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ORIGINAL ARTICLE

Preemptive QP001, a fast-acting meloxicam formulation, provides analgesia and reduces opioid consumption 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 (30 mg or 60 mg) or a placebo pre-surgery. The primary efficacy endpoint was the total morphine consumption within 24 h 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 30 mg group and 60 mg group, versus placebo group, were significantly lower over the following 24 h (5.11[5.46] vs 8.86[7.67], $P=0.011$; 3.11[3.08] vs 8.86[7.67], $P<0.001$), respectively. The total morphine consumption in the QP001 30 mg and 60 mg groups, versus placebo group, was also significantly decreased over the following 48 h, including the 24–48 h period ($P\leq0.001$). The QP001 30 mg and 60 mg groups, versus placebo, showed a significant decrease in the area under the curve for pain intensity-time as well as a significant decrease in the effective pressing times of the analgesic pump over the 24 h and 48 h periods ($P<0.05$). The QP001 groups, versus placebo, show no significant different in Adverse Events or Adverse Drug Reactions ($P>0.05$).

Conclusion Preoperative/preemptive QP001 provides analgesia and reduces opioid consumption in patients with moderate to severe pain following abdominal surgery, while maintaining a favorable safety profile.

Keywords Long-lasting analgesia · QP001 · Abdominal surgery · Postoperative pain · NSAIDs

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 increases other negative outcomes, including prolonged hospital stay, delayed wound healing, and raised medical costs (Rawal 2005; Argoff 2014; Kehlet 2018). Although the management of postoperative pain has made significant progress, it still faces great challenges (Buvanendran et al. 2015). Moderate or severe pain is experienced by 48% and 19% of patients, respectively, in the 24 h period following surgery, according to the Perioperative Quality Improvement Programme (PQIP) annual reports (Small et al. 2020). Consequently, the development of safe and effective medications and treatment protocols for postoperative pain is of significant clinical relevance.

Current 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,

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dizziness, and dependence (Ringold et al. 2015; Fiore et al. 2019; Grant et al. 2022), whilst their abuse can be fatal (Glare et al. 2019). NSAIDs, such as ibuprofen, diclofenac sodium, and acetaminophen, generally have weaker analgesic effects and shorter durations of action (4–6 h), making them more suitable for treating mild to moderate pain (Amaechi et al. 2021). NSAIDs also have potent side effects, including digestive ulcers, gastrointestinal bleeding, and liver damage (Moore et al. 2018; Radi et al. 2019).

As no current pharmaceutical can effectively mitigate pain without adverse effects, the clinical challenge is to achieve efficacious postoperative pain control without hindering patient recovery. The advent of postoperative multimodal analgesia shows promise in achieving this. Multimodal analgesia facilitates a reduction in individual drug dosages, thereby minimizing associated adverse effects, augmenting analgesic efficacy, and optimizing the therapeutic effect/side effect ratio (Kehlet et al. 1993; Manworren 2015). Furthermore, multimodal analgesia expedites the Enhanced Recovery After Surgery (ERAS) process (Joshi et al. 2019), resulting in its endorsement by numerous guidelines as well as its 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/preoperative as well as reactive/postoperative analgesic 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 and postoperative opioid requests, as well as suppress postoperative pain (Doleman et al. 2015; Ren et al. 2020). However, the commonly used NSAIDs are only suitable for mild and moderate pain, with a short duration of action and significant gastrointestinal side effects (Moore et al. 2018; Radi et al. 2019; Amaechi et al. 2021).

Meloxicam, a long-acting enolic acid NSAID, acts primarily via cyclooxygenase-2 (COX-2) inhibition, thereby inhibiting prostaglandin synthesis and significantly reducing gastrointestinal adverse reactions. Meloxicam has a potent analgesic effect lasting up to 24 h and is mainly 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 4–5 h 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. Previous study shows QP001 to exhibit rapid distribution, reaching peak concentrations at 1.8 min following administration, with the 15–60 mg dosage range being 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.

Methods

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 patients 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 https://www.chictr.org.cn (ChiCTR2200055326). Written informed consent was obtained from all patients before enrollment.

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

Subjects

Participants were 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 ≥ 3 cm. Male and female patients aged between 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/m^2 were included in the study. The anticipated duration of the operation was between one and three hours, with patient-controlled intravenous analgesia (PCIA) treatment being required postoperatively for 48 h.

