

CHAPTER IV

RESULTS

4.1 Characteristics of Patients and Baseline Data

A total of 96 patients who were scheduled for transurethral prostatectomy were enrolled in this study. They were randomly and equally allocated into four groups. The patients' demographic data and operation information are shown in Table 5. There were no statistical differences in all variables between the four treatment groups. Most of the patients had acquired their analgesic level at the 10th thoracic dermatomes.

Table 5 Patient baseline characteristics by treatment group

	Mean \pm SD (Min - Max)				p-value
	Placebo (n=24)	Etoricoxib (n=24)	Flavoxate (n=24)	Combined (n=24)	
Age (yrs)	69.1 \pm 6.3 (60 - 85)	69.5 \pm 6.8 (58 - 83)	71.5 \pm 7.1 (57 - 81)	67.3 \pm 8.2 (50 - 86)	0.245
Body weight (kg)	64.2 \pm 9.1 (50 - 83)	61.8 \pm 8.9 (50 - 81.5)	67.0 \pm 11.3 (50 - 89)	64.7 \pm 10.2 (50 - 81)	0.355
Ht (cm)	163.5 \pm 7.1 (153 - 180)	163.6 \pm 6.1 (149 - 174)	166.1 \pm 6.3 (152 - 180)	163.9 \pm 5.7 (150 - 170)	0.511
ASA (1:2:3)	(3:18:2)	(3:21:0)	(1:20:1)	(6:17:1)	0.346
Premedication (yes: no)	(15:9)	(16:8)	(10:14)	(13:11)	0.314
Anesthetic time (min)	64.6 \pm 28.1 (25 - 120)	68.9 \pm 28.9 (25 - 135)	72.4 \pm 28.6 (45 - 150)	61.3 \pm 19.9 (30 - 100)	0.462
Surgical time (min)	48.2 \pm 25.9 (10 - 95)	50.2 \pm 26.2 (55 - 110)	67.2 \pm 37.0 (20 - 165)	45.2 \pm 21.5 (15 - 100)	0.305
Level of analgesia*	T10 (T2 - T11)	T10 (T5 - T11)	T10 (T6 - T11)	T10 (T6 - T12)	0.462

* Values were median (Max - Min)

4.2 Analysis of Primary Outcome

All patients in the placebo group required postoperative morphine. However, seven patients in the treated group (3 in the combined group, 2 in the etoricoxib and flavoxate groups) did not require any postoperative morphine. Figure 3 displays a box-and-whisker plot of cumulative morphine usage at 3-, 5-, and 24-hour postoperative in all 96 patients by treatment group. It revealed that cumulative morphine usage at each time and also in each treatment group was very positively skewed with outliers and extremes on the top of the box.

