

Original Article

A Comparison of Intravenous Oxycodone and Parecoxib in the Treatment of Visceral Pain after Laparoscopic Cholecystectomy

Rui Wang, Dong-Xu Yao, Tian-Long Wang, Wei Xiao, and Yang Liu

ABSTRACT

Background: Visceral pain is the most common form of pain that affects human beings. Laparoscopic cholecystectomy (LC) is also accompanied by severe postoperative pain, especially visceral pain. Non-steroidal anti-inflammatory drugs (NSAIDs) can relieve the postoperative pain but with a high percentage of side effects. It has been suggested that the analgesic effect on visceral pain of oxycodone is superior and with less side effects. This study is to compare the effects of parecoxib sodium with oxycodone on visceral pain.

Methods: Seventy patients were randomized to two groups. Patients in group oxycodone (group O, N=35) received oxycodone 0.05 mg/kg intravenously (i.v.) and patients in group parecoxib (group P, N=35) received parecoxib 40 mg i.v. before the end of surgery. Patients in both groups were local anesthetized with 10 ml 1% ropivacaine (10 mg/ml) at the four trocar sites. Then the numeric rating scale (NRS) scores at rest and when coughing were assessed at the following time points: at arrival to postanesthesia care unit (PACU) (T1), 30 minutes in the PACU (T2), 2 (T3), 6 (T4) and 24 hours (T5) postoperatively, furthermore, side effects and rescued analgesic were also recorded.

Results: Deep abdominal pain on NRS scores in group O at 6 hours was significantly lower than that in group P at rest (2[1-3] vs. 3[2-4.5], $P=0.002$) and when coughing (2[2-3] vs. 4[3-6], $P<0.001$). Ratios of mild/severe deep abdominal pain at rest at 6 hours were 20/13 vs. 30/3 ($P=0.008$) in group P and group O, respectively. Ratios of mild/severe deep abdominal pain were 14/19 vs. 23/10 ($P=0.046$) at 2 hours and 14/19 vs. 25/8 ($P=0.012$) at 6 hours when coughing in group P and group O, respectively.

Conclusions: Oxycodone was more potent than parecoxib for visceral pain relief with no obvious side effects.

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Visceral pain is the most common form of pain that human beings endure throughout a lifetime. Pain resulting from visceral dysfunction is far more common than somatic disorders (1). So it is important to relieve visceral pain (2).

Laparoscopic cholecystectomy (LC) is also accompanied by severe postoperative pain including three components: pain located at the trocar sites (somatic pain), deep abdominal pain (visceral pain) and other referred pain like shoulder pain (3).

There are many factors may affect the postoperative pain after LC, including high insufflation pressures, increased insufflation rates, decreased intraperitoneal power of hydrogen (pH)-values, long operation duration, amount of residual gas, etc. Many disorders can cause visceral pain, such as distension from impaction ischemia, inflammation, and traction on the mesentery (4-6).

Non-steroidal anti-inflammatory drugs (NSAIDs), such as parecoxib, which selectively inhibits the cyclooxygenase-2 enzyme, may reduce the

production of inflammatory factor. Previous study showed that combining parecoxib sodium (40 mg, intravenous, i.v.) with 1% ropivacaine wound infiltration after LC had respectable analgesic effect; however, it didn't solve the problem of visceral pain (82.4%) (7).

In an experimental pain model in humans, oxycodone had a superior analgesic effect in visceral pain compared with equivalent dose of morphine (8, 9). When compared with morphine in patient undergoing abdominal surgery, oxycodone demonstrated higher potency and less sedation in the visceral pain in 2 hours after surgery (10).

The aim of our study was to compare parecoxib sodium with oxycodone to see if the later can specifically relieve the visceral pain.

MATERIALS AND METHODS

Patients and Ethical Approval

Seventy patients scheduled for LC at Xuanwu Hospital, Beijing, China. All the patients were randomized to Group Oxycodone (Group O, N=35) or Group Parecoxib (Group P, N=35) for the treatment of postoperative pain. Inclusion criteria were people aged 18-65 years, graded as American Society of Anesthesiologists (ASA) physical status I- II, body mass index (BMI) 19-35 kg/m² (10, 11) and scheduled for elective LC. Exclusion criteria were having serious cardiopulmonary diseases, serious hepatic and renal dysfunction, peptic ulcer, allergies history of sulfonamides, abuse of opioids and treatment with monoamine oxidase inhibitor. Cases were removed from the study if the intraoperative conversion to open surgery.

