



HTX-011 in Combination with Multimodal Analgesic Regimen Minimized Severe Pain and Opioid Use after Total Knee Arthroplasty in an Open-Label Study

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Abstract

Total knee arthroplasty (TKA) can be associated with significant postoperative pain despite multimodal analgesic (MMA) protocols, and most patients require the use of opioids postoperatively. HTX-011 is a dual-acting local anesthetic containing bupivacaine and low-dose meloxicam in an extended-release polymer. In a prior randomized controlled trial (RCT), HTX-011 reduced pain and opioid use through 72 hours after TKA compared with bupivacaine hydrochloride. This open-label study (NCT03974932) evaluated the efficacy and safety of HTX-011 combined with an MMA regimen in patients undergoing TKA under spinal anesthesia. All patients received intraoperative HTX-011 (400 mg bupivacaine/12 mg meloxicam) in combination with an MMA regimen consisting of preoperative acetaminophen, celecoxib, and pregabalin and postoperative acetaminophen and celecoxib until discharge. Opioid rescue was allowed upon patient request for additional pain control. Pain scores, opioid consumption, discharge readiness, and adverse events were recorded. Fifty-one patients were treated. Compared with the prior RCT, HTX-011 with this MMA regimen further lowered pain scores and reduced opioid use. Mean patient-reported pain scores remained in the mild range, and 82% of patients or more did not experience severe pain at any individual time point through 72 hours after surgery. Mean total opioid consumption was low over 72 hours: 24.8 morphine milligram equivalents (1–2 tablets of oxycodone 10 mg/day). Approximately 60% of patients were ready for discharge by 12 hours, and 39% were discharged without an opioid prescription and did not call back for pain management. The treatment regimen was well tolerated, and no added risk was observed with the addition of MMA. HTX-011 with an MMA regimen reduced postoperative pain and opioid use following TKA.

Keywords

- ▶ HTX-011
- ▶ multimodal analgesia
- ▶ postoperative pain
- ▶ total knee arthroplasty

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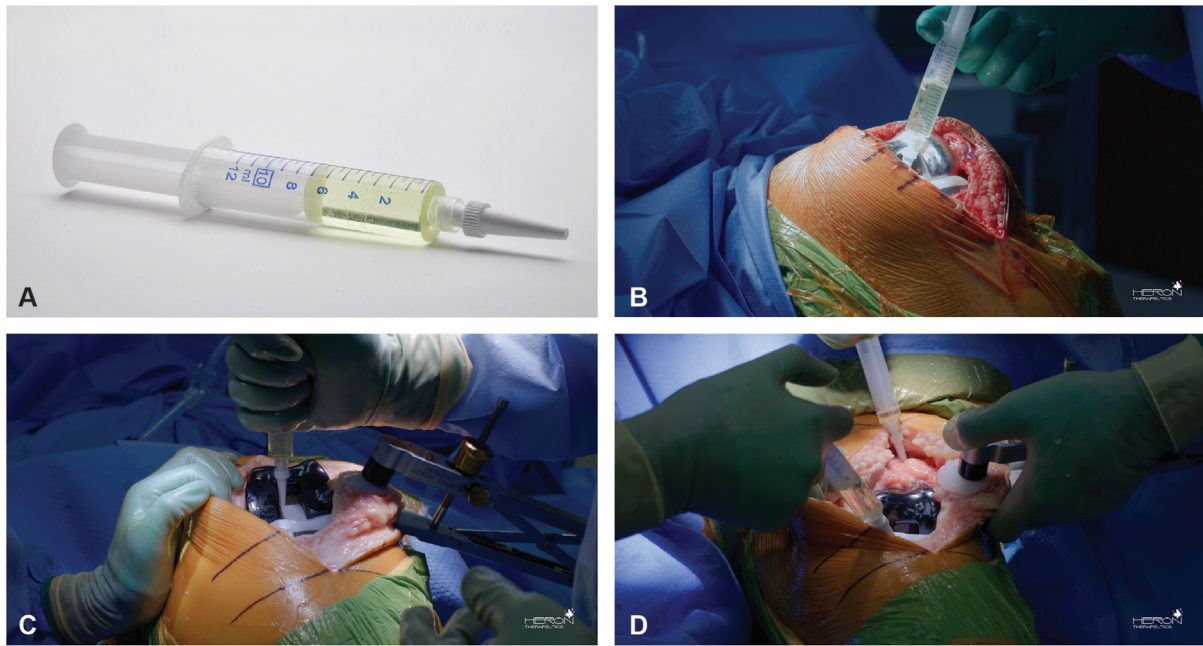


Fig. 1 (A) HTX-011 is a viscous formulation administered without a needle. (B–D) HTX-011 application during total knee arthroplasty.