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 was comprised of three phases: the screening period (from signing the informed consent form to successful randomization); the treatment period (from successful randomization to 48 h after anesthesia recovery); and the follow-up observation period (from 48 h 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 during abdominal surgery. Immediately following surgery conclusion, the remifentanil infusion was stopped (± 2 min), and an additional injection of sufentanil (0.1 μg/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 min prior to the beginning of surgery, and the injection was completed within 15 to 30 s. The second intravenous injection was administered 24 h (± 15 min) 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 patients emerged from anesthesia. Anesthesia recovery was recorded as 0 h and pain intensity was evaluated at 0 h, 1 h, 2 h, 3 h, 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 0 h 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 1 mg, locking time interval of 5 min, maximum cumulative administration of morphine within 24 h not exceeding 60 mg. If PCIA analgesia was insufficient during the treatment period, 2 mg morphine could be administered intravenously as rescue analgesia. The minimum interval between two consecutive rescue analgesics was 15 min, 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 electronic case report form (eCRF).

Efficacy assessments

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

Safety assessments

Safety assessments included adverse events (AEs), vital signs, physical examination, laboratory tests (blood routine, blood biochemistry, urinalysis, coagulation function), and electrocardiogram, as well as 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 occurred, it was 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-h time window (W4LOCF) was used as NRS pain score

during rescue administration, i.e., 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 h after the first administration, times of effective button-pressing within 24 and 48 h, 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 h 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 the three treatment groups using the log-rank test.

Safety endpoints include the incidence of AEs, ADRs, SAEs, SADRs, and most common ADRs were summarized 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 ≤ 0.05 (two-sided) for all treatment comparisons.

Results

A total of 122 patients were screened in this study, of whom 14 cases failed to be successfully screened, leaving 108 cases to be randomly enrolled. 36 cases were in each group, and 106 cases completed the trial. Two participants 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.

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 30 mg and 60 mg groups, versus placebo group, was significantly lower within 24 h after the first administration (5.11[5.46] vs 8.86 [7.67], P = 0.011; 3.11[3.08] vs 8.86 [7.67], $P < 0.001$), respectively (Table 2). Preemptive administration of QP001 injection significantly reduced morphine consumption in patients with moderate to severe pain following abdominal surgery, indicating an administration effect.

The Numerical rating scale (NRS) for pain intensity—time curves after preemptive application of QP001 injection and placebo are shown in Fig. 2A, B. Compared to the placebo control group, the total morphine consumption within 48 h and 24–48 h after the first administration, as well as the effective pressing times of analgesic pump within 24 h and 48 h after the first administration were significantly reduced in the QP001 groups ($P < 0.05$). There were no significant differences of pain intensity scores immediately after anesthesia recovery at rest and during movement, and