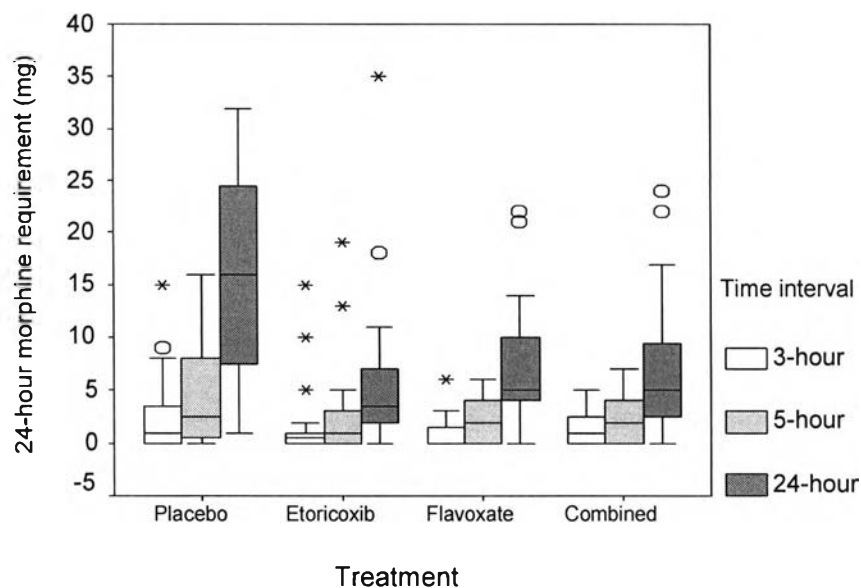


Figure 2 Box plot of total morphine requirement in each treatment group

Table 6 shows descriptive statistics e.g., mean, median, SD and geometric mean (GM) of cumulative postoperative morphine consumption at each hour and in each treatment group. Comparison of the cumulative morphine consumption at each hour between the four treatment groups using Kruskal-Wallis test revealed that there was no statistically significant difference in cumulative morphine usage at 3- and 5-hour postoperatively between the four treatment groups ($p=0.491$, 0.321 respectively). However, there was a statistically significant difference in total morphine usage at

24-hour between four treatment groups ($p < 0.001$). The median 24-hour total morphine consumption in the placebo group was much higher than that in the other three treated group (16 vs. 4.5, 5.0 and 5.0). Further pairwise comparisons using a Mann-Whitney test demonstrated a statistically significant difference in 24-hour morphine consumption only between the placebo and each treated group (Table 7). There were no difference in the 24-hour morphine doses between etoricoxib alone and flavoxate alone ($p=0.459$), between etoricoxib alone and the combined group ($p=0.368$) and between flavoxate alone and the combined group ($p=0.543$).

Table 6 Cumulative dose of PCA morphine usage (mg) in each treatment group

Postoperative time interval		Placebo (n=24)	Etoricoxib (n=24)	Flavoxate (n=24)	Combined (n=24)	p-value (2-sided)
3-hour	Mean \pm SD	2.5 \pm 3.8	1.5 \pm 3.5	1.0 \pm 1.5	1.5 \pm 1.7	0.491
	Median	1	0.5	0.5	1	
	GM	0.00	0.00	0.00	0.00	
	Min - Max	(0 - 15)	(0 - 15)	(0 - 6)	(0 - 5)	
5-hour	Mean \pm SD	4.3 \pm 4.7	2.4 \pm 4.4	2.3 \pm 2.1	2.3 \pm 2.4	0.321
	Median	2.5	1.0	2.0	2.0	
	GM	0.00	0.00	0.00	0.00	
	Min - Max	(0 - 16)	(0 - 19)	(0 - 6)	(0 - 7)	
24-hour	Mean \pm SD	16.1 \pm 9.3	6.0 \pm 7.4	7.46 \pm 5.7	6.9 \pm 6.5	<0.001
	Median	16	4.5	5.0	5.0	
	GM	12.02	0.00	0.00	0.00	
	Min - Max	(1 - 32)	(0 - 32)	(0 - 22)	(0 - 24)	

Table 7 Pairwise comparisons of 24-hour morphine usage between four groups

	p-value		
	Etoricoxib	Flavoxate	Etoricoxib and flavoxate
Placebo	<0.001	0.001	0.001
Etoricoxib		0.459	0.368
Flavoxate			0.543



The four treatment groups could be considered as four treatment combinations from a 2x2 factorial design where the first factor (i.e., factor A) was flavoxate (no, yes) and the second factor (i.e., factor B) was etoricoxib (no, yes). Thus, there were 4 treatment combinations i.e., (1) no A and no B, (2) only A, (3) only B, and (4) both A and B. Statistical analysis could then be carried out using a 2-way Analysis of Variance (ANOVA). Using a 2-way ANOVA to compare four treatment groups has some advantages over 1-way ANOVA or Kruskal-Wallis analog since it can test the effect of factor A, factor B and interaction between factor A and B. However, for a 2-way ANOVA variable to be compared needs to have approximately normal distribution. Since total morphine consumption at 24 hours was of major interest, 2-way ANOVA was performed as a secondary statistical analysis. Cumulative morphine consumption at 24 hours was log 10 transformed due to its positive skewness.