Primary total knee arthroplasty (TKA) can be associated with significant postoperative pain, which often requires the use of opioids.^{1,2} Currently, postoperative pain after TKA is managed using a wide variety of multimodal analgesic (MMA) regimens to reduce a patient's pain and avoid opioid use.^{3–5} These regimens often include pre- and postoperative administration of analgesic medications with distinct mechanisms of action, typically in combination with perioperative administration of local anesthetics. Periarticular injections at the time of TKA have been shown to reduce pain and opioid consumption when combined with a robust MMA protocol following TKA.⁶ Several studies have also shown periarticular injections to be as efficacious in relieving pain as peripheral nerve blocks without the potential complications of neurovascular nerve injury, motor dysfunction, or falls.⁷ However, the duration and efficacy of these injections can be variable and often limited to less than 24 hours. Extended-release formulations of local anesthetics (i.e., liposomal bupivacaine) have failed to show superiority compared with conventional bupivacaine in various randomized trials or to provide consistent pain relief beyond 24 hours compared with controls.^{8,9}

Consequently, opioid consumption following TKA remains high, with opioid prescriptions at discharge nearly universal in the United States.^{2,10–12} Minimizing patient exposure to opioids at the time of surgery can have significant personal and public health implications. Opioids are associated with opioid-related adverse reactions and can result in worse patient outcomes and increased hospital costs.^{13,14} Postoperative use of opioid medications also increases the risk of long-term use, misuse, and dependence.¹⁵ In addition, in a recent analysis of an administrative database, Politzer et al showed that 5% of opioid-naïve patients undergoing TKA became chronic opioid users 2 years

following TKA.¹⁶ Therefore, there remains a need for an effective extended-release local anesthetic that can provide longer term pain relief and minimize the need for the use of opioids.

HTX-011 (ZYNRELEF; Heron Therapeutics, San Diego, CA) is an extended-release, dual-acting, local anesthetic formulation consisting of bupivacaine and low-dose meloxicam in a novel, tri(ethylene glycol) poly(orthoester) polymer, which allows for the controlled diffusion of active ingredients over 72 hours.^{17,18} HTX-011 is a viscous solution that is applied without injection or needle directly to the joint capsule, periosteum, and other pain generating tissues. It is applied after irrigation and suction and prior to suturing. This direct coating of the joint tissues during the procedure allows for extended release of the drug to all tissues throughout the surgical site (► **Fig. 1**). In an animal model, the anti-inflammatory effect of meloxicam in HTX-011 normalized the local pH, allowing enhanced penetration of bupivacaine into the nerves and potentiation of the analgesic effect.¹⁷ Notably, the synergistic effect of local bupivacaine and meloxicam in HTX-011 was observed in an animal model and confirmed in human clinical studies. This effect could not be replicated by administering extended-release bupivacaine locally and meloxicam systemically.¹⁷

A prior randomized controlled trial (RCT) compared HTX-011 (400 mg bupivacaine and 12 mg meloxicam) with bupivacaine hydrochloride (HCl) and saline placebo in patients undergoing primary unilateral TKA under general anesthesia.¹⁹ In that study, HTX-011 was more effective than bupivacaine alone at reducing pain and total opioid consumption over the first 72 hours; however, in the absence of other nonopioid MMA agents, all patients treated with HTX-011 alone required the use of rescue postoperative opioids. The objectives of this study were to assess postoperative pain

control and opioid consumption following primary TKA in patients administered HTX-011 with a scheduled MMA regimen consisting of acetaminophen and a nonsteroidal anti-inflammatory drug (NSAID), thereby addressing some limitations of the prior RCT. Results from the prior RCT are presented here for comparison. Discharge readiness, patient satisfaction, and safety were also assessed.

