flow Diagram of Patients Progress Through the Phases of a Randomized Trial



4.2 Demographic and Baseline Data

The demographic and baseline data are shown in Table 1. The characteristics of the patients, colonoscopic indication and diagnosis are matched in both groups of the patients. However, it is noticed that controlled group has higher proportion in constipation, laxative users and tea drinkers.

Table 1: Demographic Data of 134 Patients

Characteristic	Senna (N = 67)	NaP (N = 67)
Sex (M:F)	22 : 45	30 : 37
Age (Mean,S.D.)	54.3 (12.7)	51.6 (12.6)
Body wt. (kg.)(Mean,S.D.)	59.1(10.7)	61.8(12.6)
Smoke habit (Yes : No)	11 : 56	5 : 62
Alcohol (Yes : No)	14 : 53	13 : 54
Tea (Yes : No)	24 : 43	35 : 32
Coffee (Yes : No)	40 : 27	40 :27
OPD : IPD patient	65 : 2	65 : 2
Constipation (Yes : No)	9 : 58	14 : 53
Laxative users (Yes : No)	6 : 61	12 : 55
Previous Obs-gyn surgery	6 : 61	7 : 60
Previous colonoscopy	5 : 62	11 : 56
Diabetes (Yes : No)	7 : 60	6 : 61

Table 2 show that the indication for colonoscopy in both group are similar except the patients in controlled group had higher proportion of bleeding per rectum, but this indication has no effect on bowel preparation and colonoscopy.

Table 2: Indication for Colonoscopy

Indication for Colonoscopy	Senna (N = 67)	NaP (N = 64)
Bleeding per rectum	26 (39.4%)	31 (48.4%)
Lower abdominal pain	10 (14.9%)	10 (15.6%)
Mucus stool	9 (13.6%)	4 (6.3%)
Cancer surveillance	7 (10.6)	6 (9.4%)
Bowel habit changed	6 (9.1%)	8 (12.5%)
Abnormal Barium enema	3 (4.5%)	1 (1.6%)
Follow-up post polypectomy	2 (3.0%)	1 (1.6%)
Chronic diarrhea	2 (3.0%)	0
Other indication	2 (3.0%)	3 (4.7%)

Table 3 show that the colonoscopic diagnosis are matched in both group. The detection rates of pathologic lesion are 34.3% and 35.8% in experimental and controlled group respectively. Both laxatives have no effect on time to reach cecum, colonoscopy time and rate of incomplete colonoscopy.

Table 3: Colonoscopic Data

	Senna (N = 67)	NaP (N = 64)
Colonoscopic diagnosis		
1. Normal study	44(65.7%)	40 (62.5%)
2. Polyp	8 (12.1%)	4 (6.2%)
3. Diverticulosis	4 (6.0%)	8 (12.5%)
4. Carcinoma	4 (6.0%)	6 (9.3%)
5. Inflammatory bowel disease	6 (9.0%)	3 (4.6%)
6. Other	1 (1.5%)	3 (4.6%)
Time to reach cecum (Mean,S.D.)	12.8 (8.8)	12.6 (6.4)
Incomplete colonoscopy	4 (6.0%)	5 (7.8 %)
Time of colonoscopy (Mean,S.D.)	19.3 (14.2)	18.2 (10.1)
Therapeutic : Diagnostic colonoscopy	16 : 51	14 : 50

Table 4 show the cause of incomplete of colonoscopy. In experimental group, one patient (study no.18) had incomplete colonoscopy due to inadequacy of bowel prep. Other causes of obstruction do not relate with bowel preparation.