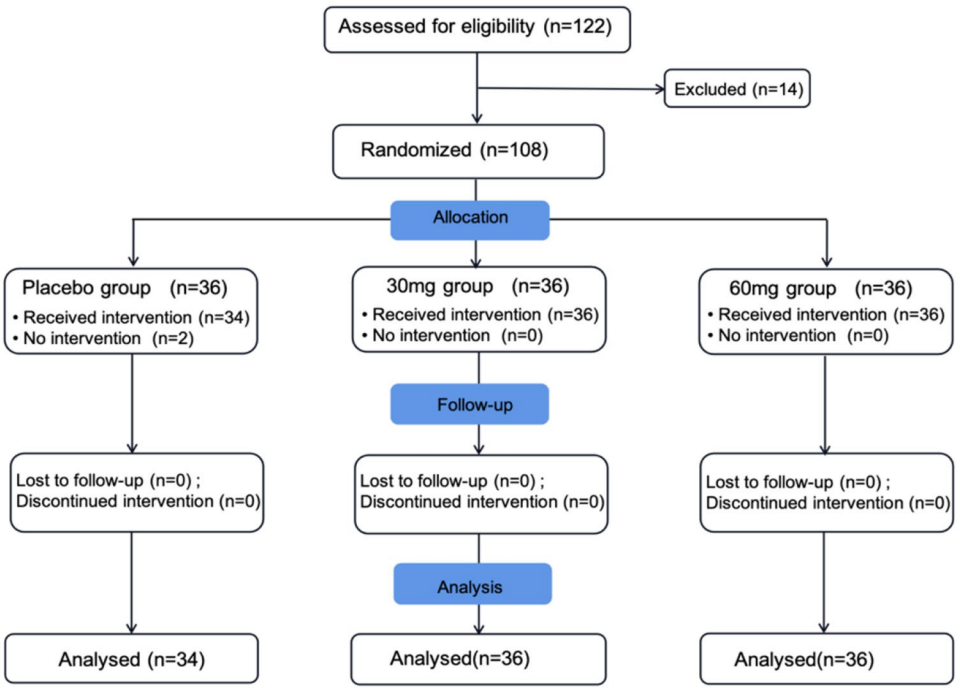

Fig. 1 Enrollment flow diagram

Table 1 Baseline characteristics of three groups

Characteristics	Placebo group (n = 34)	30 mg group (n = 36)	60 mg group (n = 36)
Age (years), median (IQR)	49.0(7.0)	50.0(7.5)	51.0(9.5)
Female, n (%)	31(91.2)	32(88.9)	35(97.2)
Han nationality, n (%)	33(97.1)	35(97.2)	35(97.2)
Height (cm), mean (SD)	157.9(5.6)	159.2(5.8)	156.8(4.6)
Weight (kg), mean (SD)	60.1(8.4)	61.7(8.5)	57.6(7.5)
BMI (kg/m^2), mean (SD)	24.0(2.6)	24.3(3.0)	23.4(2.6)
ASA classification, n (%)			
I	6(17.6)	8(22.2)	10(27.8)
II	28(82.4)	28(77.8)	26(72.2)
Type of surgery, n (%)			
Gynecologic surgery	29(85.3)	27(75.0)	33(91.7)
Other abdominal surgery	5(14.7)	9(25.0)	3(8.3)
Duration of surgery (hr), mean (SD)	2.1(1.0)	2.0(1.0)	1.8(1.0)
Intraoperative sufentanil dosage (ug), mean (SD)	24.2(3.3)	24.7(3.4)	23.0(3.0)
Time of awakening (min), mean (SD)	18.1(17.1)	15.5(9.1)	16.1(11.6)

SD standard deviation, *IQR* interquartile range

Table 2 Primary endpoint analysis

Group	Total morphine consumption within 24 h after the first administration			
	n	Mean (SD)	*β (SE)*	*p* value[a]
Placebo group	33	8.86(7.67)	Reference	–
30 mg group	36	5.11(5.46)	− 3.04(1.20)	0.011
60 mg group	36	3.11(3.08)	− 4.80(1.19)	< 0.001

[a]Generalized linear regression model (GLM) was used to test the differences of total morphine consumption within 24 h 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 proportion of morphine rescue analgesia within 24 h and 48 h ($P > 0.05$) (Table 3). The AUC of pain intensity-time during movement in the QP001 groups were significantly decreased ($P < 05$). The AUC of pain intensity-time at rest was significantly decreased only in the 60 mg group ($P < 05$), as shown in Fig. 2C, 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), see Fig. 3.

Preemptive analgesia with QP001 30 mg and 60 mg was well tolerated in patients with moderate to severe pain following abdominal surgery (Table 4). 88 of 106 participants (83.0%) experienced at least one AE, including 29 (85.3%) in the placebo group, 28 (77.8%) in the QP001 30 mg 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 were not more than grade 3. The incidence of ADRs was 67.6% (23 cases) in placebo group, 55.6% (20 cases) in QP001 30 mg group and 50.0% (18 cases) in QP001 60 mg group. The main ADRs were nausea, vomiting, abdominal distension, increased/decreased blood pressure, positive fecal occult blood, hypokalemia, dizziness, anemia, and fever. Except for one case (2.8%) of anemia grade 3 ADR in QP001 60 mg 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).

Discussion

This multicenter, randomized, double-blind, placebo-controlled clinical trial indicates the efficacy and safety of QP001 injection for moderate to severe pain following abdominal surgery, with preemptive QP001 injected administration providing analgesia and reducing opioid consumption in patients 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 preemptive candidate for acute postoperative pain

