CHAPTER V

DISCUSSION

The cumulative 24-hour morphine requirement in the patients who received a placebo was varied from 1-32 mg with a mean and median of 16.1 and 16 mg respectively, which was nearly the same. This showed that pain after transurethral prostatectomy does really exist. Therefore patients who underwent TURP do require postoperative analgesia. However the median 24-hour morphine usage in this study is higher than the study of Alhashemi JA et al. (36) which required only 10.6 mg. This may be due to the difference in the technique of analgesic that was given to the patient. In this study PCA was used, while in the other study of Alhashemi JA et al. analgesics were given gave on the patient's request. Conventional pain therapy would not be fully effective because of the delay in treatment by the process of giving pain medication (68,69).

However, the mean dose of 24-hour morphine requirement in the etoricoxib group was only 6.0 mg which was significantly lower than the placebo group. The effectiveness of etoricoxib in alleviating postoperative pain was also compared with the placebo group by using a factorial model. The results showed that mean cumulative 24-hour morphine patients with and without etoricoxib were 6.4 $\pm$ 6.9 and 11.8 $\pm$ 8.8 mg respectively, which was a statistically significant difference. This result confirmed the usefulness of etoricoxib in pain relief after TURP. Again the 24-hour cumulative morphine requirement in this study was lower than the study of Carbrera MC et al. (40). They compared the cumulative 24-hour morphine requirement between patients who received 50 mg of rofecoxib given preoperatively with patients who received 100 mg ketoprofen given intravenously every 8 hours for 24 hours after surgery (control group). The total 24-hour morphine usages were 28.9 and 36.8 mg in the rofecoxib and ketoprofen groups respectively, which was not statistically significantly different. The difference in cumulative morphine dosages between the etoricoxib group and the

rofecoxib group from the study of Carbrera MC et al. (40) may be due to the potency of different COX-2 inhibitors. Otherwise it may due to the difference in pain response dependent on cultural patterns of behavior and ethnic differences (70,71).

While the good results of using COX-2 inhibitors in treating postoperative pain have been demonstrated, the results of using a urinary antispasmodic such as oxybutynin hydrochloride for the relief of pain after transurethral prostatectomy were still controversial (55,56). Chen Q et al. (57) have studied the efficacy of tolterodine another urinary antispasmolytic drug and found that 25.6% and 54.9% of the patients were totally relieved of pain at 24- and 72- hours postoperatively. The increase in the percentage of the patients who were pain free at 72 hours might be because of the relief of the traction of the urinary catheter. Here in this study, the mean cumulative 24-hour morphine usage in the flavoxate group was 7.5 mg which was significantly less than the placebo group. Therefore flavoxate can be used to alleviate pain after TURP. However, the better result of flavoxate over the placebo in pain relief after TURP could not be demonstrated in this study by using factorial design. When the results were combined, the cumulative 24-hour morphine usages in patients with and without flavoxate were 7.2 $\pm$ 6.7 and 10.9 $\pm$ 9.9 mg respectively which was not a statistically significant difference. This may be due to the inconsistency effect of etoricoxib that was experienced in both treatment groups. And this was the weak point in using factorial design in this situation.

Regarding the mechanism of pain after transurethral prostatectomy as stated previously, the use of a combination of COX-2 inhibitor and urinary antispasmodic should be very useful in alleviating pain following transurethral prostatectomy. Gbandi R et al. (11) gave continuous intravenous infusion of combined tramadol and butylscopolamine, compared with analgesia, on demand which was one of the following i.e., oral tramadol, subcutaneous piritramid, dipyrone, diclofinac, or butylscopolamine. They demonstrated significantly less pain intensity in the patients who received a continuous infusion of analgesia. In this study the cumulative 24-hour morphine requirement in the combined treatment group was 6.9 mg which was significantly less than the placebo group. Therefore the combination of the 2 treatments showed good results in managing postoperative analgesia after TURP over the placebo group.