Table 8 was a rewritten version of Table 6 showing descriptive statistics of cumulative morphine usage at 24 hours in a format of a 2x2 factorial design. To determine the effect of flavoxate, a column marginal median of 7 mg (without flavoxate) was compared with 5 mg (with flavoxate). That is, patients without flavoxate required 2 mg more morphine than those with flavoxate (7 vs. 5 mg). However, it was not statistically significantly different ($p = 0.294$).

Table 8 Descriptive statistics of 24-hour morphine usage (mg) in the format of a 2x2 factorial design

		With flavoxate	Without flavoxate	Total
With etoricoxib	Mean \pm SD	6.9 \pm 6.5	5.8 \pm 7.5	6.4 \pm 6.9
	Median	5	3.5	5
	GM	0.00	0.00	0.00
	Min-Max	(0 - 24)	(0 - 35)	(0 - 35)
Without etoricoxib	Mean \pm SD	7.5 \pm 5.7	16.1 \pm 9.3	11.8 \pm 8.8
	Median	5	16	10
	GM	0.00	12.02	0.00
	Min-Max	(0-22)	(1-32)	(0 - 32)
Total	Mean \pm SD	7.2 \pm 6.7	10.9 \pm 9.9	
	Median	5	7	
	GM	0.00	0.00	
	Min-Max	(0 - 24)	(0 - 35)	

For the effect of etoricoxib, row marginal median of 10 mg (without etoricoxib) was compared with 5 mg (with etoricoxib). That is, patients without etoricoxib required as much as 5 mg more morphine than those with etoricoxib (10 vs. 5) and this difference was statistically significant ($p = 0.014$).

Interaction between flavoxate and etoricoxib can be explained in 2 ways: (1) the effect of etoricoxib depends on a group of flavoxate, and (2) the effect of flavoxate depends on a group of etoricoxib. In general, if the effect of factor A depends on a level of factor B or equivalently the effect of factor B depends on a level of factor A, it is said that interaction between factor A and B exists.

For the first meaning of interaction, the effect of etoricoxib (i.e., the difference in median morphine usage at 24 hours between patients with and without

etoricoxib) was as big as 12.5 mg (= 16 – 3.5 mg) among patients without flavoxate compared to 0 mg (= 5 – 5 mg) among those with flavoxate (Figure 4). That is, the effect of etoricoxib depended on whether patients received flavoxate or not. Once the patients had already got flavoxate, adding etoricoxib did not help much in terms of reduction in total morphine usage. In summary, there seemed to be an interaction between flavoxate and etoricoxib.

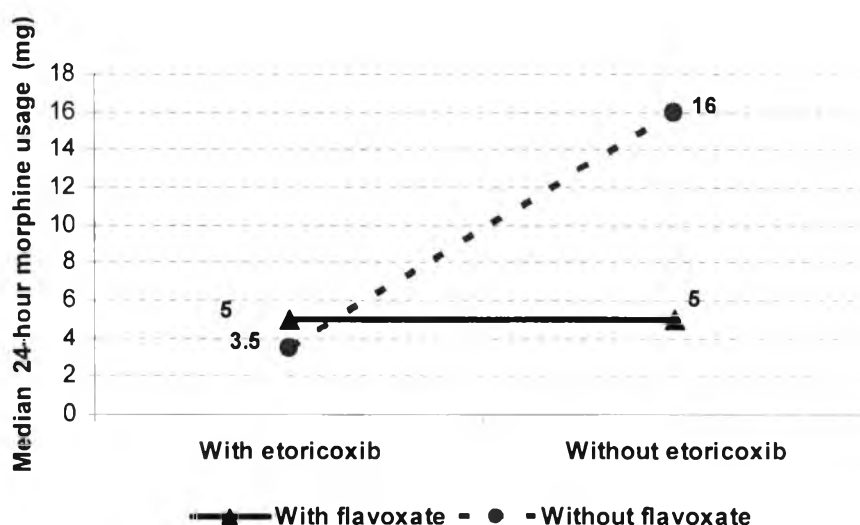


Figure 3 Effect of etoricoxib on 24-hour morphine usage in patients with and without flavoxate