Methods

This open-label study was conducted by eight surgeons at six sites across the United States from May 2019 through November 2019. These six sites also participated in the prior RCT. The study protocol, protocol amendments, and informed consent forms were approved by Aspire, IRB (Santee, CA) and other relevant Institutional Review Boards before patients were screened. Each patient was provided written informed consent before undergoing any study-related procedures. The study design and entry criteria for this study were similar to those of the prior RCT of HTX-011.¹⁹ The MMA regimen and primary end point were selected based on a published phase 4 study of a long-acting liposomal bupivacaine with a scheduled MMA regimen in TKA.²⁰

Patient Population

Patients were screened within 28 days before the scheduled surgery, and eligibility was confirmed on the day of surgery.

The patient population mirrored the prior RCT of HTX-011 and included males and females of at least 18 years of age who were scheduled to undergo their first unilateral TKA and who had an American Society of Anesthesiologists Physical Status classification of I, II, or III. Patients were excluded if they had planned concurrent surgical procedures (e.g., bilateral TKA) or had preexisting conditions expected to require analgesic treatment not related to TKA. Patients taking any of

the following medications before surgery were also excluded: NSAIDs (including meloxicam) within 10 days, long-acting opioids within 3 days, any opioids within 24 hours, and bupivacaine HCl within 5 days. In addition, patients with known or suspected daily use of opioids for 7 or more consecutive days within 6 months before their scheduled surgery, known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a history of alcohol abuse (within 10 years) were also excluded from the study.

Anesthesia and Surgical Considerations

All surgeries were performed under bupivacaine spinal anesthesia (≤ 20 mg). As in the prior HTX-011 RCT, surgery was performed based on investigators' preferred surgical techniques (including the use of drains, tourniquet time, and type of prosthesis). Intraoperative pain control with intravenous (IV) fentanyl (≤ 4 μ g/kg) was allowed.

All patients in the study received IV tranexamic acid (TXA) for antifibrinolysis and oral (PO) acetylsalicylic acid for deep vein thrombosis prophylaxis.²¹ TXA 1 g was administered before surgery, with a second dose up to 8 hours later, and acetylsalicylic acid 325 mg was administered twice a day following surgery until discharge.

Study Design and Treatments

The study design is presented in ►Fig. 2. All patients were administered a single 14-mL dose of HTX-011 (400 mg bupivacaine and 12 mg meloxicam) during surgery after final irrigation and suction, just prior to suture closure. HTX-011 was applied without a needle: 3.5 mL to the posterior capsule, 5.25 mL to the anteromedial tissues and periosteum, and 5.25 mL to the anterolateral tissues and periosteum. All patients also received MMA while in the hospital. On the day of surgery, patients were administered 1 g acetaminophen, 200 mg celecoxib, and 300 mg pregabalin (all PO) before

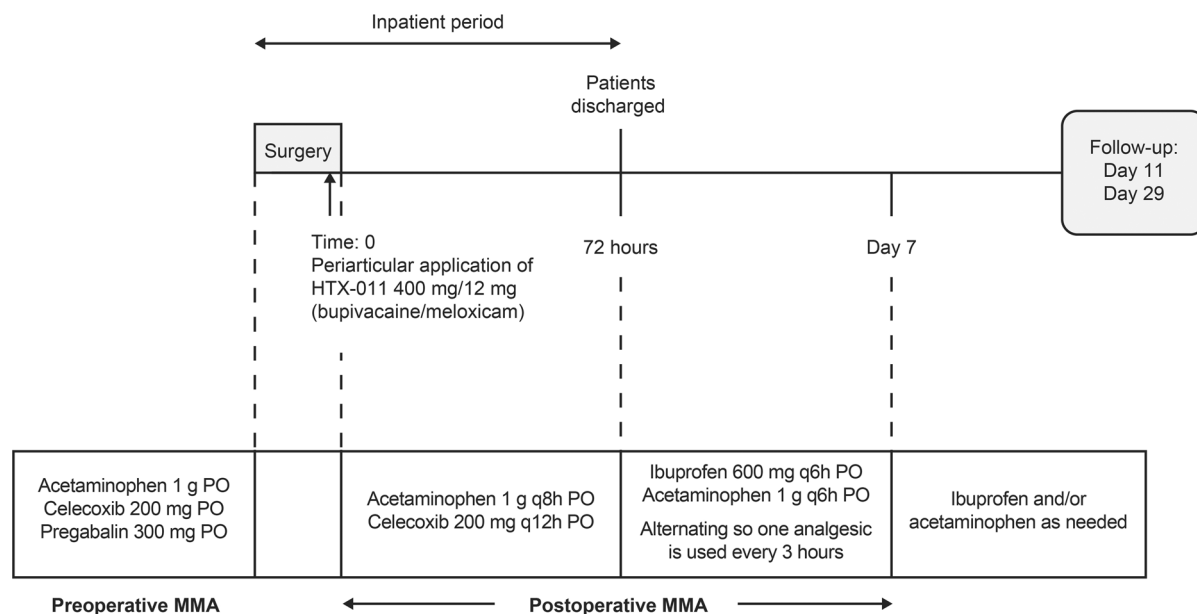


Fig. 2 Follow-on study design. MMA, multimodal analgesia; PO, oral; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours.