Anesthesia and Assessment

All the patients followed the standard protocol. Anesthesia was induced with sufentanil 0.3 µg/kg, etomidate 0.15-0.2 mg/kg, and rocuronium 0.6-1.0 mg/kg, and then laryngeal mask was performed. The patients were ventilated with 50% oxygen in air. Partial pressure of end tidal carbon dioxide (P_{ET}CO₂) was maintained between 35-45 mm Hg. Sedation was monitored by bispectral index (BIS, Covidien, MA, USA) and maintained between 40-60 during surgery. Anesthesia was maintained with a continuous infu-

sion of propofol (3-6 mg/kg/hour), remifentanyl (0.02-0.4 µg/kg/minute), and additional rocuronium was administered if necessary. Patients in group P was administered 40 mg parecoxib i.v. 30 minutes before the end of surgery, and patients in group O received 0.05 mg/Kg oxycodone i.v. 10 minutes before the surgery. At the end of surgery, both groups were local anesthetized with 10 ml 1% ropivacaine (10 mg/ml) at the four trocar sites (7).

Surgery was performed using a standard four-trocar technique. The pressure of carbon dioxide (CO₂) insufflation was maintained at 12 cm H₂O. CO₂ was evacuated completely before at the end of surgery. The duration of surgery and anesthesia was recorded.

Primary Outcomes/Index

Prior to the operation, the patients were instructed in the use of a numeric rating scale (NRS) and informed about the different components of pain after LC.

Pain at rest and during coughing was assessed separately at arrival and 30 minutes in the post-anesthesia care unit (PACU) and 2, 6, 24 hours in the ward by nurses who didn't know which groups the patient were in. The patients were asked to discriminate postoperatively pain between abdominal pain (deep, dull, hard to locate), incisional pain (pain located at the trocar sites) and shoulder pain (12). In the PACU, patients in group O were administered 2 mg oxycodone if NRS>3 (any one of those three types of pain) and reassessed with an interval of 10 minutes. The process was repeated till the NRS<3, then the patient could be discharged from the PACU. Patients in group P received 5 µg sufentanil i.v. if NRS>3 and reassessed after 10 minutes. For the safety of patients, the total dose of sufentanil was 10 µg. If the patients' score were still more than 3, they would be treated by surgeons.

Secondary Index

The overall incidence of postoperative nausea and vomiting (PONV), sedation, itching, and additional analgesic were recorded at arrival, after 30 minutes, 2, 6, and 24 hours. We record first aerofluxus time additionally. The PONV scores were scored on a scale of 0 to 3: 0 equals "No", 1 equals "mild nausea", 2 equals "serious nau-

sea", and 3 equals "nausea and vomiting". Sedation level was assessed by Ramsay scores: awake and alert=1; quiet and cooperative=2; drowsy, responded to commands=3; asleep, easily aroused=4; falls asleep=5; somnolent, no response to stimulation=6 (13).

Statistical Analysis

According to the preliminary experiment, a sample size of 35 patients per group would give a power of 90% at a level of 0.05 to detect 30% or more difference in NRS. A standard biostatistician formula $N = [Z_{\alpha/2} \sqrt{P(1-P)(1+C)/C} + Z_{\beta} \sqrt{P_1(1-P_1) + P_2(1-P_2)/C}]^2 / (P_1 - P_2)^2$ was used. Data were presented as mean ± standard deviation (SD) or medians with ranges, 25% and 75% percentiles by SPSS17.0. Mann-Whitney U-test was used to analyze the differences of NRS between the two groups and X² test was used for categorical data. P<0.05 was considered as a statistical significance.

RESULTS

Seventy patients were recruited in the study, N=35 in group P and group O, respectively (Figure 1). Demographic data and anesthesia characteristics were similar in the two groups except for BMI (group P: 24.2 ± 3.4 vs. group O: 25.9 ± 2.9) (Table 1).

The pain locations were divided into incisional pain, deep abdominal pain and shoulder pain referred to LC. Deep abdominal pain was defined as 0 in those patients who only feel the incisional pain. 6 patients had shoulder pain and 1 patient had chirobrachialgia.

Deep abdominal pain level at rest at all-time points in group O was lower than that in group P, and was significantly reduced at 6 hours (P=0.002) (Figure 2).