For the second meaning of interaction, the effect of flavoxate was as high as 11 mg (= 16 – 5 mg) among patients without etoricoxib compared to -1.5 mg (= 3.5 – 5 mg) among those with etoricoxib (Figure 5). Again, the effect of flavoxate depended on whether patients got etoricoxib or not. If patients had already received etoricoxib, adding flavoxate did not add much in terms of total morphine consumption after 24 hours.

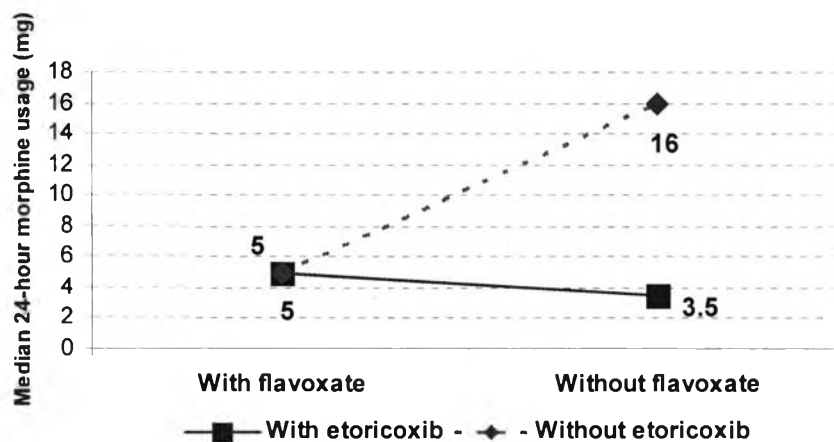


Figure 4 Effect of flavoxate on 24-hour morphine usage in patients with and without etoricoxib

Thus, both meanings of interaction suggested that interaction existed. However, a test of interaction showed that interaction was not statistically significant ($p = 0.140$).

In conclusion, 2-way ANOVA of total morphine usage at 24 hours revealed that etoricoxib was better than flavoxate due to the statistically significant effect of etoricoxib, but not of flavoxate. Furthermore, using only either flavoxate or etoricoxib seemed to be adequate compared to a placebo. This conclusion agreed well with a Kruskal-Wallis test which showed no difference between either flavoxate alone or etoricoxib alone and a combination of them.

4.3 Analysis of Secondary Outcome

4.3.1 Pain score using Numerical Rating Scale (NRS), trigger time.

Throughout the first 24-hour postoperative period, postoperative pain at 3-, 5- and 24-hours were assessed using a numerical rating scale (0-10). Similar to cumulative morphine consumption, the pain score via NRS was positively skewed (Figure 6).