surgery. For 72 hours following surgery, patients received a scheduled MMA regimen consisting of 1 g acetaminophen PO every 8 hours and 200 mg celecoxib PO every 12 hours.

To allow for complete and rigorous data collection, patients were required to stay in the treatment facility for at least 72 hours after surgery. Pain was assessed before and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after surgery using the visual analog scale (VAS) and the numerical rating scale (NRS). Additional efficacy assessments included patient global assessment (PGA) of pain control, ability to participate in scheduled rehabilitation sessions (one on the night of surgery, then twice a day while in the hospital), and discharge readiness based on the modified postanesthetic discharge scoring system (MPADSS). Safety assessments included adverse event (AE) recording, physical examinations, clinical laboratory tests (hematology and serum chemistry), and vital signs.

In addition to their scheduled MMA regimen, patients could receive opioid rescue medication for pain control only upon request during the 72-hour inpatient period. Permitted rescue medication included PO immediate-release oxycodone (≤ 10 mg within a 4-hour period), IV morphine (2.5–5.0 mg within a 4-hour period), and/or IV hydromorphone (0.5–1.0 mg within a 4-hour period). Other rescue medications and patient-controlled analgesia were prohibited.

After completion of the 72-hour inpatient assessment, patients were discharged with instructions to continue their scheduled MMA regimen, which consisted of 600 mg ibuprofen every 6 hours alternating with 1 g acetaminophen every 6 hours (so that one analgesic was taken every 3 hours), for the next 4 days. Only patients who received ≥ 10 mg of oxycodone within 12 hours before discharge were eligible to receive a discharge prescription for up to 30 5-mg PO immediate-release oxycodone tablets. All patients were provided a daily diary to record whether they took any opioids between discharge and the day 11 follow-up assessment. Patients returned to the study site for follow-up assessments on days 11 and 29.

Outcome Measures

All patients who received study drug were included in efficacy and safety analyses. The primary efficacy end point was the mean area under the curve (AUC) of VAS pain intensity scores from 12 through 48 hours after surgery (AUC_{12-48}). Secondary efficacy end points included mean AUC of pain intensity scores through 72 hours using the NRS and VAS, the proportion of patients with severe pain at each time point, mean total postoperative opioid consumption in IV morphine milligram equivalents (MME) through 72 hours, and the proportion of patients who did not receive an opioid prescription between discharge and the day 11 follow-up visit. Additional prespecified end points included the proportion of patients achieving a PGA score of >1 (“good” or “excellent” pain control over the preceding 24 hours),²² the proportion of patients unable to participate in rehabilitation sessions because of pain, and the proportion of patients considered ready for discharge (MPADSS score of ≥ 9 on a 0–10 scale).^{23,24}

For the primary end point analysis, pain intensity scores during periods of rescue medication administration were replaced by the highest observed score before rescue medication use to adjust for opioid use.^{19,20} Prespecified secondary analyses of pain were performed using observed patient-reported pain scores because these reflect the level of pain the patient is experiencing. All end points were assessed using descriptive statistics. For total opioid consumption, both arithmetic and log-transformed geometric means were analyzed.⁸

Safety end points included the incidence of AEs and serious AEs (SAEs). Safety data were summarized using observed cases.

Results

Efficacy Findings—Primary and Secondary End Points

A total of 51 patients received study treatment, and all completed the study. All patients had osteoarthritis. The mean age was 65 years and 60.8% were women (►Table 1).

