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ORIGINAL ARTICLE

Efficacy and safety of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazin-3-carboxamide 1,1-dioxide, a rapid-acting meloxicam formulation, for analgesia after orthopaedic surgery under general anaesthesia: a randomized controlled trial

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Abstract

Background Postoperative pain management is one of the most challenging treatments after orthopaedic surgery, and improved medical treatment options are urgently needed. This study aimed to evaluate the efficacy and safety of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazin-3-carboxamide 1,1-dioxide (QP001) for moderate to severe pain following orthopaedic surgery.

Methods This randomized clinical trial enlisted patients experiencing moderate to severe pain following orthopaedic surgery in 20 hospitals in China. We allocated randomly 132 participants to receive 30 mg QP001 and 66 participants to receive 0.9% saline pre-surgery. The primary efficacy outcome was the total morphine consumption within 24 h.

Results The total morphine consumption in the QP001 group, versus placebo group, was significantly lower over the following 24 h [12.53 (10.51) vs. 26.13 (13.98), $P<0.001$]. The total morphine consumption in the QP001 group, versus placebo group, was also significantly decreased over the following 48 h ($P<0.001$). The QP001 group, versus placebo, showed a significant decrease in the effective pressing times of the analgesic pump, morphine relief analgesia ratio over the 24 h and 48 h periods and the area under the curve for pain intensity-time as well as a significant prolonged in the time of first pressing the analgesic pump and the time of first morphine rescue analgesia ($P<0.001$). The QP001 groups, versus placebo, show no significant difference in adverse events, but the incidence of adverse drug reactions decreased (59.4% vs. 75.8%, $P=0.023$).

Conclusion QP001 provides analgesia and reduces opioid consumption in patients with moderate to severe pain after orthopaedic surgery, with a favorable safety profile.

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

Introduction

Postoperative pain is an unpleasant experience that occurs after surgery and is one of the most challenging treatments after surgery (Kehlet 2018; Mitra et al. 2018). The American Pain Brief Research reported that 66% of patients experience moderate to severe postoperative pain during hospitalization (Buvanendran et al. 2015). orthopaedic surgery, especially total joint replacement, results in moderate to severe pain in a majority of patients (Maheshwari et al. 2009; Chunduri et al. 2022), and even 59% of patients still experience the same level of pain after 2 weeks (Buvanendran et al. 2015). Improvement in pain management is amongst the most substantial advances in the practice of total joint replacement surgery (Maheshwari et al. 2009). Early and adequate postoperative pain treatment is essential for early ambulation, prognosis and quality of life of patients (Russo et al. 2017).

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Despite significant advancements in modern medicine, postoperative pain continues to be a prevalent issue (Mitra et al. 2018). Opioids have always been common drugs for postoperative pain due to their rapid onset and powerful analgesic effect, but they also are associated with numerous risks, such as gastrointestinal reactions, respiratory depression, hyperalgesia, nausea, constipation, dizziness, lethargy, dependence, etc. (Hina et al. 2015; Ringold et al. 2015; Fiore et al. 2019; Grant et al. 2022), and even death due to overdose (Baker 2017). Although calls have been made to implement opioid-free analgesia, there is currently insufficient evidence that true opioid-free analgesia, would be appropriate on a broad scale, especially for moderate to severe pain (Lirk et al. 2019). Therefore, it is necessary to reduce opioid consumption under adequate analgesia. Non-steroidal anti-inflammatory drugs (NSAIDs), as commonly used non-opioid analgesics (American Society of Anesthesiologists Task Force on Acute Pain 2012; Chou et al. 2016), can reduce the occurrence of hyperalgesia and postoperative opioid requests, thereby reducing opioid-related adverse reactions and improving postoperative pain (Doleman et al. 2015; Ren et al. 2020). However, the commonly used NSAIDs have 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, primarily inhibits cyclooxygenase-2 (COX-2) to provide strong analgesic effect that lasts up to 24 h and is well tolerated in the gastrointestinal tract (Khalil et al. 2020; Yu et al. 2022). However, 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 formulation of meloxicam, demonstrates enhanced water solubility, rapid onset of action, prolonged duration of effect, and potent analgesic efficacy following intravenous administration (Zhou et al. 2023). Previous clinical trial has shown that administration of QP001 injection 30 mg and 60 mg significantly reduced postoperative morphine consumption and postoperative pain in patients with moderate to severe pain after abdominal surgery, and the incidence of Adverse Events (AEs) are lower in the 30 mg dose group (Zhou et al. 2023). To further verify the efficacy and safety of QP001, 30 mg was selected as the experimental dose to conduct this multicenter, randomized, double-blind, placebo-controlled clinical trial in subjects with moderate to severe pain following orthopaedic surgery.

