CHAPTER II

LITERATURE REVIEW

Literature search strategy

The literature search strategy used to locate the information in this review was found in the MEDLINE reference database and additionally by going through the reference lists of other articles and institutional databases. The years covered by the search were from 1966-March 10, to date. The search terms used were (transurethral prostectomy OR transurethral resection of the prostate OR TURP OR TUR-P) AND (postoperative pain OR postoperative analgesia OR pain relief). Forty articles were retrieved. These included 15 randomized controlled trials on interventions to alleviate acute postoperative pain after TURP.

Transurethral resection of the prostate is the standard treatment of benign prostatic hyperplasia. Many interventions have been reported as the treatments for postoperative analgesia after TURP. Conventionally postoperative pain after TURP is treated by using parenteral narcotics as mentioned previously, which posses many side effects. Since TURP is commonly done under spinal anesthesia, many opioid drugs have been added to the local anesthetic agent in order to prolong postoperative analgesia. Various low dosages of intrathecal morphine have been used with successful outcomes (30-33). But this method also carries many complications such as nausea, vomiting, pruritus and respiratory depression which is of most concern (33,34). Pethidine 0.3 mg/kg was also reported to prolong postoperative pain and reduce analgesic requirement (35). Tramadol which is another weak opioid has been added to 0.5% bupivacaine for spinal block in patients undergoing TURP. But there were no differences between the groups with regard to postoperative morphine requirements (36).

For the other pharmacological treatments, postoperative oral diazepam has been reported to be effective in the treatment of pain after TURP (37). Bricker SR et al. (38) have studied the effect of diclofenac on perioperative blood loss in patient undergoing TURP. It was found that the total blood loss and the blood loss per gram of prostate resected did not differ significantly between the patients who received diclofenac and placebo. In addition 80% of the patients in their study remained pain free at 8 and 24 hours postoperative period and the remaining 20% of the patients had low pain scores (38). However the European Association of Urology (EAU) guidelines on pain management have recommended diclofenac for postoperative analgesia in transurethral surgery (39). As a result of the lesser gastrointestinal side effect than conventional NSAIDs, selective COX-2 inhibitors have also been introduced to treat pain after TURP. Cabrera MC et al. have demonstrated that patients who received preoperative oral rofecoxib required less morphine consumption during the first 24 hours postoperative period after TURP than those who received intravenous ketoprofen (40). But the difference was not statistically significance.

However, rofecoxib has been withdrawn from the market because of the results from a well known trial on long term COX-2 inhibitors usage that has been stopped recently (41). It was the APPROVe trial (41) that was a 3-year study of the treatment with rofecoxib 25 mg on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenomas. The study was terminated 2 months earlier than the planned date based on the recommendation by an External Safety Monitoring Board (ESMB). The mean durations of treatments were 2.4 and 2.6 years in the rofecoxib and placebo groups respectively. The study showed that the relative risk of a confirmed cardiovascular event in patients taking rofecoxib was 1.92 (95% CI 1.19, 3.11; p=0.008) (41). The other study involving long term use of celecoxib for colorectal adenoma prevention (APC) was also terminated early (42). The patients, except those who died, were followed-up after 28-32 months. It was found that the incidence of death from cardiovascular cause (myocardial infarction, stroke or heart failure) was higher in patients receiving 200 mg of celecoxib twice daily than in a placebo group (1% compared with 2.3%). The hazard ratio was 2.3 (95% CI 0.9, 5.5).

But the hazard ratio of patients receiving 400 mg of celecoxib twice daily was 3.4 (95% CI 1.4, 8.8).

Besides the long term studies of rofecoxib and celecoxib, Ott E et al. have studied the analgesic effect of combined parecoxib sodium and valdecoxib for a total of 14 days for the management of postoperative pain in patients undergoing coronary bypass graft surgery (CABGs) through a median sternotomy. They demonstrated a higher incidence of sternal wound infection when compared with the treatment group with the placebo (43). Nussmeier NA et al. have also studied the safety of using parecoxib and valdecoxib after CABGs by giving the treatment for a total of 10 days (44). They found that both the patients who received parecoxib with valdecoxib and those who received placebo with valdecoxib when compared with an ordinary placebo had a higher incidence of at least one confirmed adverse event. The cardiovascular adverse events were significantly higher in the groups that received valdecoxib and parecoxib with the risk ratio 3.7 (95% CI 1.00, 13.5; p=0.03). Even though they found a higher incidence of cardiovascular events in the group receiving placebo and valdecoxib when compared with just a placebo, it was not statistically significant with the risk ratio 2.0 (95% CI 0.5, 8.1; p=0.31). Conversely there was a recent report from Nussmeier NA et al. about the safety and efficacy of using these 2 COX-2 inhibitors (parecoxib and valdecoxib) for postoperative analgesia in patients undergoing noncardiac surgical procedures. The trial consisted of 10 days of treatment and 30 days of follow-up. They found that the predefined adjudicated adverse events among the treatment (2.7%) and the placebo groups (3.2%) were similar (45). So using etoricoxib in this study might not be a problem to the patient because etoricoxib will be given in a single dose.