Throughout the 72-hour postoperative period, mean patient-reported pain scores remained in the mild range when assessed using the VAS (VAS score of 5–44 mm) or NRS (NRS score of ≤ 4). The mean AUC_{12-48} of the VAS score was 145.4 (standard error [SE], 13.00; primary end point). Mean pain scores were lower at each time point over the 72-hour period compared with the prior RCT (►Fig. 3A). Although the difference in anesthesia between studies may have accounted for initially lower pain scores, the mean AUC of the NRS scores was also lower in this study from 12 to 72 hours postoperatively compared with the RCT (177.4 vs. 214.2), respectively. In the prior RCT, HTX-011 in the absence of an MMA regimen reduced the proportion of patients with severe pain compared with bupivacaine HCl and saline placebo, and the addition of an MMA regimen in this study provided further improvement (►Fig. 4). More than 82% of patients who received the HTX-011-based MMA regimen did not experience severe pain (NRS score of ≥ 7) at any individual time point.

Table 1 Follow-on study demographics and baseline characteristics

	HTX-011 + MMA (N = 51)
Age, y, mean (min, max)	65.4 (39, 83)
Sex, n (%)	
Female	31 (60.8)
Male	20 (39.2)
Race, n (%)	
White	47 (92.2)
Black or African American	4 (7.8)
Body mass index, kg/m ² , mean (min, max)	30.97 (24.0, 39.9)

Abbreviations: max, maximum; min, minimum; MMA, multimodal analgesia.

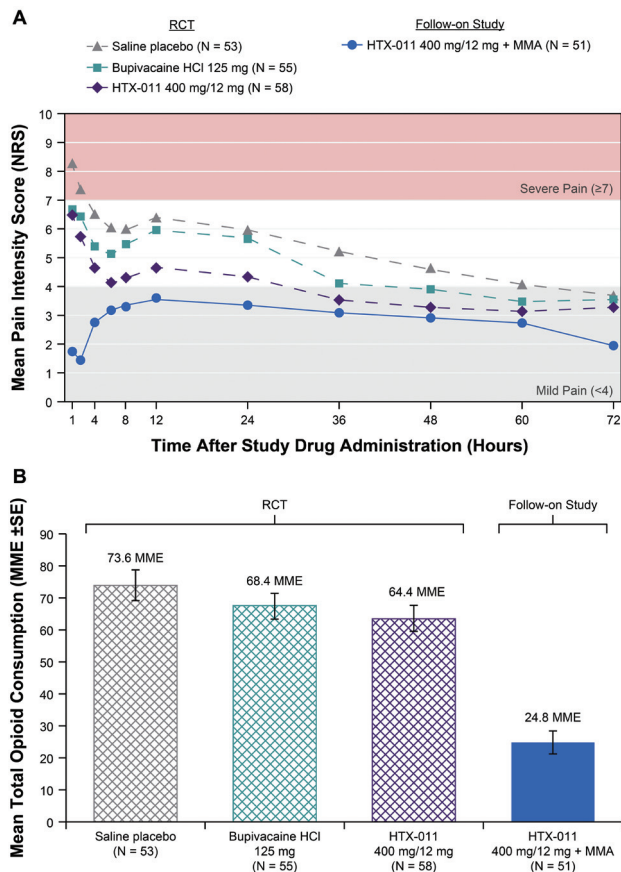


Fig. 3 An HTX-011-based MMA regimen reduced mean (SE) patient-reported pain scores (A) and total opioid consumption (B) over 72 hours. Opioid consumption presented in intravenous MME. HCl, hydrochloride; MMA, multimodal analgesia; MME, morphine milligram equivalents; NRS, numeric rating scale of pain intensity; RCT, randomized controlled trial; SE, standard error.

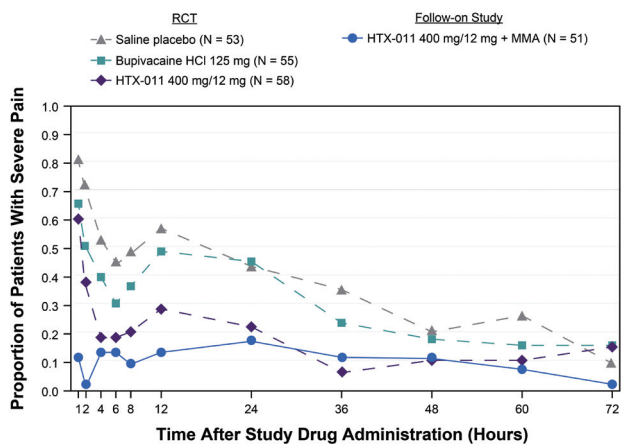


Fig. 4 An HTX-011-based MMA regimen reduced the proportion of patients with severe pain (NRS ≥ 7) at each time point through 72 hours. HCl, hydrochloride; MMA, multimodal analgesia; NRS, numerical rating scale of pain intensity; RCT, randomized controlled trial.

