Preemptive QP001 provides analgesia and reduces opioid consumption in subjects with moderate to severe pain following abdominal surgery: a randomized controlled trial

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Abstract

Background

QP001, a novel meloxicam formulation, has been developed to manage moderate to severe postoperative pain. This study aimed to evaluate the efficacy and safety of QP001 injections for moderate to severe pain following abdominal surgery.

Method

This prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial enlisted patients experiencing moderate to severe pain following abdominal surgery. These patients were randomized to receive either QP001 injections (30mg or 60mg) or a placebo pre-surgery. The primary efficacy endpoint was the total morphine consumption within 24 hours after the first administration.

Results

A total of 108 patients were enrolled, and 106 patients completed the study. The total morphine consumption in the QP001 30mg group and 60mg group were significantly lower than that in the placebo group within 24 hours after the first administration (mean [SD] 5.11[5.46] vs 8.86[7.67], P = 0.011; 3.11[3.08] vs 8.86[7.67], P < 0.001). Compared with the placebo group, the total morphine consumption in the QP001 30mg and 60mg groups significantly decreased within 48 hours and 24–48 hours after the first administration (P ≤ 0.001); the area under curve of pain intensity-time and the effective pressing times of analgesic pump within 24 h and 48 h after the first administration was significantly reduced (P < 0.05). The QP001 groups did not show more Adverse Events and Adverse Drug Reactions than the placebo group (P > 0.05).

Conclusion

Preemptive QP001 provides analgesia and reduces opioid consumption in subjects with moderate to severe pain following abdominal surgery, while maintaining a favorable safety profile.

Introduction

Postoperative pain is an acute pain that occurs immediately after surgery and is one of the most common complaints after surgery (Kehlet 2018, Mitra et al. 2018). Unrelieved postoperative pain not only seriously affects the function and quality of life of patients, but also leads to negative outcomes such as prolonged hospital stay, delayed wound healing, and increased medical costs (Rawal 2005, Argo 2014, Kehlet 2018). With the development of modern medicine, although the management of postoperative pain has made significant progress, it still faces great challenges (Buvanendran et al. 2015). Within 24
hours after surgery, 48% and 19% of patients, respectively, experienced moderate or severe pain, according to the Perioperative Quality Improvement Programme (PQIP) annual reports (Small et al. 2020). Therefore, it is of great significance to explore safe and effective medications and treatment protocols for postoperative pain.

Currently, the prevalent postoperative analgesics employed in clinical practice include opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Opioids are commonly used for postoperative pain relief. However, they are associated with numerous risks, including gastrointestinal reactions, pruritus, respiratory depression, hyperalgesia, nausea, constipation, dizziness, and dependence (Ringold et al. 2015, Fiore et al. 2019, Grant et al. 2022), and their abuse can even lead to death (Glare et al. 2019). NSAIDs, such as ibuprofen, diclofenac sodium, and acetaminophen, generally have weaker analgesic effects and shorter durations of action (4–6 hours), making them suitable for treating mild to moderate pain (Amaechi et al. 2021). Additionally, NSAIDs are associated with potential side effects, such as digestive ulcers, gastrointestinal bleeding, and liver damage (Moore et al. 2018, Radi et al. 2019).

Thus far, no therapeutic agent has been identified that effectively mitigates pain devoid of adverse effects. Consequently, the challenge lies in achieving efficacious postoperative pain control without hindering patient recovery. The advent of postoperative multimodal analgesia has shown promise. Multimodal analgesia facilitates a reduction in individual drug dosages, thereby minimizing associated adverse effects, augmenting analgesic efficacy, and optimising the therapeutic effect-to-side effect ratio (Kehlet et al. 1993, Manworren 2015). Furthermore, it expedites the Enhanced Recovery After Surgery (ERAS) process (Joshi et al. 2019), resulting in its endorsement by numerous guidelines and adoption as the standard of care for postoperative patients (Chou et al. 2016, Ladha et al. 2016). A critical element of multimodal pain management is preemptive analgesic dosing as opposed to reactive medication use (Barr et al. 2020). NSAIDs are frequently employed for preventive analgesia (American Society of Anesthesiologists Task Force on Acute Pain 2012, Chou et al. 2016), which can reduce central sensitization caused by surgical incisions, reduce the need for postoperative opioids, and relieve postoperative pain (Doleman et al. 2015, Ren et al. 2020). However, the commonly used NSAIDs are only suitable for mild and moderate pain, with short duration and large gastrointestinal side effects (Moore et al. 2018, Radi et al. 2019, Amaechi et al. 2021).