Abdominal pain when coughing was also lower in group O at arrival, 30 minutes, 60 minutes and 24 hours, and was significantly less at 6 hours (group P: 4 [3-6] vs. group O: 2 [2-3], P<0.001). (Figure 3)

In general, compared with group P, the ratio of mild pain (NRS<3) was higher and of severe pain (NRS>3) was lower in group O either at rest or coughing at all points of time. Even more, there were statistical significances

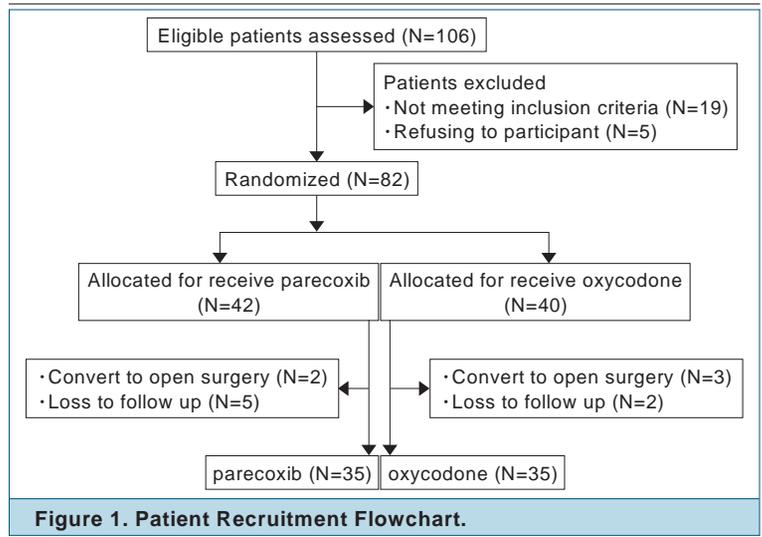


Figure 1. Patient Recruitment Flowchart.

Table 1. Demographic Data and Anesthesia Characteristics.

	Group P	Group O	P
Gender (male/female)	13/22	16/19	0.317
ASA (I/II)	22/11	15/18	0.083
GP/CP	7/26	6/27	0.757
Age (year)	49.5±11.5	47.2±10.5	0.420
BMI (kg/m2)	24.2±3.4	25.9±2.9	0.039
Catheter	6/35	5/35	0.564
Anesthesia time (minutes)	78.2±15.1	79.1±14.8	0.825
Surgery time (minutes)	48.2±12.6	49.3±13.3	0.712
Sufentanil (µg)	21.4±3.1	19.3±3.3	0.061
Propofol (mg)	229±88.3	241±58.8	0.232
Remifentanyl (µg)	770±370	730±255	0.665
Anal aerofluxus (days)	1.28±0.63	1.33±0.71	0.762
Rescued analgesic	9/35	6/35	0.378

Measurement data were expressed as means ± SD (N=70). χ² test was used for analysis on gender ratio and catheter. GP=gallbladder polypus, CP=chronic cholecystitis.

between the two groups at 6 hours (when at rest and coughing) and at 2 hours (when coughing) (Figure 4). The dosage of rescued analgesic was not statistically different between the two groups (group O: 6/35 vs. group P: 9/35).

Sedation scale was recorded until 24 hours after surgery. There seemed to be no statistically significant in sedation scale in both groups (Table 2).

The incidence of PONV is 38% in group P and 34% in group O individually (P=0.558). Three patients in group O experienced itching. One patient in group O had atrial premature beat.

DISCUSSION

LC is one of the most popular procedures in

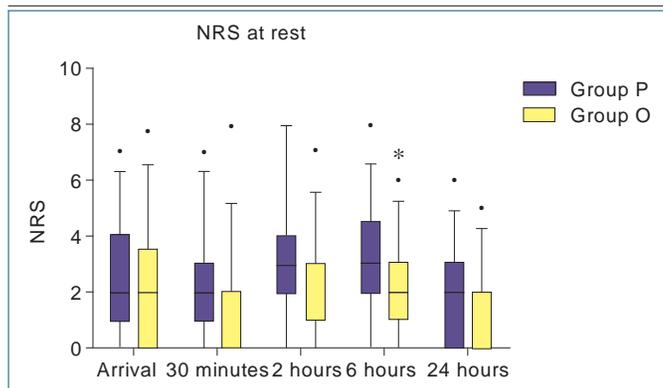


Figure 2. Deep Abdominal Pain on NRS at Rest. Mann-Whitney U-test was used. Results were shown as box-plots with medians represented by horizontal lines with the 75th percentiles at the top and the 25th percentiles at the bottom, 5% and 95% were given as whisker. Pain at rest at arrival, 30 minutes, 2, 6, 24 hours in group O was lower than that in group P, and was significantly lower at 6 hours (2[1-3] vs. 3 [2-4.5], $P^*=0.002$).