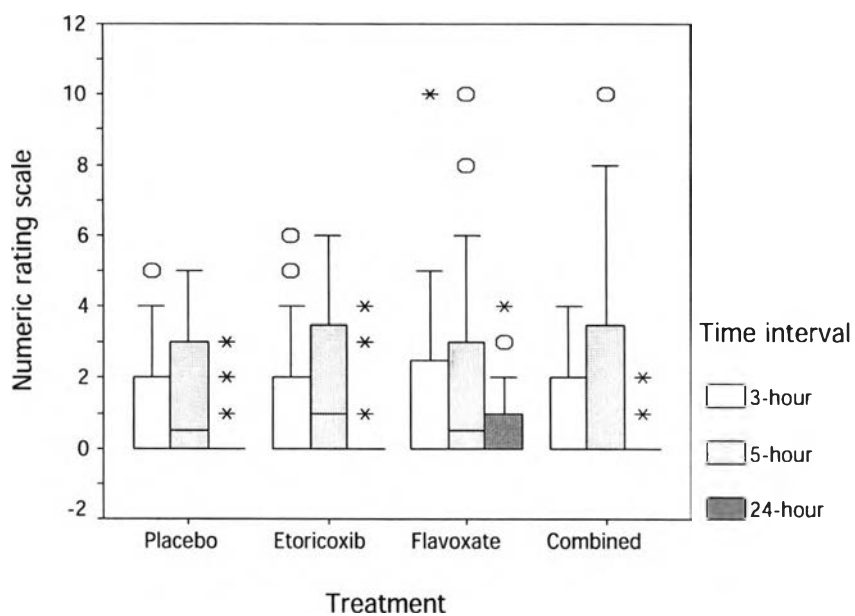


Figure 5 Box plot of pain intensity (NRS) in each treatment group

Table 9 displays descriptive statistics of the pain score using NRS at 3-, 5- and 24-hours in each treatment group. At each hour, there seemed to be no pain (median pain score of 0) in all four treatment groups. In terms of mean and minimum-maximum pain score, it seemed that the pain score decreased a little bit over time. However, a Kruskal-Wallis test revealed that there was no statistically significant difference in the pain score at 3-, 5- and 24-hour postoperative between the four treatment groups ($p = 0.905, 0.977$ and 0.928 respectively).

Table 9 Descriptive statistics of pain intensity (NRS) in each treatment group

NRS		Placebo (n=24)	Etoricoxib (n=24)	Flavoxate (n=24)	Combined (n=24)	p-value
3-hour	Mean \pm SD	1.0 \pm 1.71	1.29 \pm 2.07	1.50 \pm 2.41	0.96 \pm 1.30	0.905
	Median	0.00	0.00	0.00	0.00	
	GM	0.00	0.00	0.00	0.00	
	Min-Max	(0 - 5)	(0 - 6)	(0 - 10)	(0 - 4)	
5-hour	Mean \pm SD	1.83 \pm 2.00	1.79 \pm 2.04	1.96 \pm 2.77	1.92 \pm 2.83	0.977
	Median	1.0	1.0	0.5	1.0	
	GM	0.00	0.00	0.00	0.00	
	Min-Max	(0 - 5)	(0 - 6)	(0 - 10)	(0 - 10)	
24-hour	Mean \pm SD	0.39 \pm 0.84	0.42 \pm 1.02	0.71 \pm 1.33	0.37 \pm 0.77	0.928
	Median	0.00	0.00	0.00	0.00	
	GM	0.00	0.00	0.00	0.00	
	Min-Max	(0 - 3)	(0 - 4)	(0 - 4)	(0 - 2)	

Regarding the time after receiving anesthesia that patients first triggered the PCA machine for morphine (i.e., trigger time), 7 patients did not require any morphine during 24 hours (2 in the etoricoxib and flavoxate group, and 3 in the combined group respectively). Among 89 patients who required morphine, the trigger time was very positively skewed in the flavoxate and combined group, but looked approximately normal in the placebo and etoricoxib group (Figure 7).