Meloxicam, a long-acting enolic acid NSAID characterized by selective cyclooxygenase-2 (COX-2) inhibition, can effectively inhibit prostaglandin synthesis and significantly reduce gastrointestinal adverse reactions. It has a potent analgesic effect lasting up to 24 hours and is primarily utilized for symptom relief in osteoarthritis and rheumatoid arthritis (Khalil et al. 2020, Yu et al. 2022). Due to its limited water solubility (Khalil et al. 2020), Meloxicam exhibits a slow onset following oral administration, with peak plasma concentrations attained at approximately 4 to 5 hours post-administration (Yu et al. 2022), rendering it suboptimal for acute pain management.

QP001, a novel solution formulation of Meloxicam, demonstrates improved water solubility, rapid onset, prolonged duration, and potent analgesic efficacy following intravenous administration. In a previous
study, QP001 exhibited rapid distribution, reaching peak concentrations at 1.8 minutes after administration. The 15–60 mg dosage range was well tolerated, with no serious adverse events observed. To further evaluate the efficacy and safety of QP001, a multicenter, randomized, double-blind, controlled clinical trial was conducted, enrolling patients presenting with moderate to severe pain following abdominal surgery.

Materials and methods

Study design and subjects

Following the Declaration of Helsinki, this multicenter, randomized, double-blind, placebo-parallel controlled clinical study was conducted at 11 medical centers in China to evaluate the efficacy and safety of QP001 injection in subjects with moderate to severe pain following abdominal surgery. The National Medical Products Administration (License 2021LP00439) and the ethics committee of each participating institution approved the study. The trial was prospectively registered at www.chictr.org.cn (ChiCTR2200055326). Written informed consent was obtained from all patients before enrollment.

A total of 108 subjects were intended for recruitment, with random assignment to either the QP001 injection 30mg group, the QP001 injection 60mg group, or the placebo group in a ratio of 1:1:1, resulting in 36 subjects per group.

In this study, participants comprised individuals scheduled for elective total hysterectomy under general anesthesia (without restrictions on surgical incision size) or other abdominal surgery (excluding total hysterectomy) with an anticipated single incision of $\geq 3$ cm. Male and female patients between the age of 18 and 65 years with an American Society of Anesthesiologists (ASA) physical status of I-II and a Body Mass Index (BMI) between 18 and 30 kg/m² were included in the study. The anticipated duration of the operation was between one and three hours, and patient-controlled intravenous analgesia (PCIA) treatment would be required postoperatively for 48 hours.

Exclusion criteria include the presence of active hemorrhagic diseases, such as gastrointestinal ulcers or perforations, which may worsen with NSAID usage; a medical history of myocardial infarction or coronary artery bypass surgery; concurrent severe liver, kidney, cardiovascular, or metabolic system diseases; coexisting chronic pain, migraine, or epileptic seizure disorders; allergy or contraindications to NSAIDs or other medications that may be used during the trial; hypertensive participants who have not undergone formal antihypertensive treatment or have poor blood pressure control; and clinically significant abnormalities detected in laboratory tests during the screening phase.

Study Procedures

The study comprised three phases: the screening period (from signing the informed consent form to successful randomization), the treatment period (from successful randomization to 48 hours after anesthesia recovery), and the follow-up observation period (from 48 hours after anesthesia recovery to
Day 5 ± 1). All eligible participants received a unique randomization number, which was assigned according to a predetermined randomization schedule, generated centrally by a computer. Both the subjects and investigators responsible for outcome data collection remained blinded to treatment assignment.