Methods

Design and participants

This multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted at 20 medical centers in China from October 10, 2022, to July 14, 2023, in accordance with the Declaration of Helsinki, applicable International Council for Harmonisation Good Clinical Practice. This study was approved by the ethics committees of the Third Xiangya Hospital of Central South University (Ethical Committee No. 22085) and each participating institution. All participants provided written informed consent prior to participation. The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (ChiCTR220006360, Date of registration: September 13, 2022. https://www.chictr.org.cn/showproj.html?proj=178440). We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for the designing and reporting of this trial.

The subjects were individuals scheduled for unilateral joint replacement or unilateral ligament reconstruction under general anaesthesia. Inclusion criteria: age 18–65 years, male or female; American Society of Anesthesiologists (ASA) grade I-III; Body Mass Index (BMI) 18–30 kg/m^2; Patient-controlled intravenous analgesia (PCIA) should be required for 48 h after surgery. Exclusion criteria included allergies or contraindications to NSAIDs and other medications that could be used during the study, active bleeding such as gastrointestinal ulcers or perforations within 6 months, a myocardial infarction or coronary bypass surgery within 1 year, chronic pain, severe cardiovascular and cerebrovascular disease, hypertension with poorly controlled blood pressure, and abnormal and clinically significant laboratory tests during the screening period.

Randomization and blinding

Eligible participants were randomly assigned to receive QP001 or placebo in a 2:1 ratio through an interactive web response system (IWRS) using a block randomization algorithm. Data were collected and managed by independent staff using an electronic data capture system.

To avoid bias, a blinded investigator and a non-blinded administrator were used in the study, as the two drugs were easily distinguishable. The non-blinded administrators were not involved in the protocol-specific assessments of postoperative outcomes.

Procedures

The study consisted of a 7-day screening period, a 2-day treatment period, and a 5-day follow-up observation period. Vital signs were monitored after entering the operating

room. QP001 or placebo was injected intravenously through the extremity 10 min prior to the beginning of surgery. Subjects underwent surgery under general anaesthesia with sufentanil and remifentanil for analgesia, other opioid or non-opioid analgesics were prohibited during the treatment period, and any regional blockade or local infiltration analgesia was prohibited. At the end of surgery, a 5 mg morphine injection was administered for analgesia. The second intravenous injection was administered 24 h (± 15 min) after the initial QP001 or placebo injection. The subjects' recovery from anaesthesia was recorded as 0 h, and the pain intensity was evaluated immediately using the 11-point numerical rating scale (NRS; where 0 no pain and 10 worst possible pain).

As soon as the 0 h NRS score was ascertained, the PCIA was started. 150 mL of morphine injection (0.5 mg/mL) was included in the PCIA pump. The parameters of PCIA pump were as follows: 1 mg of bolus administered with a 5-min locking time interval. During the course of the therapy, 2 mg of morphine may be given intravenously as rescue analgesia if PCIA analgesia proved insufficient. The minimum time between two rescue analgesics was 15 min, and the maximum cumulative dose was 60 mg within 24 h. The trial does not permit the use of prophylactic antiemetics. Investigators were allowed to prescribe antiemetic drugs according to the occurrence of nausea and vomiting, which was meticulously documented in the original records as well as electronic case report form (eCRF).