Table 4: Cause of Incomplete Colonoscopy and Site of Obstruction

Study No.	Study Group	Sex	Age	Indication for Colonoscopy	Cause	Site
75	E*	F	35	Bleeding per rectum	Endometriosis coli	Sigmoid
86	E	F	49	Abdominal pain	Bowel perforation	Desc.colon
101	E	F	23	Bleeding per rectum	Bowel spasm	Sigmoid
118	E	F	77	Bleeding per rectum	Numerous feces	Desc.colon
18	C**	F	47	Abdominal pain	Carcinoma	Sigmoid
22	C	M	45	Mucus bloody stool	Carcinoma	Asc.colon
42	C	F	83	Bleeding per rectum	Carcinoma	Rectum
104	C	F	57	Abdominal pain	Bowel spasm	Sigmoid
120	C	F	43	Bleeding per rectum	Bowel spasm	Desc.colon

E *= Experimental group, C** = Controlled group

Since there are two observers who rated the colon-cleanliness score, it is necessary to see whether they agree sufficiently before data analysis. The best approach, recommended by Altman[40], was to calculate 95 % limit of agreement as shown in Table 5 below. The 95 % limit of agreement lies between d – 2 S.D. and d + 2 S.D. , if the differences are normally distributed, where d denotes the mean difference of the score in each patient rated by two observers.

Table 5: Agreement of Rating Colon Cleanliness Score between Two Observers

	Difference (d) Average	S.D. of the Differences	95 % Limit of Agreement
Rectum	0.004	0.779	-1.523 to 1.531
Sigmoid Colon	0.022	0.704	-1.402 to 1.435
Descending Colon	0.138	0.661	-1.158 to 1.435
Transverse Colon	0.168	0.758	-1.318 to1.654
Ascending Colon & Cecum	0.022	0.691	-1.331 to 1.376

From Table 5, there are minimal differences between two raters in each segment of colon. It is judged by colonoscopists that the differences score should lay within 2 points and the 95 % limit of agreement in all segments of colon are lower than 2 points. Then, we judged that the colon-cleanliness-scores, rated by two observers, are agreed sufficiently and can be used for further analysis.

4.3 Numbers analyzed

Before study, the sample size was estimated about 136 patients with 10% dropped out. From Figure 1, 134 patients are analyzed as intention-to-treat analysis; we excluded two patients who did not receive laxatives due to error in package. This is because the timing of allocation is started when the patients take laxatives and this event cannot occur in clinical practice.

Three patients (2.2%) are non-compliance to attend colonoscopy and 10 patients (7.3%) had missing data due to incomplete colonoscopy and data-recording error. So, 121 patients are analyzed as per protocol analysis.

4.4 Primary outcome analysis

The efficacy of laxative in bowel preparation before colonoscopy are measured by colon cleanliness score as shown in Table 6.1-Table 6.4. The score of any segment is the average score of two observers.

Table 6.1: Colon Cleanliness Score of 121 patients (Per Protocol Analysis)

Segment of Colon	Senna (N = 62) Mean(S.D.)	NaP (N = 59) Mean(S.D.)	Mean Difference	95 % CI of Differences
Rectum	8.12 (1.08)	8.53 (0.93)	-0.41	-0.07 to -0.75
Sigmoid Colon	8.35 (1.20)	8.61 (0.77)	-0.26	0.08 to -0.61
Descending Colon	8.45 (0.97)	8.61 (0.69)	-0.16	0.12 to -0.45
Transverse Colon	8.36 (0.99)	8.42 (0.78)	-0.06	0.25 to -0.36
Ascending Colon & Cecum	7.41 (0.84)	7.12 (0.83)	0.29	0.57 to 0.01

For per protocol analysis strategy (Table 6.1), the mean score of four segments of colon in controlled group are slightly better than experimental group but the difference of mean score in all segments are lie within the pre-specified range -1 to +1.