In order to reduce bias and human intervention factors, the trial employed a blinded evaluator and an unblinded administrator, given that the two drugs were readily distinguishable from one another. The unblinded administration investigators were not involved in protocol-specific postoperative outcome assessments. Propofol, sufentanil, remifentanil, and inhaled anesthetics were used to induce and maintain general anesthesia in abdominal surgery. Immediately following the conclusion of surgery, the remifentanil infusion was stopped (± 2 minutes), and an additional injection of sufentanil (0.1µg/kg) was given. Other opioid or non-opioid analgesics were prohibited during anesthesia. According to the randomization table, QP001 or placebo was injected intravenously through the upper extremity 10 minutes prior to the beginning of surgery, and the injection was completed within 15 to 30 seconds. The second intravenous was administered 24 hours (± 15 minutes) after the initial QP001 or placebo injection.

Pain intensity was scored by an 11-point numerical rating scale (NRS; 0–10 points, 0 no pain, 10 worst pain) immediately after the subjects emerged from anesthesia. Anesthesia recovery was recorded as 0h and pain intensity was evaluated at 0h, 1h, 2h, 3h, 6 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 30 h, 36 h, 42 h, 48 h after anesthesia recovery. The PCIA was initiated as soon as the 0h NRS score was determined. The PCIA pump contained morphine hydrochloride injection (0.2 mg/mL prepared with normal saline, total volume ≥ 200 mL). The parameters of PCIA equipment were as follows: Bolus administration of 1mg, locking time interval of 5min, maximum cumulative administration of morphine within 24 hours not exceeding 60mg. If PCIA analgesia was insufficient during the treatment period, 2mg morphine could be administered intravenously as rescue analgesia. The minimum interval between two consecutive rescue analgesics was 15min, and the dosage of rescue analgesic morphine was included in the total dosage of morphine. Prophylactic antiemetics were not allowed in the study. According to the occurrence of nausea and vomiting in the subjects, researchers were able to prescribe antiemetics, which was accurately recorded in both the original records and eCRF.

### Efficacy assessments

The primary efficacy endpoint was the total morphine consumption (including the sum of PCIA and rescue analgesic morphine consumption) within 24 hours after the first administration. Secondary efficacy endpoints included: total morphine consumption within 48 hours and 24–48 hours after the first administration; the effective pressing times of PCIA within 24 hours and 48 hours after the first administration; The area under curve(AUC) of pain intensity-time at the following different intervals: AUC$_{0-24}$, AUC$_{24-48}$, AUC$_{0-48}$, AUC$_{18-24}$, AUC$_{42-48}$; Pain intensity score immediately after anesthesia recovery; The time to first use of rescue analgesic; Morphine relief analgesia ratio within 24 hours and 48 hours.

### Safety assessments
Safety assessments included adverse events (AEs), vital signs, physical examination, laboratory tests (blood routine, blood biochemistry, urinalysis, coagulation function), electrocardiogram, etc., and early withdrawal due to safety or tolerability reasons. All AEs and laboratory variables were evaluated according to the Common Terminology Criteria for Adverse Events 5.0 (CTCAEs 5.0). The investigators rated the association of AEs with the study drug as definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated according to whether the AE occurred in a reasonable chronological order with the study drug administration, the type of drug reaction, and whether the reactions abated, disappeared, or recur after drug discontinuation. AEs that were judged to be related to the trial product were considered adverse drug reactions (ADRs). When an AE occurs, it should be managed aggressively, regardless of whether the event is causally related to the study drug. Serious adverse events (SAEs) were identified when daily functions were impaired or life-threatening and hospitalization or prolonged hospitalization was required.

**Statistical analysis**

This study is exploratory, and no estimation of sample size is performed. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed as frequency(percentage).