Measures

The primary efficacy outcome was the total morphine consumption (including the sum of postoperative additional, PCIA and rescue analgesic) within 24 h. Secondary efficacy outcomes included: total morphine consumption within 48 h; the effective pressing times of PCIA within 24 and 48 h; the area under curve (AUC) of pain intensity-time at the following different intervals: $AUC_{0–24}$, $AUC_{24–48}$, $AUC_{0–48}$, $AUC_{18–24}$, $AUC_{42–48}$; the time of first pressing PCIA; the time of first morphine rescue analgesia; morphine relief analgesia ratio within 24 h and 48 h. Analysis was on an intention-to-treat basis, with a secondary analysis of the primary outcome for participants without protocol deviation.

Safety assessments included adverse events (AEs), adverse drug reactions (ADRs), physical examination, vital signs, laboratory tests, and electrocardiogram. All AEs and laboratory values were assessed according to the Common Terminology Criteria for Adverse Events version 5.0. AEs determined to be associated with the investigational product were classified as adverse drug reactions (ADRs). Serious adverse events (SAEs) were identified by impairment of daily functions, life-threatening nature, and requirement for hospitalization or prolonged hospitalization.

Statistical analysis

Combined with the preliminary experiment and literature reports (Berkowitz et al. 2021), the total morphine consumption within 24 h in the QP001 group was expected to be 19 mg, and that in the placebo group was 27 mg, with a combined standard deviation of 17 mg. A two-sided test with a p value of 0.05 and a power value of 0.8 was used, the experimental group and the control group were in a 2:1 ratio. PASS 14.0 software was used to estimate the sample size, and the QP001 group and the control group needed 107 and 54 cases, respectively. Considering a dropout rate of approximately 20%, a total of 198 participants were to be enrolled in this study, 132 cases in the QP001 group and 66 cases in the control group.

Missing pain scores were imputed with a score of 3 when the investigator confirmed that the participant was asleep. Data on other missing NRS pain scores were calculated using multiple substitutions. For the subjects without pressing PCIA or rescue analgesia within 48 h, the time of first pressing PCIA and morphine rescue analgesia was recorded as 48 h. Generalized linear regression models were used to compare the total morphine consumption within 24 and 48 h, effective pressing times of PCIA within 24 and 48 h, the time of first pressing PCIA and morphine rescue analgesia, 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. Kaplan–Meier survival analysis was conducted to analyze time to first pressing PCIA and first rescue medication. The log-rank test was applied to compare survival curves between the two treatment groups, while Cox regression model was utilized for adjusting potential confounding factors. Adjustment for potential confounders included age, sex, height, weight, study site, Type of surgery, Duration of surgery, and intraoperative sufentanil dosage.

SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) and Graphpad Prism 9.3.1 (Graphpad Software, Inc., California) were used for the statistical analyses and plots. All statistical tests were two-sided and p value ≤ 0.05 was considered statistically significant.

Results

Of 227 subjects evaluated for eligibility, 198 cases were included and randomized. Four participants in the QP001 group withdrew from the study prematurely without intervention, and 194 subjects accepted the intervention, 128 cases in the QP001 group and 66 cases in the control group, of whom 182 were analyzed per protocol (Fig. 1).

The characteristics of the two treatment groups are presented in Table 1.

