

2003 Spring A54

Reduction of opioid use and related side effects after laparoscopic cholecystectomy surgery (LCS): benefits of the oral COX-2 specific inhibitor valdecoxib, and its injectable prodrug parecoxib sodium, in postoperative pain management

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Objective: To assess reduction of opioid-related side effects in the first 24 h, and on Days 1 to 4 postdischarge, among patients who used preoperative IV parecoxib followed by oral valdecoxib, for managing postoperative pain after laparoscopic cholecystectomy surgery (LCS).

Methods: This study was a secondary analysis using data from a randomized clinical trial to assess the efficacy and safety of parecoxib and valdecoxib in patients after laparoscopic cholecystectomy surgery (LCS). All patients (n = 193) received standard of care fentanyl IV on demand for treatment of pain before discharge, and acetaminophen 500mg/hydrocodone 5 mg po q4-6h prn postdischarge for up to 7 days postsurgery. The comparator arm received placebo in place of parecoxib and valdecoxib. Every 24 h patients completed an opioid-related Symptom Distress Scale (SDS) questionnaire. This analysis only focuses on reduction of opioid utilization and related side effects up to Day 4 postdischarge because study drug was taken on a prn basis on Days 5 to 7. Twelve opioid-related symptoms—nausea, vomiting, constipation, difficulty passing urine, difficulty concentrating, drowsiness, dizziness, confusion, itchiness, dry mouth, fatigue, and headache—were assessed by 3 ordinal measures—frequency, severity, and bothersomeness. For each symptom patients with responses of “frequently” to “almost constantly”, “moderate” to “very severe”, or “quite a bit” to “very much” bothered were considered to have had a clinically meaningful event (CME). Group comparisons were made using the 2-sample Wilcoxon test for average symptom score and Fisher’s exact test for CME. Opioid use was converted to morphine equivalent doses (MEDs).

Results: Significant reduction in MED was observed in the parecoxib/valdecoxib treatment group compared with placebo on Day 1 (12.1 mg vs 17.9 mg; $P < 0.001$), and during Days 1 to 4 (30.9 mg vs 48.5 mg; $P < 0.001$) postdischarge (an average 32% reduction). Additionally, patients in the parecoxib/valdecoxib treatment group experienced improved pain relief compared with patients receiving placebo in the postdischarge period ($> 30\%$ reduction in pain severity; $P < 0.001$). In the immediate 24 h postdischarge, parecoxib/valdecoxib-treated patients had significantly lower average SDS scores related to symptom frequency, severity, and bothersomeness compared with placebo ($> 30\%$ reduction; $P < 0.001$), and experienced significantly fewer CMEs than placebo for symptoms of nausea (RR = 2.73, 95%CI = 1.09-6.80), vomiting (RR = ∞ , $P < 0.01$ – no parecoxib/valdecoxib patients experienced vomiting), difficulty passing urine (RR = 12.85, 95%CI = 1.69-97.6, $P < 0.01$), fatigue (RR = 1.67, 95%CI = 1.16-2.43, $P < 0.01$), and itchiness (RR = 6.43, 95%CI = 1.46-28.23, $P < 0.01$). Patients in the placebo group reported a significantly higher rate of multiple CMEs on Day 1 compared to those in the treatment group (RR = 1.79, 95%CI = 1.22-2.63, $P < 0.01$ for ≥ 2 CMEs; and RR = 3.39, 95%CI=1.76-6.56, $P < 0.01$ for ≥ 3 CMEs). Similarly, during Days 1 to 4 postdischarge, placebo-treated patients had a significantly higher number of patient-days with CMEs than the parecoxib/valdecoxib group; nausea (RRadj = 2, 95%CI = 1.1-3.6; $P < 0.05$), vomiting (RRadj = 6, 95%CI = 1.3-30.1; $P < 0.05$), difficulty passing urine (RRadj = 2, 95%CI = 1.0-4.6; $P < 0.05$), fatigue (RRadj = 2, 95%CI = 1.4-2.4; $P < 0.001$), and itchiness (RRadj = 3, 95%CI = 1.5-4.6; $P < 0.001$). Additionally, there was an overall reduction in number of patient-days with CMEs in the parecoxib/valdecoxib group versus the placebo group on Days 1 to 4 postdischarge; RRadj for patient-days with ≥ 1 CME was 1.3 (95%CI = 1.1-1.6; $P < 0.01$), with ≥ 2 CMEs was 1.7 (95%CI = 1.3-2.3, $P < 0.001$), and with ≥ 3 CMEs was 2.4 (95%CI = 1.6-3.6, $P < 0.001$).

Conclusions: Preoperative administration of parecoxib and follow-up oral valdecoxib treatment significantly reduced postoperative opioid use, improved pain relief, and reduced opioid-related side effects in the first 24 h, and on Days 1 to 4, in the postoperative recovery period after LCS. All CMEs occurred with a lower frequency in the parecoxib/valdecoxib treatment group compared with placebo.

Sponsored by Pharmacia Corporation