Missing pain scores were imputed with a score of 3 when the investigator confirmed that the participant was asleep. The Last Observation carried forward in the 4-hour time window (W4LOCF) was used as NRS pain score during rescue administration, that is, the NRS pain score at the scheduled scoring point was replaced with the NRS pain score before rescue. Other NRS pain scores with missing data were imputed using Last observation carried forward (LOCF). The mean AUC of NRS pain intensity scores was calculated by the trapezoidal method for each treatment group. Generalized linear regression models were used to compare the total morphine consumption within 24 and 48 hours after the first administration, times of effective button-pressing within 24 and 48 hours, pain intensity score immediately after anesthesia recovery, and cumulative NRS pain intensity score between the QP001 groups and placebo group. A multivariate logistic regression model was used to compare the rates of rescue use between the QP001 groups and the placebo group within 24 and 48 hours after the first administration. Multiple regression models adjusted for potential confounders, including age, height, weight, sex, study center, type of surgery, duration of surgery, and intraoperative sufentanil dosage. The time to first rescue medication was analyzed using Kaplan-Meier survival analysis, and the survival curves of three treatment groups using the log-rank test.

Safety endpoints including the incidence of AEs, ADRs, SAEs, SADRs, and most common ADRs were summarised using descriptive statistics by treatment group.

SPSS statistical software 26.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis. A statistically significant difference was considered as a $P$-value $\leq 0.05$ (two-sided) for all treatment comparisons.
Results

A total of 122 subjects were screened in this study, of whom 14 cases failed to be screened, 108 cases were randomly enrolled, 36 cases were in each group, and 106 cases completed the trial. Two subjects in the placebo group withdrew from the study prematurely without intervention (Fig. 1). Subject characteristics of the three treatment groups are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo group (n = 34)</th>
<th>30mg group (n = 36)</th>
<th>60mg group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>49.0 (7.0)</td>
<td>50.0 (7.5)</td>
<td>51.0 (9.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>31 (91.2)</td>
<td>32 (88.9)</td>
<td>35 (97.2)</td>
</tr>
<tr>
<td>Han nationality, n (%)</td>
<td>33 (97.1)</td>
<td>35 (97.2)</td>
<td>35 (97.2)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>157.9 (5.6)</td>
<td>159.2 (5.8)</td>
<td>156.8 (4.6)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>60.1 (8.4)</td>
<td>61.7 (8.5)</td>
<td>57.6 (7.5)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>24.0 (2.6)</td>
<td>24.3 (3.0)</td>
<td>23.4 (2.6)</td>
</tr>
<tr>
<td>ASA classification, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (17.6)</td>
<td>8 (22.2)</td>
<td>10 (27.8)</td>
</tr>
<tr>
<td>II</td>
<td>28 (82.4)</td>
<td>28 (77.8)</td>
<td>26 (72.2)</td>
</tr>
<tr>
<td>Type of surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic surgery</td>
<td>29 (85.3)</td>
<td>27 (75.0)</td>
<td>33 (91.7)</td>
</tr>
<tr>
<td>Other abdominal surgery</td>
<td>5 (14.7)</td>
<td>9 (25.0)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Duration of surgery (h), mean (SD)</td>
<td>2.1 (1.0)</td>
<td>2.0 (1.0)</td>
<td>1.8 (1.0)</td>
</tr>
<tr>
<td>Intraoperative sufentanil dosage (ug), mean (SD)</td>
<td>24.2 (3.3)</td>
<td>24.7 (3.4)</td>
<td>23.0 (3.0)</td>
</tr>
<tr>
<td>Time of awakening (min), mean (SD)</td>
<td>18.1 (17.1)</td>
<td>15.5 (9.1)</td>
<td>16.1 (11.6)</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range