For intention-to-treat analysis, sensitivity analysis is performed for missing data in three way as "carry forward " (Table 6.2), "moderate case" (Table 6.3) and "extreme case" (Table 6.4)

Table 6.2: ITT-1 Analysis of Colon Cleanliness Score

Segment of Colon	Senna (N= 67) Mean(S.D.)	NaP (N = 67) Mean(S.D.)	Mean Difference	95 % CI of Differences
Rectum	7.86 (1.84)	8.15 (2.15)	- 0.29	- 0.97 to 0.39
Sigmoid Colon	8.01 (1.96)	8.34 (2.06)	- 0.33	- 1.01 to 0.35
Descending Colon	8.11 (1.75)	8.31 (2.03)	- 0.21	- 0.85 to 0.43
Transverse Colon	8.16 (1.68)	8.00 (2.05)	0.16	- 0.47 to 0.79
Ascending Colon & Cecum	7.46 (1.40)	6.69 (1.88)	0.77	0.21 to 1.33

Table 6.3: ITT-2 Analysis of Colon Cleanliness Score

Segment of Colon	Senna (N= 67) Mean(S.D.)	NaP (N = 67) Mean(S.D.)	Mean Difference	95 % CI of Differences
Rectum	7.86 (1.84)	8.15 (2.15)	- 0.29	- 0.97 to 0.39
Sigmoid Colon	8.01 (1.96)	8.21 (2.29)	- 0.20	- 0.92 to 0.52
Descending Colon	7.77 (2.40)	7.94 (2.65)	- 0.17	- 1.02 to 0.69
Transverse Colon	7.77 (2.49)	7.49 (2.77)	0.28	- 0.61 to 1.17
Ascending Colon & Cecum	7.06 (2.19)	6.06 (2.49)	1.00	0.21 to 1.79

Table 6.4: ITT-3 Analysis of Colon Cleanliness Score

Segment of Colon	Senna (N= 67) Mean(S.D.)	NaP (N = 67) Mean(S.D.)	Mean Difference	95 % CI of Differences
Rectum	7.86 (1.84)	8.15 (2.15)	- 0.29	- 0.97 to 0.39
Sigmoid Colon	8.01 (1.96)	8.34 (2.06)	- 0.33	- 1.01 to 0.35
Descending Colon	7.77 (2.40)	8.34 (2.02)	- 0.57	- 1.33 to 0.18
Transverse Colon	7.77 (2.49)	8.04 (2.04)	- 0.27	- 1.04 to 0.50
Ascending Colon & Cecum	7.06 (2.19)	6.72 (1.9)	0.34	- 0.36 to 1.03

4.5 Secondary outcome analysis

The acceptance and side effects of both drugs are measured by visual analog score as shown in Table 7. For the taste score and likeliness score, the higher score are the better taste and the more likeliness. For the side effects score, the higher are the worse symptom. Since the boundary limit of the difference in these secondary outcome are not defined before the study so P value are demonstrated instead of 95 % CI.

Table 7 : Acceptance and Side Effects of Laxatives

	Senna (N = 67)	NaP (N = 67)	P value
Acceptance (Mean,S.D.)			
Taste score	8.6 (1.9)	5.1 (2.8)	<0.001
Likeliness	8.3 (2.0)	5.7 (2.9)	<0.001
Side effects (Mean,S.D.)			
Nausea & Vomitting	0.9 (0.2)	3.0 (3.5)	<0.001
Abdominal pain	1.3 (2.3)	1.4 (2.4)	0.80
Vertigo	0.7 (1.6)	1.3 (2.3)	0.08
Sleeplessness	1.2 (2.7)	1.4 (2.5)	0.65
Adverse event	2 : 67	2 : 64	

From Table 7, there are two adverse events, each occurred in both group. In experimental group, one patient had post-polypectomy bleeding which prolonged procedure and required admission. Another patient had iatrogenic perforation from colonoscopic procedure due to fixation of sigmoid colon. Her cleanliness score in rectum and sigmoid are 9.5 and 10, so the perforation is not related to bowel preparation. She had long-term steroid for underlying myasthenia gravis and had previous left hip surgery. After perforation, explor laparotomy was done immediately and diverting colostomy was performed. She recovers uneventfully in one week. Two patients in controlled group develop bronchospasm during colonscopy from general anesthesia. Both of them are admitted for observation and discharged after 24 hours later.