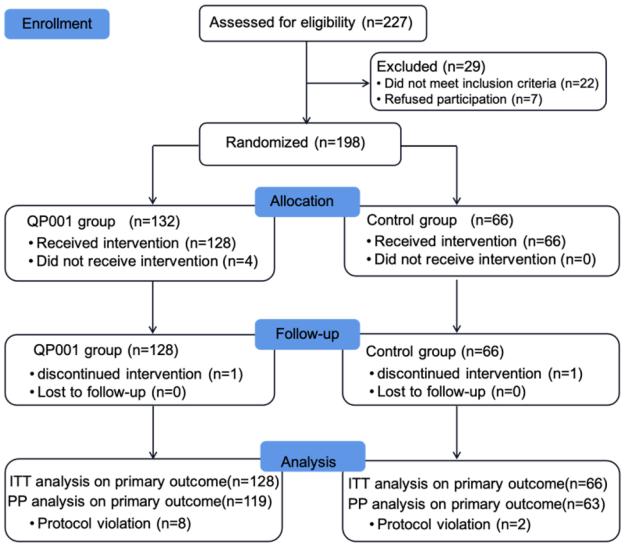

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ITT, intention to treat; PP, per protocol

Primary outcome

In the analysis of the primary outcome in patients with moderate to severe pain following orthopaedic surgery, the total morphine consumption in the QP001 group was found to be significantly lower within 24 h after the first administration compared to the placebo group [mean (SD): 12.53 (10.51) vs. 26.13 (13.98), mean differences (95% CI) − 12.41 (− 15.62 to − 9.19), $P < 0.001$] (Table 2). In a secondary analysis of the primary outcome for participants without protocol deviation, the total morphine consumption in the QP001 group, versus placebo group, was also significantly lower within 24 h [mean (SD): 12.26 (9.19) vs. 26.62 (14.02), mean differences (95% CI) − 13.41 (− 16.53 to − 10.30), $P < 0.001$] (Table 3). Intravenous administration of QP001 injection significantly reduced morphine consumption in patients with moderate to severe pain after orthopaedic surgery.

Secondary outcomes

The time curves of pain intensity scores in the QP001 group and the placebo group are depicted in Fig. 2A, B. Compared to the placebo control group, the QP001 groups demonstrated a significant reduction in total morphine consumption within 48 h, effective pressing times of analgesic pump within 24 and 48 h, and morphine rescue analgesia

Table 1 Baseline characteristics of two groups

Characteristics	Control group ($n = 66$)	QP001 group ($n = 128$)	Standardized difference[a]
Age (years), mean (SD)	50.03 (16.54)	49.26 (16.40)	− 0.047
Female, *n* (%)	35 (53.0)	59 (46.1)	− 0.138
Height (cm), mean (SD)	163.68 (8.84)	165.27 (8.43)	0.185
Weight (kg), mean (SD)	66.24 ± 11.15	66.91 ± 11.00	0.061
BMI (kg/m^2), mean (SD)	24.65 ± 3.21	24.41 ± 2.93	− 0.079
ASA classification, *n* (%)			
I	26 (39.4)	41 (32.0)	− 0.149
II	40 (60.6)	85 (66.4)	
III	0 (0)	2 (1.6)	
Type of surgery, *n* (%)			
Hip arthroplasty	25 (37.9)	60 (46.9)	0.101
Knee arthroplasty	14 (21.2)	17 (13.3)	
Knee ligament reconstruction	27 (40.9)	50 (39.1)	
Meniscus suture	0 (0.0)	1 (0.8)	
Duration of surgery (h), mean (SD)	1.68 (0.76)	1.65 (0.86)	− 0.040
Intraoperative sufentanil dosage (ug), mean (SD)	19.88 (3.33)	20.12 (3.30)	0.073
Time of awakening (h), mean (SD)	0.30 (0.24)	0.28 (0.21)	− 0.109

BMI Body mass index; *SD* standard deviation; *ASA* American Society of Anesthesiologists

[a]Standardized differences were calculated using Cohen d, and the difference in means or proportions was divided by the pooled SDs. Standardized differences ≥ 0.20 were considered imbalanced