In the analysis of the primary efficacy endpoint in subjects with moderate to severe pain following abdominal surgery, the total consumption of morphine in the QP001 30mg and 60mg groups was significantly lower than that in the placebo group within 24 hours after the first administration (mean [SD]: 5.11 [5.46] vs 8.86 [7.67], P = 0.011; 3.11 [3.08] vs 8.86 [7.67], P < 0.001) (Table 2). Preemptive administration of QP001 injection significantly reduced morphine consumption in subjects with moderate to severe pain following abdominal surgery, and there was a certain administration effect.
### Table 2
Primary endpoint analysis.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean (SD)</th>
<th>β (SE)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group</td>
<td>33</td>
<td>8.86(7.67)</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>30mg group</td>
<td>36</td>
<td>5.11(5.46)</td>
<td>-3.04(1.20)</td>
<td>0.011</td>
</tr>
<tr>
<td>60mg group</td>
<td>36</td>
<td>3.11(3.08)</td>
<td>-4.80(1.19)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Generalised linear regression model (GLM) was used to test the differences of total morphine consumption within 24 hours after the first administration between the QP001 groups and Placebo group. Models were adjusted for age, sex, height, weight, study site, Type of surgery, Duration of surgery and intraoperative sufentanil dosage. SD, standard deviation; SE, standard error.

The Numerical rating scale (NRS) pain intensity–time curves after preemptive application of QP001 injection and placebo was shown in Fig. 2(A,B). Compared to the placebo control group, the total morphine consumption within 48 hours and 24–48 hours after the first administration, as well as the effective pressing times of analgesic pump within 24 hours and 48 hours after the first administration were significantly reduced in the QP001 groups (P<0.05). There were no significant differences of pain intensity score immediately after anesthesia recovery at rest and during movement, and the proportion of morphine rescue analgesia within 24 hours and 48 hours (P>0.05) (Table 3). The area under curve of pain intensity-time during movement in the QP001 groups were significantly decreased (P<0.05). The area under curve of pain intensity-time at rest was significantly decreased only in the 60mg group (P<0.05) (Fig. 2(C,D)). The proportion of morphine rescue analgesia was low in all three treatment groups (<20%), and there was no statistically significant difference in survival distribution between survival curves (P = 0.218)(Fig. 3).
### Table 3
Secondary endpoints analysis.

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Placebo group (n = 34)</th>
<th>30mg group (n = 36)</th>
<th>60mg group (n = 36)</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) /n(%)</td>
<td>Mean (SD) /n(%)</td>
<td>Mean (SD) /n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total morphine consumption within 48 hours after the first administration (mg)</td>
<td>12.50(11.96)</td>
<td>6.02(6.45)</td>
<td>3.57(3.53)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Total morphine consumption within 24–48 hours after the first administration (mg)</td>
<td>3.64(5.80)</td>
<td>0.91(1.97)</td>
<td>0.46(0.89)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Times of effective pressing within 24 hours after the first administration</td>
<td>8.7(7.6)</td>
<td>5.1(5.1)</td>
<td>3.0(2.5)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Times of effective pressing within 48 hours after the first administration</td>
<td>12.6(11.8)</td>
<td>6.1(6.2)</td>
<td>3.5(2.9)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Pain intensity score immediately after anesthesia recovery at rest</td>
<td>1.4(1.6)</td>
<td>0.9(1.6)</td>
<td>1.2(1.3)</td>
<td>0.391</td>
<td></td>
</tr>
<tr>
<td>Pain intensity score immediately after anesthesia recovery during movement</td>
<td>1.8(2.0)</td>
<td>1.4(2.0)</td>
<td>1.7(1.5)</td>
<td>0.676</td>
<td></td>
</tr>
<tr>
<td>Morphine relief analgesia ratio within 24 hours</td>
<td>6(18.2)c</td>
<td>4(11.1)</td>
<td>3(8.3)</td>
<td>0.190</td>
<td></td>
</tr>
<tr>
<td>Morphine relief analgesia ratio within 48 hours</td>
<td>6(18.2)c</td>
<td>4(11.1)</td>
<td>3(8.3)</td>
<td>0.190</td>
<td></td>
</tr>
</tbody>
</table>

*a Generalised linear regression model (GLM) was used to test the differences between the QP001 groups and Placebo group. *b Logistic regression model was used to test the differences in rescue medication rate between the QP001 groups and Placebo group. Models were adjusted for age, sex, height, weight, study site, Type of surgery, Duration of surgery, and intraoperative sufentanil dosage. SD, standard deviation. *c one subject withdrew early from the trial. *P values are for comparison with placebo control.