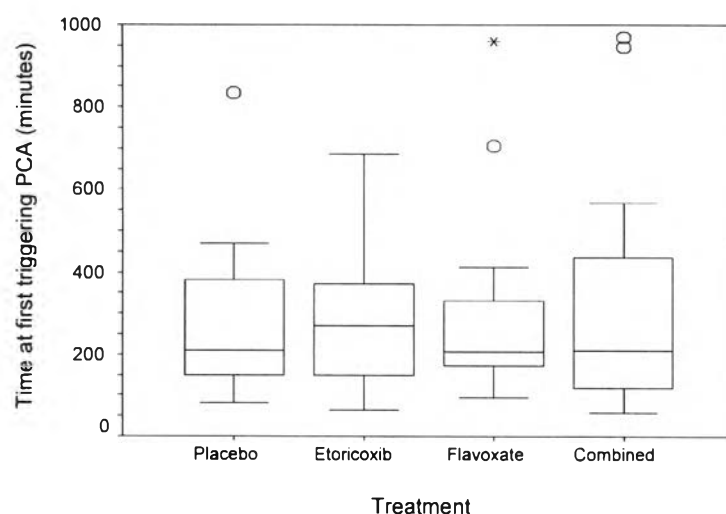


Figure 6 Box plot of trigger time in 89 patients who required morphine

The mean (\pm SD) of the time (minutes) of first triggering the PCA machine for morphine since the beginning of anesthesia in the placebo, etoricoxib, flavoxate, and combined groups were 272.3 ± 370.2 , 266.8 ± 153.9 , 294.9 ± 205.8 , and 206.8 ± 370.2 respectively (Table 10). Due to non-normal distribution of the trigger time in some treatment groups, a Kruskal-Wallis test was applied revealing no statistically significant difference in trigger time between the four treatment groups ($p=0.964$).

Table 10 Descriptive statistics of trigger time in 89 patients who required morphine

Trigger time (minutes)	Placebo ($n=24$)	Etoricoxib ($n=22$)	Flavoxate ($n=22$)	Combined ($n=21$)
Mean \pm SD	272.3 ± 172.1	266.8 ± 153.9	294.9 ± 205.8	307.8 ± 266.3
Median	211	270	206	210.5
GM	231.2	225.5	247.5	226.7
(Min-Max)	(80 - 835)	(64 - 686)	(93 - 961)	(56 - 969)

Analysis of the time to first trigger the PCA machine could also be performed using the concept of survival analysis. That is, the event of most interest in this study was the first triggering of the PCA machine and the survival time was the time from starting anesthesia till the first triggering of the PCA i.e., painfree time. Thus, 7 patients who did not require any morphine from the PCA machine during 24 hours were considered as having censored trigger time and the time at first triggering was then equal to 24 hours or 1,440 minutes. Using the Kaplan-Meier survival curve, the median painfree time in the placebo group was 197 minutes compared to 275, 206 and 214 in the etoricoxib group, flavoxate group and combined group respectively (Figure 7). Though the placebo group had a shorter painfree time than the others, a logrank test revealed no statistically significant difference in painfree time between the four groups ($p = 0.510$).