Table 2 Primary and secondary outcome analyses

Outcomes	Control group ($n=66$)	QP001group ($n=128$)	p value	MD/OR (95% CI)
Total morphine consumption within 24 h (mg), mean (SD)[a]	26.13 (13.98)	12.53 (10.51)	< 0.001	− 12.41 (− 15.62 to − 9.19)
Total morphine consumption within 48 h (mg), mean (SD)[a]	36.38 (20.26)	16.21 (15.76)	< 0.001	− 18.64 (− 23.24 to − 14.04)
Times of effective button-pressing within 24 h, mean (SD)[a]	18.70 (12.78)	6.96 (9.12)	< 0.001	− 10.62 (− 13.48 to − 7.76)
Times of effective button-pressing within 48 h, mean (SD)[a]	29.22 (18.93)	10.56 (14.25)	< 0.001	− 17.59 (− 21.82 to − 13.36)
Time of first pressing PCIA (h), median (IQR)[a]	2.35 (1.30)	2.90 (8.10)	< 0.001	7.18 (3.68 to 10.69)
Time of first morphine rescue analgesia (h), median (IQR)[a]	24.30 (45.30)	48.00 (0)	< 0.001	11.12 (6.53 to 15.70)
Times of morphine rescue analgesia within 24 h, median (IQR)[a]	0.50 (2.00)	0 (0)	< 0.001	− 1.12 (− 1.64 to − 0.61)
Times of morphine rescue analgesia within 48 h, median (IQR)[a]	1.00 (2.00)	0 (0)	< 0.001	− 1.38 (− 2.01 to − 0.74)
Morphine rescue analgesia ratio within 24 h, n (%)[b]	33 (50.00)	26 (20.30)	< 0.001	0.08 (0.03 to 0.23)
Morphine rescue analgesia ratio within 48 h, n (%)[b]	34 (51.50)	26 (20.30)	< 0.001	0.08 (0.03 to 0.23)

[a]Generalised linear regression model (GLM) was used to test the QP001 group and Control groups

[b]Logistic regression model was used to test the differences of rescue medication rate between the QP001 group and Control groups

SD standard deviation, IQR interquartile range, MD mean differences, OR odds ratio, CI confidence interval

Table 3 Per protocol primary outcome analysis

Primary outcomes	Control group ($n=63$)	QP001group ($n=119$)	p value	MD (95% CI)
Total morphine consumption within 24 h (mg), mean (SD)*	26.62 (14.02)	12.26 (9.19)	< 0.001	− 13.41 (− 16.53 to − 10.30)

*Generalised linear regression model (GLM) was used to test the QP001 group and Control groups

MD mean differences; *CI* confidence interval

ratio within 24 and 48 h ($P<0.001$). Additionally, the time of first pressing PCIA and the time of first morphine rescue analgesia were significantly prolonged in the QP001 group ($P<0.001$) (Table 2). The AUC of pain intensity-time at rest and during movement in the QP001 groups also showed a significant decrease ($P<0.01$), as depicted in Fig. 2C, D. Furthermore, the survival curves of the first pressing PCIA and morphine rescue analgesia indicated that the survival distribution time of the QP001 group was significantly longer than that of the control group ($P<0.001$), as illustrated in Fig. 3.

Safety assessments

The incidence of AEs was 93.9% (62 cases) in the control group and 85.9% (110 cases) in the QP001 group, and there was no significant difference between the two groups ($P>0.05$), as shown in Table 4. There was a significant decrease in ADRs and nausea in the QP001 group compared with placebo, and there was no significant difference in other common ADRs ($P>0.05$). The severity of AEs was 1–2 in both groups, with the exception of 1 case (1.5%) in the control group and 1 case (0.8%) in the QP001 group that experienced a Grade 3 AE (classified as SAE, but the outcome was cured). No serious adverse drug reactions (SADRs) and no AEs leading to death occurred in either group during the entire study period (Table 4).

Discussion

This randomized clinical trial demonstrates the efficacy and safety of QP001 injection, a fast-acting formulation of meloxicam, for moderate to severe pain following orthopaedic surgery. The study shows that QP001 Injection provides effective pain relief and reduces the need for opioid consumption in patients with moderate to severe pain following orthopaedic surgery. Therefore, it is a promising option as a first once-daily postoperative NSAID analgesic option.