Preoperative Preemptive analgesia with 30mg and 60mg of QP001 was well tolerated in subjects with moderate to severe pain following abdominal surgery (Table 4). 88 of 106 subjects (83.0%) experienced at least one AE, including 29 (85.3%) in the placebo group, 28 (77.8%) in the QP001 30mg group, and 31 (86.1%) in the QP00160mg group.

According to the CTCAE5.0 criteria, AEs were mainly grade 1–2. Except for one case of intraoperative bleeding in the placebo group that led to premature withdrawal from the trial, the severity of other AEs was not more than grade 3. The incidence of ADRs was 67.6% (23 cases) in placebo group, 55.6% (20
cases) in QP001 30mg group and 50.0% (18 cases) in QP001 60mg group. The main ADRs were nausea, vomiting, abdominal distension, increased/decreased blood pressure, positive fecal occult blood, hypokalemia, dizziness, anemia, fever, etc. Except for 1 case (2.8%) of anemia grade 3 ADR in QP001 60mg group, the others were grade 1 or 2 ADR. There were no serious adverse drug reactions (SADRs) and no AEs leading to death in the three groups during the whole study period (Table 4).
Table 4
Analysis of Adverse Events and Adverse Reactions Incidence.

<table>
<thead>
<tr>
<th>Index</th>
<th>Placebo group (n = 34)</th>
<th>30mg group (n = 36)</th>
<th>60mg group (n = 36)</th>
<th>QP001 group, Total (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs, n(%)</td>
<td>29(85.3)</td>
<td>28(77.8)</td>
<td>31(86.1)</td>
<td>59(81.9)</td>
</tr>
<tr>
<td>Levels 3–5 AEs, n(%)</td>
<td>3(8.8)</td>
<td>1(2.8)</td>
<td>1(2.8)</td>
<td>2(2.8)</td>
</tr>
<tr>
<td>SAEs, n(%)</td>
<td>2(5.9)</td>
<td>1(2.8)</td>
<td>1(2.8)</td>
<td>2(2.8)</td>
</tr>
<tr>
<td>Poor healing</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>1(2.8)</td>
<td>1(1.4)</td>
</tr>
<tr>
<td>Intraoperative bleeding</td>
<td>1(2.9)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Gastric/pancreatic fistula</td>
<td>1(2.9)</td>
<td>1(2.8)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>AEs that lead to withdrawal, n(%)</td>
<td>1(2.9)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>ADRs, n(%) (≥ 5% in either group)</td>
<td>23(67.6)</td>
<td>20(55.6)</td>
<td>18(50.0)</td>
<td>38(52.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10(29.4)</td>
<td>4(11.1)</td>
<td>10(27.8)</td>
<td>14(19.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9(26.5)</td>
<td>3(8.3)</td>
<td>6(16.7)</td>
<td>9(12.4)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>7(20.6)</td>
<td>2(5.6)</td>
<td>2(5.6)</td>
<td>4(5.6)</td>
</tr>
<tr>
<td>Decreased Blood pressure</td>
<td>4(11.8)</td>
<td>8(22.2)</td>
<td>9(25.0)</td>
<td>17(23.6)</td>
</tr>
<tr>
<td>Increased Blood pressure</td>
<td>1(2.9)</td>
<td>1(2.8)</td>
<td>2(5.6)</td>
<td>3(4.2)</td>
</tr>
<tr>
<td>Positive occult blood of fecal</td>
<td>1(2.9)</td>
<td>4(11.1)</td>
<td>1(2.8)</td>
<td>5(6.9)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6(17.6)</td>
<td>2(5.6)</td>
<td>2(5.6)</td>
<td>4(5.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4(11.8)</td>
<td>1(2.8)</td>
<td>1(2.8)</td>
<td>2(2.8)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2(5.9)</td>
<td>4(11.1)</td>
<td>2(5.6)</td>
<td>6(8.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1(2.9)</td>
<td>2(5.6)</td>
<td>1(2.8)</td>
<td>3(4.2)</td>
</tr>
<tr>
<td>Fever</td>
<td>4(11.8)</td>
<td>1(2.8)</td>
<td>1(2.8)</td>
<td>2(2.8)</td>
</tr>
<tr>
<td>Levels 3–5 ADRs, n(%)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>1(2.8)</td>
<td>1(0)</td>
</tr>
<tr>
<td>SADRs, n(%)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>