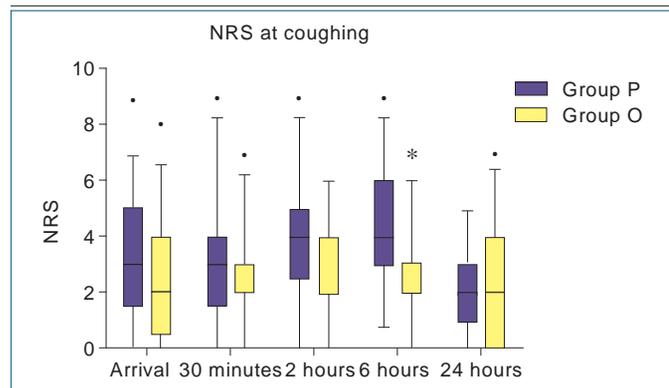


Figure 3. Deep Abdominal Pain on NRS at Coughing. Mann-Whitney U-test was used. Results were shown as box-plots with medians represented by horizontal lines with the 75th percentiles at the top and the 25th percentiles at the bottom, 5% and 95% were given as whisker. Pain when coughing was also lower in group O at arrival, 30 minutes, 60 minutes and 24 hours than that in group P, and was significantly less at 6 hours (2[2-3] vs. 4[3-6], $P^*<0.001$).