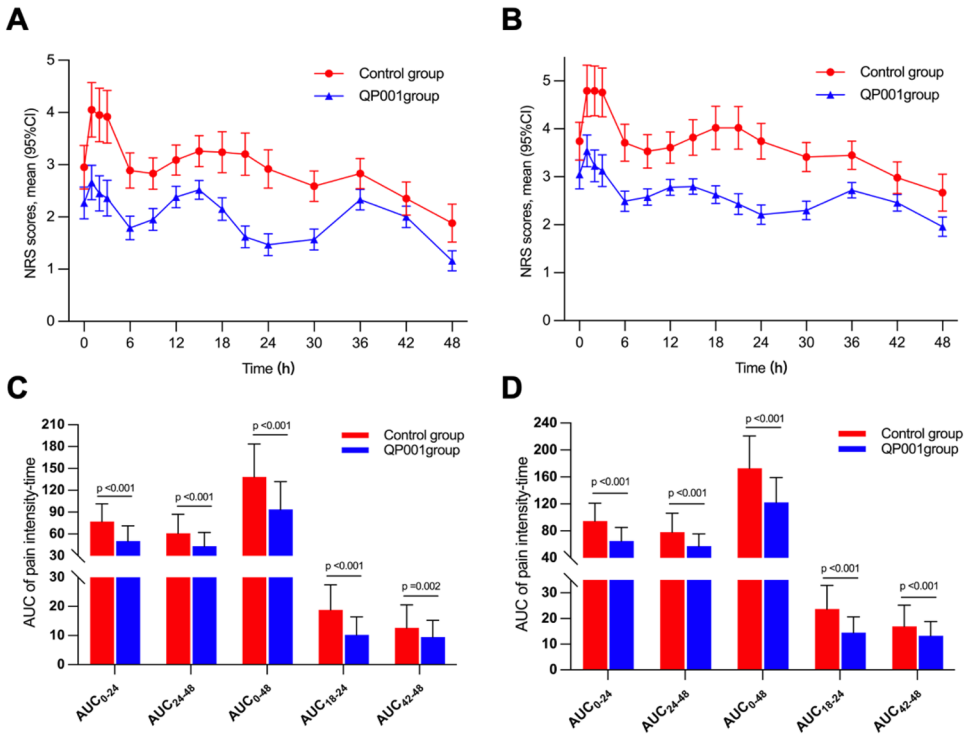

Fig. 2 NRS–time curves and AUC of pain intensity–time for two groups at rest **A**, **C** and during movement **B**, **D**. NRS, Numerical rating scale; AUC, Area under curve; CI, confidence interval

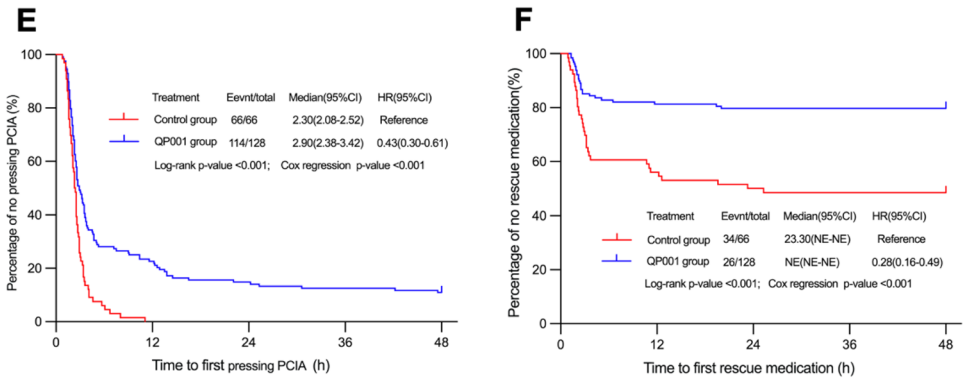

Fig. 3 Kaplan–Meier plot of time to first pressing PCIA (**E**) and first rescue medication (**F**) through 48 h. Cox regression models were adjusted for age, sex, height, weight, study site, type of surgery, duration of surgery and intraoperative sufentanil dosage. PCIA, patient-controlled intravenous analgesia