AEs, Adverse Events; ADRs, Adverse Drug Reaction; SAEs, Serious Adverse Events; SADRs, Serious ADRs.

Discussion

This multicenter, randomized, double-blind, placebo-controlled clinical trial confirmed the efficacy and safety of QP001 injection for moderate to severe pain following abdominal surgery, and preoperative
preemptive administration of QP001 injection provided analgesia and reduces opioid consumption in subjects with moderate to severe pain following abdominal surgery.

NSAIDs and COX-2 inhibitors are widely endorsed as non-opioid analgesics for postoperative pain management, as supported by numerous guidelines (American Society of Anesthesiologists Task Force on Acute Pain 2012, Chou et al. 2016, Coccolini et al. 2022). QP001 injection, a novel formulation of meloxicam solution, demonstrates selective COX-2 inhibition, high water solubility, rapid onset, prolonged duration, and potent analgesic effects, making it a viable candidate for acute postoperative pain relief. This study indicated that preemptive administration of 30 mg and 60 mg QP001 injections reduced total opioid consumption following abdominal surgery by 42.33% and 64.90% for moderate to severe pain, respectively. After controlling for potential confounders, significant reductions in opioid consumption and the number of successful analgesic pump compressions were observed at 24 hours, 48 hours, and 24–48 hours. In the phase 2 study conducted by Rechberger et al. (2019), an intravenous nanocrystal formulation of meloxicam was administered the day following open uterine surgery. Results indicated that intravenous meloxicam doses ranging from 5 mg to 60 mg produced rapid analgesia, reduced the need for opioid rescue, and were well tolerated. However, the prophylactic use of meloxicam during hysterectomy, as reported by Thompson et al. (2000) and Anwari et al. (2008), decreased postoperative pain but did not reduce opioid consumption. This outcome may be attributed to the low solubility and slow absorption of meloxicam, necessitating opioid rescue for acute pain relief. The QP001 solution and nanocrystals suspension injection address the issue of low solubility, enabling rapid effects upon administration, thereby facilitating improved acute pain management and a subsequent decrease in opioid consumption.