But the significant different among the 3 treatment groups could not be demonstrated especially the difference between the combined group and the other 2 treatment groups. The possible mechanism may be because urinary bladder is also a site of local prostaglandin (PG) production. When there is bladder outlet obstruction, inflammation or mucosal injury, the level of bladder PG can significantly increase (72). PGs then activate C fibers to cause involuntary bladder spasm (73). Therefore the use of NSAIDs should suppress bladder contraction. And this has been clinically demonstrated by the study of Park JM et al. (74). They found that ketolorac could significantly reduce the severity and frequency of bladder spasms after ureteroneocystostomy when compared with placebo. Since the antispasmodic effect of flavoxate is also directly on the urinary tract smooth muscles, then combined etoricoxib and flavoxate might not demonstrated further additive or synergistic effect. However the reason why the 24-hour morphine usage in the flavoxate group was not different with the etoricoxib and the combined groups still can not be explained by the earlier postoperative pain mechanism that has been proposed.

The other reason that this study could not demonstrated the significant different among the 3 treatment groups may be owing to the inadequate sample size. Since the sample size that was calculated for this study was based on the primary question that either etoricoxib 120 mg or flavoxate 200 mg or both administered preoperatively effectively reduces the first 24 hours of postoperative morphine consumption from the control group. The trial was said to be tailored to detect only the main effects of each treatment (75). If the interaction of each treatment is of primary interest then it is necessary that the trial should be tailored to detect reasonable target interaction effects (75). The sample size calculation should take into account the interaction effect too, which would enlarge it.

Postoperative NRS at 3-, 5- and 24-hours after the start of spinal anesthesia and the incidence of side effects in each group did not show any statistically significant differences. However pain intensity in the control group was not significantly different with the other 3 treatment groups because the patients received morphine for their pain relief. The incidence of nausea in this study was between 20.8-37.5% among

the 4 groups which did not show a statistically significant difference. The highest was in the flavoxate group and the lowest were the placebo and etoricoxib groups.

Another disturbing side effect for surgical patients was pruritus which was found in only 4.2-8.3% in this study. Pruritus can really distress the painfree patient and was a common side effect of coaxial narcotics. Sakai T et al. have demonstrated good pain relief after TURP by using a dosage as low as 0.05 and 0.1 mg of spinal morphine (31). But the incidence of pruritus was 43% and 93% respectively. However, there was no patient in their study who required treatment.

In choosing an appropriate method of postoperative pain management, one must be concerned about the efficacy, the side effects, the feasibility and also the cost of the treatment, since the patients in the placebo group had the same postoperative pain intensity as the other three groups. All the three treatment groups were able to reduce their mean cumulative 24-hour morphine requirements compared with the placebo group. But the patients in the combined group required nearly the same amount of 24-hour morphine as the other two treatment groups. In addition the cost of the PCA machine is high and it may not be available in every hospital. Furthermore the operation and usage of the PCA machine by both nurse and patient might require training to acquire the necessary expertise. Yet the use of etoricoxib could significantly reduce postoperative 24-hour morphine dosage and it is so simple that the patient needs only one pill per day. But using this COX-2 inhibitor has so many contraindications of concern such as renal function, hepatic function and heart disease. Therefore in this situation, flavoxate can be used as an alternative by taking 200 mg 3 times daily in order to reduce the requirement of conventional postoperative pain analgesia.

Conclusion

Etoricoxib in a dose of 120 mg given orally 1 hour before surgery or oral flavoxate 200 mg in 3 equal doses given 1 hour preoperatively and then 6 hours later,

or the combination of the 2 treatments, can significantly reduce 24-hour cumulative morphine usage when compared with a placebo. But the combination of etoricoxib and flavoxate could not demonstrate in this study a further reduction in the total 24-hour morphine requirement from the etoricoxib and flavoxate group. According to the cost of each treatment, flavoxate can be used for pain relief after TURP though the patient had to take the drugs 3 times.