NSAIDs are widely endorsed as non-opioid analgesics for postoperative pain management due to their non-respiratory depression and addiction, as supported by numerous guidelines (American Society of Anesthesiologists Task Force on Acute Pain 2012; Chou et al. 2016; Coccolini et al. 2022). However, the current common NSAIDs, such as ibuprofen, and diclofenac sodium, generally have weaker analgesic effects and short duration (Amaechi et al. 2021). QP001, a fast-acting meloxicam formulation, has a long duration and potent analgesic effect, which may be an ideal choice for moderate and severe postoperative pain (Zhou et al. 2023). Our study indicated that preemptive administration of QP001 injection 30 mg reduced total opioid consumption by 52.05% and 55.44% within 24 and 48 h for moderate to severe pain following orthopaedic surgery, respectively. After adjusting for potential confounders, the consumption of opioids and the number of successful analgesic pump compressions were significantly reduced within 24 and 48 h, which supported the efficacy of QP001 in reducing morphine consumption. This is consistent with previous findings in subjects with moderate to severe pain following abdominal surgery (Zhou et al. 2023). The clinical study of Berkowitz et al. (2021) in total knee arthroplasty also confirmed that preemptive administration of 30 mg meloxicam, an intravenous nanocrystal formulation, could significantly reduce morphine consumption. However, preoperative meloxicam rectally in hysterectomy surgery, 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 (Yu et al. 2022), necessitating opioid rescue for acute pain relief. The QP001 solution

Table 4 Analysis of adverse events and adverse reactions incidence

Index	Control group ($n=66$)	QP001group ($n=128$)	p value
AEs, *n* (%)	62 (93.9)	110 (85.9)	0.096
SAEs, *n* (%)	1 (1.5)	1 (0.8)	1.00
Surgical incision poor healing	0 (0)	1 (0.8)	1.00
Respiratory failure	1 (1.5)	0 (0)	1.00
Disorders of consciousness	1 (1.5)	0 (0)	1.00
AEs that lead to withdrawal, *n* (%)	0 (0)	0 (0)	NA
ADRs, *n* ((%)	50 (75.8)	76 (59.4)	0.023
Positive occult blood of fecal	2 (3.0)	10 (7.8)	0.227
Increased Alanine transaminase	6 (9.1)	5 (3.9)	0.189
Increased Aspartate transaminase	4 (6.1)	5 (3.9)	0.492
Increased Blood pressure	5 (7.6)	4 (3.1)	0.278
Tachycardia	4 (6.1)	2 (1.6)	0.183
Vomiting	15 (22.7)	20 (15.6)	0.223
Nausea	11 (16.7)	5 (3.9)	0.002
Constipation	5 (7.6)	11 (8.6)	0.807
Fever	11 (16.7)	24 (18.8)	0.721
Anemia	12 (18.2)	24 (18.8)	0.923
Hypokalemia	4 (6.1)	5 (3.9)	0.492
Postoperative urinary retention	6 (9.1)	6 (4.7)	0.345
SADRs, *n* (%)	0 (0)	0 (0)	NA

AEs Adverse Events; *ADRs* Adverse Drug Reaction; *SAEs* Serious Adverse Events; *SADRs* Serious ADRs. Only the most common adverse effects are listed, occurring in ≥ 5% of patients in either study group

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. Previous study in healthy volunteers indicated that QP001 injection reached peak concentration at 1.8 min post-administration and distributed rapidly (Zhou et al. 2023). Compared to meloxicam tablets, a single dose of QP001 injection resulted in higher Cmax and AUC, with no significant change in elimination half-life. Steady state was achieved after 5 days of multiple doses, with Cmax and AUC0-24 approximately 1.37 and 1.99 times higher than those from a single dose.