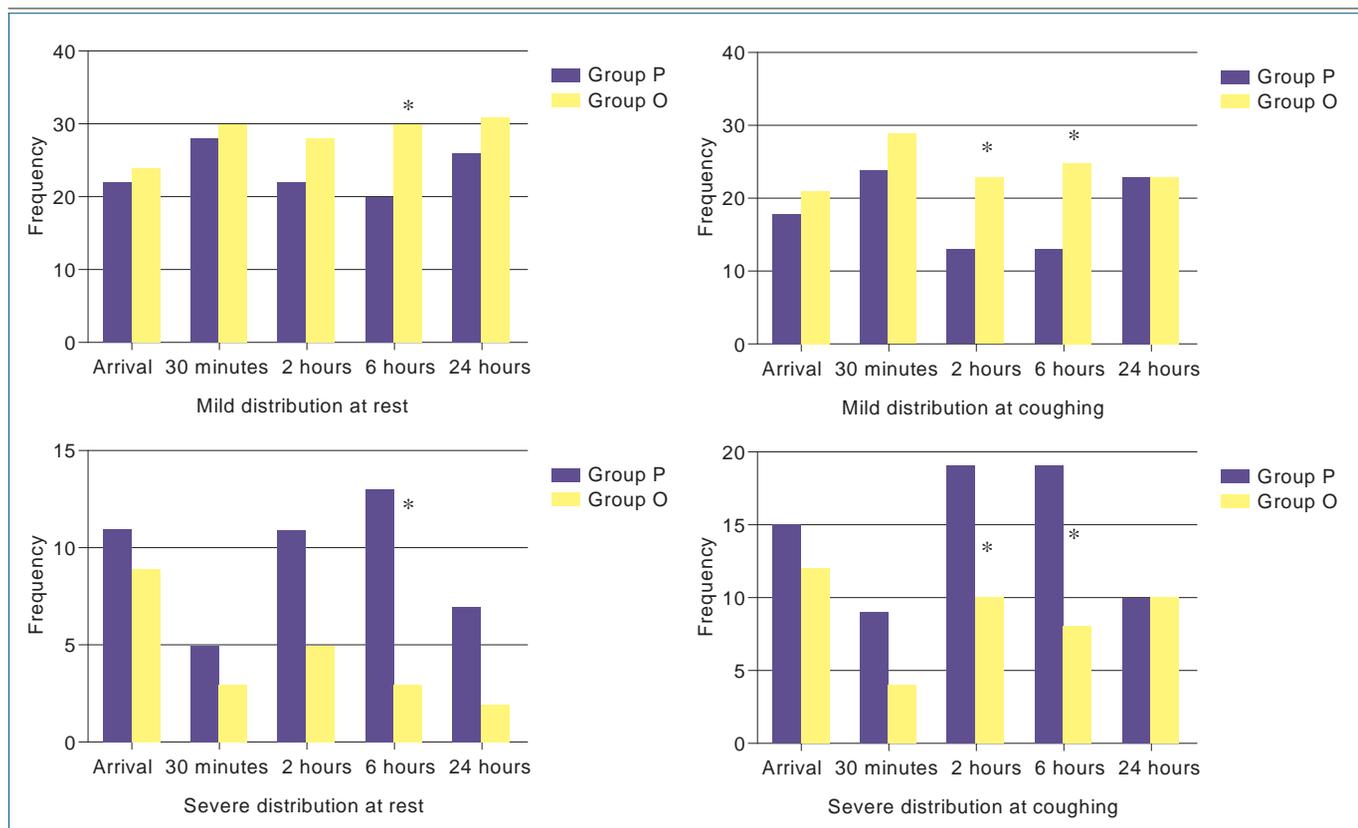


Figure 4. The Ratio of Mild and Severe Abdominal Pain in Two Groups. Chi-Squared Test. Pain was scored by deep abdominal pain. Data were presented by frequency distribution. $P^*=0.008$ at 6 hours at rest. $P^*=0.046$ at 2 hours and $P^*=0.012$ at 6 hours when coughing.

general surgery. Overall, the complication rate is less than 1.5%, and the mortality rate is less

than 0.1% (14). The so-called post-laparoscopic algia is a specific impairment of about 63%

of the patients who undergo laparoscopic surgical operations (15). Postoperative pain, in general, was mild to moderate after LC. The most severe pain comes from the incision site or intra-abdominally (16). As discussed before, there are many factors may affect the postoperative pain after LC, including high insufflation pressures, increased insufflation rates, decreased intraperitoneal pH-values, long operation duration, amount of residual gas, etc. So we well controlled all these factors in our study. A recent study found that high visual analogue scale (VAS) scores for visceral pain during the first postoperative week were associated with chronic pain 12 months after cholecystectomy (17). Therefore, postoperative visceral pain is an important issue need to be well controlled. I. v. analgesia has particular advantages in the postoperative acute pain and there is a trend toward the use of oxycodone (18) in recent years.

According to our observation, when compared within the 30 minutes after surgery, deep abdominal pain would be more severe from 2 to 6 hours after surgery. The reason is that within 30 minutes after surgery, the analgesic effects of anesthetics used during procedure is still reserved. There was a strong tendency that oxycodone was superior to parecoxib in controlling visceral pain. It may be good for patients in controlling anxiety and encouraging them to exercise earlier (19). It is consisted with previous studies (8, 20) and the view of well analgesia is an important part of enhanced recovery after surgery (ERAS) (21, 22). The $t_{1/2}$ of Oxycodone was 3.5 hours (23). This may explain why oxycodone was more effective on 2 and 6 hours after surgery. Oxycodone, work primarily at central μ -receptors and κ -opioid re-

Table 2. Sedation Scale.

	0 minute	30 minutes	2 hours	6 hours	24 hours
Group P	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)
Group O	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)
P value	0.554	0.675	1.000	—	—

Mann - Whitney U-test was used. Because the sedation score at 6 and 24 hours were the same, so there was insignificance to calculate P value.

ceptors on peripheral nerves. This may be an important feature for antinociception in the visceral pain system as well as less side effects (23, 24).

There were no significant differences in sedation scores, the incidence of nausea, vomiting or itching. It may because the total dose of oxycodone we administrated was less than recommended dose (25).

There are some limitations of our study. Firstly, our study only assessed pain on NRS without assessment of education, occupation level (26), biliary pain attacks and so on. Secondly, previous studies compared oxycodone with morphine or fentanyl, or combined opioid like oxycodone with NSAIDs, but our study assessed the oxycodone and parecoxib separately. Finally, demographic data and anesthesia characteristics were similar in the two groups except for BMI. Further study should enlarge the sample size to eliminate the difference.

Further study with multi-modal (mechanical, thermal and electrical) pain tests in the skin, muscles and viscera is needed (8, 26, 27). Moreover, further study can focus on optimal dose with least side effects for the treatment of the visceral pain after LC (28).

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