

2003 Spring A55

Empirical dose-response relationship between the utilization of opioids and related side effects after laparoscopic cholecystectomy surgery (LCS)

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Objective: To determine the dose-response relationship between opioid utilization and opioid-related symptoms in the first 24 h, and on Days 1 to 4, postdischarge after laparoscopic cholecystectomy surgery (LCS).

Methods: This study was a secondary analysis using data from a multicenter, 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 500 mg/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. Opioid use was converted to morphine equivalent doses (MEDs). This analysis only focuses on the opioid-dose relationship 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, 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). Dose-response relationship between MED and CMEs on Day 1 after surgery were determined by N-way ANOVA and regression analysis. The dose-response relationship between number of patient-days with CMEs for study symptoms and cumulative MED used over Days 1 to 4 were tested by regression analysis.

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). There was a significant correlation between the MED and the incidence of CMEs throughout the postoperative period. At the end of Day 1 postsurgery, after adjusting for confounding factors, patients with a CME had significantly higher cumulative MED (Day 0 and 1) than those without (45.2 mg vs 36.9 mg; $P < 0.001$). On average patients with a CME used 4 mg more morphine per day than those without, and once the daily morphine dose exceeded 11 to 14 mg, each additional CME was associated with an approximate additional 4 mg MED per day. By combining all CMEs occurring in Days 1 to 4, this analysis found that the number of patient-CME-days was significantly related to cumulative MED used in Days 1 to 4, and regression analysis suggested that when cumulative MED exceeded a threshold, each additional 4.3 mg of MED was associated with an additional patient-CME-day ($P < 0.001$).

Conclusions: Patients receiving parecoxib/valdecoxib used significantly less MED than patients receiving placebo throughout the 4 days following LCS. Furthermore, this reduction in MED correlates with a reduction in the number of CMEs experienced postoperatively, and with significantly more symptom-free days. Finally, all CMEs occurred with a lower frequency in the parecoxib/valdecoxib treatment group compared with placebo.

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