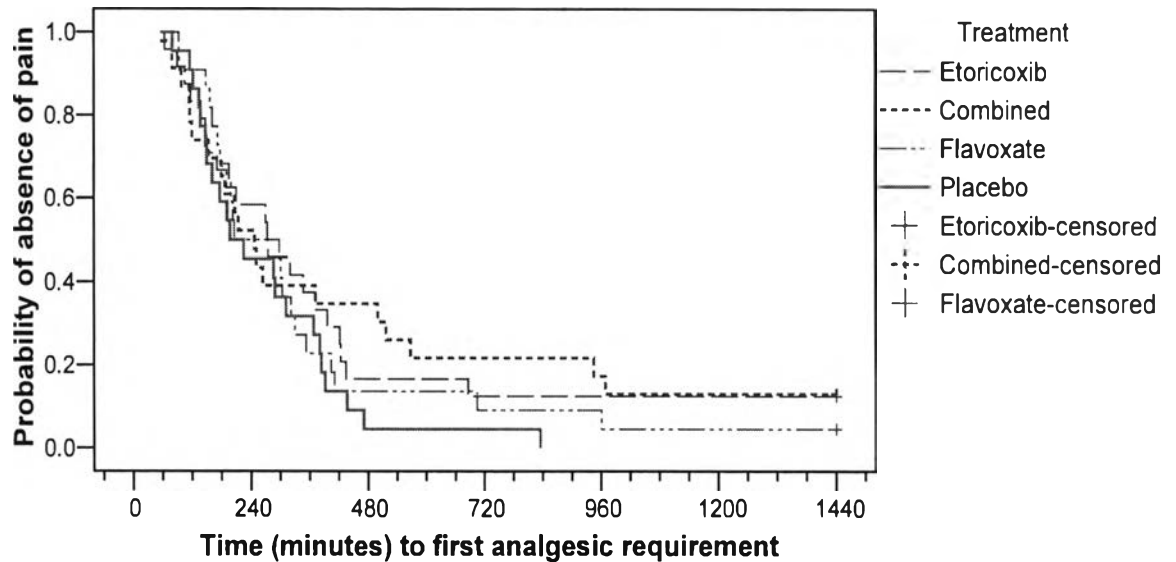


Figure 7 Kaplan-Meier curve of time to first trigger of the PCA machine by treatment

4.3.2 Side Effects

No patient in this study had respiratory depression. There was only one patient in the flavoxate group that reported dizziness. Two patients in the flavoxate group and one in each of the other groups had pruritus and only 2 of them needed treatment. There were no other adverse effects reported.

Table 11 Side effects and treatment

	Number				p-value
	Placebo (n=24)	Etoricoxib (n=24)	Flavoxate (n=24)	Combined (n=24)	
Pruritus	1(4.2%)	1(4.2%)	2(8.3%)	1(4.2%)	1.000
Nausea	5(20.8%)	5(20.8%)	9(37.5%)	8(33.3%)	0.514
Vomiting	5(20.8%)	5(20.8%)	5(20.8%)	8(33.3%)	0.741
Ondanzetron	7(29.2%)	8(33.3%)	7(29.2%)	9(37.5%)	1.000
Diphenhydramine	1(4.2%)	0	0	1(4.2%)	1.000

4.3.3 Cost minimization analysis

There was no difference between the 4 treatment groups in terms of postoperative pain intensity at each period of time that was evaluated. Therefore a cost minimization analysis was performed by calculating all drug costs, material costs related to drug administration and emesis clean up together with the labor costs of nurses who gave injections or took care of patients who vomited. All data of costs were obtained from the pharmacy unit and hospital administrators of Siriraj Hospital. The salary of each nurse was based on the data between April - September 2005 which was 3.36 baht/min

The material costs per one injection include the costs of disposable syringes, needles, and alcohol pads which totaled 7 baht. The labor cost of each nurse was based on the average care time for each patient. The labor cost for one injection

was 33.60 baht. The labor cost for cleaning up the emesis was 50.40 baht. The material cost of cleaning emesis was 20 baht which included tissue together with the cost of cleaning bed sheets and patient's clothes. However, the labor cost of preparing morphine for PCA usage and the cost of the PCA machine were not included in the calculations because they were the same in all groups. There was no patient in the study who had abdominal discomfort.

Table12 Cost analysis

	Price (baht)	Treatment			
		Placebo	Etoricoxib	Flavoxate	Combined
Drug cost:					
Morphine (10mg/vial)	19	30.59	11.4	14.25	13.11
Etoricoxib (120mg/tab)	47.90	-	47.90	-	47.90
Flavoxate (60mg/tab)	8.20	-	-	24.60	24.60
Ondanzetron (8mg/vial)	23	161	184	161	207
Diphenhydramine (25mg/tab)	2.30	2.30	-	-	2.30
Material cost:					
Material for injection	7	49	56	49	63
Material for emesis clean up	20	100	100	100	160
Labor cost:					
Cost of drug injection	33.40	233.80	267.20	233.80	300.60
Cost of emesis clean up	50.40	252.00	252.00	252.00	302.40
Total		828.69	918.50	834.65	1,120.91

In consequence of these cost calculations, the costs in each group were 828.69, 918.50, 834.65 and 1,120.91 baht respectively. Therefore the cost in the placebo group was the lowest and the cost in the combined group was the highest.