Etoricoxib is a new orally administrated COX-2 inhibitor that has anti-inflammatory, analgesic and antipyretic properties. Its mechanism of action is due to inhibition of prostaglandin synthesis primarily through inhibition of COX-2. Etoricoxib achieves mean peak plasma concentrations in approximately 1 hour (46). The absolute bioavailability of etoricoxib is nearly 100% following oral administration. The elimination

half-life of etoricoxib is 22 hours which is longer than other coxibs particularly rofecoxib and valdecoxib (47).

Etoricoxib has a rapid onset of action, provides pain relief (including the alleviation of pain intensity) (48-50) and has opioid-sparing effects in acute postoperative pain (51). Most of the study of etoricoxib in acute postoperative pain is in the dental model. Preoperative oral administrations of etoricoxib in different dosages (60, 120, 180, 240 mg) have a significantly greater effect in delaying analgesic drugs in the first 24 hours longer than patients who received a placebo (49). In the same study they also found that the pain intensity in the treatment group was significantly lower when compared with the placebo group. The study also demonstrated that etoricoxib 120 mg was the minimal effective dose to provide maximal efficacy in alleviating moderate to severe pain associated with dental surgery. Single oral etoricoxib 120 mg given preoperative has also shown significantly lower opioid consumption during day 1-7 after hip or knee replacements when compared with a placebo (51).

Concerning the safety profile of selective COX-2 inhibitors, etoricoxib has shown an improved GI safety profile compared with non-selective NSAIDs (52). It was found that there was 52% fewer confirmed GI perforation, ulcer and bleeds (PUBs) and 51% fewer investigator-reported PUBs compared with treatment with non-selective NSAIDs. Valdecoxib has no effect on platelet function (53). The other incidences of adverse effects such as nausea, dyspepsia and headache were low even in patients receiving etoricoxib for 7 days when compared with a placebo and naproxen (51). However etoricoxib should be used with caution in patients with hepatic or renal impairment as should the other coxibs. Etoricoxib is contraindicated in patients who have a history of allergy to other NSAIDs.

Yates V et al. have studied and found that bladder spasm is common following transurethral surgery (54). So pain mechanisms after TURP should consist of 2 components as mention above. Moreover antispasmodics should be useful in treating postoperative effects in this group of patients. Several studies have been done by using a urinary antispasmodic for postoperative analgesia in patients having TUPR done.

Paulson DF. has demonstrated that oxybutynin hydrochloride was effective in controlling post-transurethral vesical pain and spasms (55). Later on Wein AJ et al. reported that patients who had undergone transurethral surgery and received oxybutynin hydrochloride for treating bladder spasm obtained no benefit over the placebo group (56). Recently Chen Q et al. have also studied the efficacy of tolterodine giving 2 mg twice daily until 24 hours before catheter removal in patients having TURP done. They reported that 25.6% and 54.9% of patients can totally alleviate pain from bladder spasms in 24- and 72-hours respectively (57). However, there was no placebo in this study.

Flavoxate hydrochloride is another synthetic urinary tract antispasmodic that exerts a direct spasmolytic effect on smooth muscle fibers and provides therapeutic benefits in a variety of urological disorders. Flavoxate is indicated for the relief of vesico-urethral spasms due to urinary catherization, cystoscope and indwelling catherization, prior to cystoscope or catherization and sequelae surgical intervention of the lower urinary tract (58). It can be easily given to the patient during the pre- and post- operative period.

There was a study using combined infusion of tramadol and butylscopolamine as the treatment for postoperative analgesia in TURP patients which also demonstrated significant reduction of the postoperative pain score when compared with analgesia as requested by the patient (11). But the objective of their study was to test the validity of the questionnaires not really to compare the efficacy of the 2 treatment regimens and they did not compare with the placebo group.

So the objective of in this study was to investigate whether etoricoxib or flavoxate or their combinations can be effectively used for postoperative pain relief in patients having TURP.