Orthopaedic procedures are considered one of the most painful procedures a patient can undergo, and multimodal analgesia has become a preferred method of pain management in orthopaedic practice (Chunduri et al. 2022). A critical element of multimodal pain management is preemptive analgesia strategy (Barr et al. 2020; Chunduri et al. 2022). 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). Therefore, we employed a preoperative/preemptive administration strategy for QP001 injection rather than reactive pharmacologic analgesia. Compared to the placebo control group, the AUC of pain intensity-time at rest and during movement were significantly reduced in the QP001 groups, while the time of first pressing PCIA and the time of first morphine rescue analgesia were significantly prolonged in QP001 group. This suggests that QP001 provides potent analgesia in subjects with moderate to severe pain following orthopaedic surgery, which is beneficial to the implementation of postoperative rehabilitation training. Our proactive administration of QP001 injection before surgery effectively prevents central sensitization and hyperalgesia by mitigating the alteration of central sensory processing and subsequent inflammatory damage caused by cytokines and prostaglandins release. This approach is more effective than interventions applied after surgery (Kissin 2000; Wilder-Smith 2000). Furthermore, compared with the inadequate analgesia of the intravenous nanocrystal formulation of meloxicam at the endpoint of treatment (18–24 h and 42–48 h) (US. Food and Drug Administration (FDA. 2020), QP001 significantly reduced the AUC of pain intensity time at the endpoint of treatment, suggesting that QP001 exerts a sustained analgesic effect. This makes it a promising option for once-daily postoperative pain management.

In order to provide an optimal analgesic experience for all participants, we opted for a proactive PCIA combined with investigator rescue analgesia strategy. The results showed that QP001 significantly reduced the proportion of postoperative morphine rescue analgesia. Further survival

analysis showed that QP001 could significantly improve the survival distribution of the survival curves of pressing PCIA and rescue analgesia. This is not consistent with the previous exploratory study in abdominal surgery (Zhou et al. 2023), and the proportion of morphine rescue analgesia is also significantly increased, which indicates that the pain degree after orthopaedic joint surgery is more severe, and the sensitivity of efficacy detection is higher, thus better reflecting the advantages of QP001 in moderate and severe pain.

Intravenous administration of QP001 30 mg has a favorable safety profile in patients with moderate to severe pain following orthopaedic surgery. There was no significant difference in AEs between the two treatment groups. The severity of AEs was 1–2 in both groups, except for 1 case in each group, which had a grade 3 AE (classified as SAE, but the outcome was cured). However, the incidence of ADRs and Nausea were significantly lower in the QP001 group than in the placebo group, possibly because QP001 reduced morphine consumption and consequently reduced opioid-related AEs, particularly gastrointestinal AEs, such as nausea.

It is necessary to acknowledge the limitations of this study. Efficacy and safety indicators were followed up to 48 h and 5 days after surgery, respectively, but long-term benefits (such as chronic pain) and side effects were not continuously studied. Additionally, to reduce bias, nerve blocks and local anaesthesia, which are commonly used for multimodal analgesia in orthopaedic surgery, were prohibited.

Conclusion

QP001 injection provides effective analgesia and reduces opioid consumption in subjects with moderate to severe pain after orthopaedic surgery, with a favorable safety profile.

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Author contributions SW, YYZ, YJ and ST conceived and designed the study. YYZ, KD, QL, MY, QL, MB, GJX, JS, CL, HZ, YZZ, YH, YG, LH, HL, YZ, YC, LZ, SC, CC, HJ, JR and WO completed the operation. YYZ and YJ analyzed the data. The first draft of the manuscript was written by YYZ, and YJ. Visualization of the manuscript was performed by SW and ST. All authors approved the final manuscript.

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Data availability The trial protocol and all the data during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

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