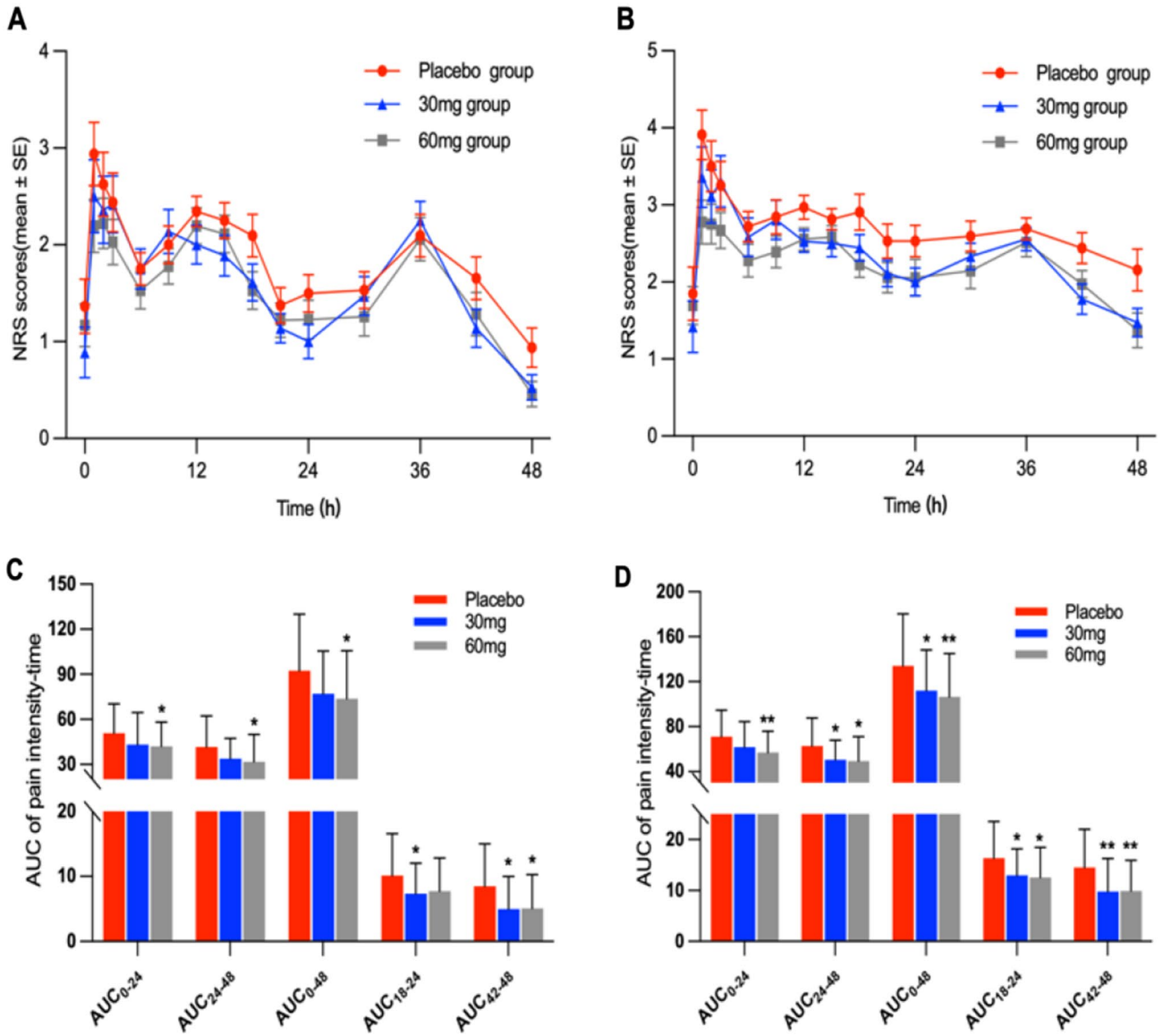

Fig. 2 Numerical rating scale (NRS) pain intensity—time curves and Area under curve (AUC) of pain intensity-time for three treatment groups at rest **A**, **C** and during movement **B**, **D**. SE, standard error. Comparison with placebo control group $*p < 0.05$, $**p < 0.01$

relief. This study indicated that preemptive administration of 30 mg and 60 mg QP001 injections reduced total opioid consumption following abdominal surgery by 42.33–64.90% 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 h, 48 h, and 24–48 h. 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 to 60 mg produced rapid analgesia, thereby reducing the need for opioid rescue, as well as being 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

Table 3 Secondary endpoints analysis

Secondary endpoints	Placebo group (n = 34)	30 mg group (n = 36)		60 mg group (n = 36)	
	Mean (SD) /n(%)	Mean (SD) /n(%)	*p*-value	Mean (SD) /n(%)	*p*-value
Total morphine consumption within 48 h after the first administration (mg)[a]	12.50(11.96)	6.02(6.45)	0.001	3.57(3.53)	< 0.001
Total morphine consumption within 24–48 h after the first administration (mg)[a]	3.64(5.80)	0.91(1.97)	0.001	0.46(0.89)	< 0.001
Times of effective pressing within 24 h after the first administration[a]	8.7(7.6)	5.1(5.1)	0.030	3.0(2.5)	< 0.001
Times of effective pressing within 48 h after the first administration[a]	12.6(11.8)	6.1(6.2)	0.001	3.5(2.9)	< 0.001
Pain intensity score immediately after anesthesia recovery at rest[a]	1.4(1.6)	0.9(1.6)	0.084	1.2(1.3)	0.391
Pain intensity score immediately after anesthesia recovery during movement[a]	1.8(2.0)	1.4(2.0)	0.066	1.7(1.5)	0.676
Morphine relief analgesia ratio within 24 h[b]	6(18.2)[c]	4(11.1)	0.208	3(8.3)	0.190
Morphine relief analgesia ratio within 48 h[b]	6(18.2)[c]	4(11.1)	0.208	3(8.3)	0.190