In this study, we employed a preoperative preemptive administration strategy for QP001 injection rather than reactive pharmacologic analgesia. Multiple studies have corroborated that preoperative preemptive analgesia is advantageous in controlling postoperative acute pain and reducing opioid consumption (Doleman et al. 2015, Nir et al. 2016, Ren et al. 2020, Xuan et al. 2022), thus forming an essential component of multimodal analgesia (Barr et al. 2020). Compared to the placebo group, the 60 mg group exhibited a significant reduction in the area under the curve (AUC) of pain intensity-time both at rest and during movement, while the 30 mg group experienced a marked decrease in the AUC of pain intensity-time during movement. Our preemptive administration of QP001 injection prior to the onset of surgical noxious stimuli mitigates the alteration of central sensory processing and the subsequent inflammatory damage stemming from cytokine and prostaglandin release, thereby preventing central sensitization and hyperalgesia more effectively than interventions applied post-surgery (Kissin 2000, Wilder-Smith 2000). Additionally, compared with the insufficient analgesia of intravenous nanocrystal formulation of meloxicam at treatment endpoint (18–24 hours and 42–48 hours) (U.S. Food and Drug Administration (FDA) 2020), QP001 significantly reduced the AUC of pain intensity-time at treatment endpoint, indicating that QP001 exerts sustained analgesic effects. Consequently, it holds promise as a once-daily postoperative analgesic option.
There was no statistically significant difference observed between pain scores at rest or during movement, and the proportion of opioid rescue at either 24 hours or 48 hours following awakening. This outcome may be associated with the study's protocol. To preempt breakthrough pain upon emergence from anesthesia, an additional 0.1µg/kg sufentanil was administered immediately after surgery completion. All subjects in the three groups awoke within 20 minutes and were within the effective analgesic timeframe of the supplemental sufentanil, which may potentially account for the lack of observed differences in pain score. In an effort to provide an optimal analgesic experience for all participants, we opted for a more proactive patient-controlled intravenous analgesia (PCIA) approach rather than passive researcher-administered rescue. Consequently, the PCIA was found to be effective, with rescue rates for all three groups totaling less than 20%. Although the survival curves for the QP001 groups tended to increase, no statistically significant difference was identified, possibly due to the lower rates of rescue analgesia.

Preemptive administration of QP001 injection at doses of 30 to 60 mg demonstrated tolerability in subjects experiencing moderate to severe pain following abdominal surgery. The overall incidence of AEs and ADRs was comparable between the QP001 group and the placebo group. Except for one grade 3 AE involving intraoperative bleeding in the placebo group and one grade 3 ADR relating to anemia in the QP001 60 mg group, all reported cases were categorized as grade 1–2. Although no statistical comparisons were conducted, the QP001 group displayed lower rates of nausea, vomiting, abdominal distension, dizziness, and fever. The lower incidences of nausea, vomiting, and dizziness may be attributable to decreased opioid utilization, while the reduced occurrence of fever could be linked to the antipyretic properties of QP001. Notably, postoperative fever is an essential clinical indicator of postoperative inflammation and infection (Vicente López et al. 2018, Hwang et al. 2020). Consequently, cautious discernment should be exercised when employing nonsteroidal anti-inflammatory drugs (NSAIDs) for analgesia in clinical settings to differentiate between these conditions. Throughout the study, there were no serious ADRs and AEs that resulted in death.

Our investigation acknowledges several constraints. Primarily, the modest cohort size and stringent selection criteria might limit the applicability of outcomes to the expansive patient population encountering moderate to severe pain after abdominal surgical procedures. Subsequently, the study medication was discontinued 48 hours after surgery, and conventional analgesics were prescribed to patients who required continued pain management. Assessment of analgesic efficacy not conducted beyond the designated 48-hour timeframe.

In conclusion, preemptive administration of QP001 injection provides effective analgesia and reduces opioid consumption in subjects with moderate to severe pain following abdominal surgery, while maintaining a favorable safety profile.

Declarations

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**Author contributions** YZ, SW and WO contributed to the study conception and design. YZ, KD, ZB, XH, MX, XL, YG, JL, MY, YZ, WZ, RD and YS performed the research. Data collection and analysis were performed by YZ, SW and BW. The first draft of the manuscript was written by YZ, BW and KD. ZW, YJ, SY and SW were responsible for the visualization of the manuscript. All authors read and approved the final manuscript.

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**Data availability** The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Conflict of interest** The authors declare that they have no conflict of interest.

**References**


Figures

Figure 1

Enrollment flow diagram
Figure 2

Numerical rating scale (NRS) pain intensity—time curves and Area under curve (AUC) of pain intensity—time for three treatment groups at rest (A,C) and during movement (B,D). SE, standard error. Comparison with placebo control group *p < 0.05, **p < 0.01
Figure 3

Kaplane-Meier plot of time to first rescue medication through 48h after the first administration