[a]Generalized 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

[c]One subject withdrew early from the trial. SD, standard deviation. *P* values are for comparison with placebo control

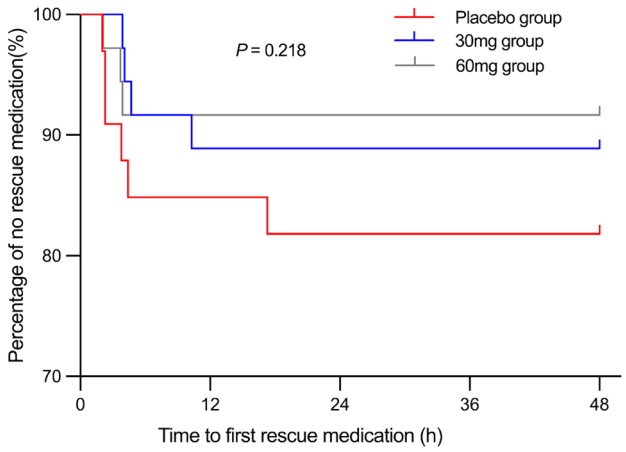

Fig. 3 Kaplane-Meier plot of time to first rescue medication through 48 h after the first administration

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), thereby 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 h and 42–48 h) (U.S. Food and Drug Administration (FDA) 2020), QP001 significantly reduced the AUC of pain intensity-time at the 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 h or 48 h following awakening. This outcome may be associated with the study's protocol. To preempt breakthrough pain upon emergence from anesthesia, an additional 0.1 μg/kg sufentanil was administered immediately after surgery completion. All subjects in the three groups awoke within 20 min 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. The PCIA was effective, with rescue rates for all three groups totaling less than 20%. Although the survival curves for the QP001 groups tended to increase,

Table 4 Analysis of adverse events and adverse reactions incidence

Index	Placebo group (n = 34)	30 mg group (n = 36)	60 mg group (n = 36)	QP001group, Total (n = 72)
AEs, n(%)	29(85.3)	28(77.8)	31(86.1)	59(81.9)
Levels 3–5 AEs, n(%)	3(8.8)	1(2.8)	1(2.8)	2(2.8)
SAEs, n(%)	2(5.9)	1(2.8)	1(2.8)	2(2.8)
Poor healing	0(0.0)	0(0.0)	1(2.8)	1(1.4)
Intraoperative bleeding	1(2.9)	0(0.0)	0(0.0)	0(0.0)
Gastric/pancreatic fistula	1(2.9)	1(2.8)	0(0.0)	1(1.4)
AEs that lead to withdrawal, n(%)	1(2.9)	0(0.0)	0(0.0)	0(0.0)
ADRs, n(%) (≥ 5% in either group)	23(67.6)	20(55.6)	18(50.0)	38(52.7)
Nausea	10(29.4)	4(11.1)	10(27.8)	14(19.4)
Vomiting	9(26.5)	3(8.3)	6(16.7)	9(12.5)
Abdominal distention	7(20.6)	2(5.6)	2(5.6)	4(5.6)
Decreased Blood pressure	4(11.8)	8(22.2)	9(25.0)	17(23.6)
Increased Blood pressure	1(2.9)	1(2.8)	2(5.6)	3(4.2)
Positive occult blood of fecal	1(2.9)	4(11.1)	1(2.8)	5(6.9)
Hypokalemia	6(17.6)	2(5.6)	2(5.6)	4(5.6)
Dizziness	4(11.8)	1(2.8)	1(2.8)	2(2.8)
Tachycardia	2(5.9)	4(11.1)	2(5.6)	6(8.3)
Anemia	1(2.9)	2(5.6)	1(2.8)	3(4.2)
Fever	4(11.8)	1(2.8)	1(2.8)	2(2.8)
Levels 3–5 ADRs, n(%)	0(0.0)	0(0.0)	1(2.8)	1()
SADRs, n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

AEs adverse events, *ADRs* adverse drug reaction, *SAEs* serious adverse events, *SADRs* serious ADRs.

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 may be mediated by 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 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 h after surgery, and conventional analgesics were prescribed to patients who required continued pain management. Assessment of analgesic efficacy not conducted beyond the designated 48-h 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.

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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 and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

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

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