Reduction in pain with the HTX-011-based MMA regimen was achieved without an increase in opioid consumption (\rightarrow Fig. 3B). Mean total opioid consumption was lower over 24, 48, and 72 hours compared with the RCT (\rightarrow Table 2).

Almost half of patients (47.1%) receiving HTX-011 with an MMA regimen took ≤ 20 MME (≤ 4 oxycodone 10 mg tablets) over the 72-hour postoperative period. The geometric mean total opioid consumption through 48 and 72 hours after surgery was 3.0 MME (SE, 1.97) and 3.7 MME (SE, 2.5), respectively. The proportion of patients who did not require the use of a postoperative opioid (i.e., were opioid free) through 72 hours was 11.8%. Additionally, 39.2% of patients were discharged without an opioid prescription and did not call the study site for additional pain medication through the day 11 follow-up visit.

Patient's satisfaction was high; 88.2, 90.2, and 100% of patients reported a PGA score of >1 ("good" or "excellent" pain control) at 24, 48, and 72 hours, respectively. No patient missed rehabilitation sessions because of pain on the day after surgery (day 2), and only two patients (3.9%) missed a rehabilitation session because of pain on day 3. Approximately half of patients (49.0%) were considered ready for discharge (had an MPADSS score of ≥ 9) by 8 hours, 60.8% were ready for discharge by 12 hours, and 68.6% by 24 hours after surgery.

Safety

Over the course of the study, 82.4% of patients reported at least one AE (\rightarrow Table 3). The most common AEs were nausea, vomiting, constipation, and dizziness. AEs considered possibly related to study drug were reported for 13.7% of patients, and all were mild or moderate in severity. There was no evidence of NSAID-related toxicity or local anesthetic systemic toxicity. No SAEs were reported.

Discussion

TKA can be associated with significant postoperative pain. Despite MMA protocols, which include periarticular injections, reproducible pain relief beyond the first 24 hours remains inconsistent, and a significant proportion of patients undergoing TKA still requires the use of opioids postoperatively.^{1,9,25,26} In a phase 4 study (PILLAR), the use of liposomal bupivacaine 266 mg admixed with bupivacaine HCl 100 mg plus an MMA regimen resulted in a mean VAS AUC₁₂₋₄₈ score of 180.8 (primary end point).²⁰ More than 80% received >20 mg of opioid medication; the geometric mean total opioid consumption over 48 hours was 18.7 mg.²⁰

HTX-011, an extended-release dual-acting local anesthetic, is designed to provide analgesia for up to 72 hours and to reduce postoperative opioid consumption; it has been shown to provide superior pain relief compared with bupivacaine HCl following TKA.¹⁹ The purpose of this study was to evaluate HTX-011 with an MMA regimen in TKA.

HTX-011 with a scheduled MMA regimen (pregabalin, acetaminophen, and celecoxib preoperatively and acetaminophen and celecoxib postoperatively) resulted in substantial and durable pain control. Mean patient-reported pain scores remained in the mild range throughout the 72-hour postoperative period, with a mean AUC₁₂₋₄₈ of the VAS score of 145.4 (primary end point). Most patients ($\geq 82\%$) did not have severe pain at any individual time point. Prior reports of

Table 2 An HTX-011–based MMA regimen reduced total opioid consumption

Total opioid consumption (MME)	Randomized controlled trial			Follow-on study
	Saline placebo (N = 53)	Bupivacaine HCl 125 mg (N = 55)	HTX-011 400 mg/12 mg (N = 58)	HTX-011 + MMA (N = 51)
0–24 h				
Mean (SE)	39.1 (2.64)	32.6 (2.05)	28.8 (1.84)	10.6 (1.30)
Median	38.0	30.0	27.8	7.5
Min, max	5.0, 82.0	0.0, 71.0	2.5, 74.0	0.0, 35.0
0–48 h				
Mean (SE)	58.5 (3.84)	52.6 (3.05)	48.8 (2.870)	19.4 (2.46)
Median	56.0	50.0	48.5	15.8
Min, max	5.0, 114.0	0.0, 108.0	2.5, 105.0	0.0, 93.3
0–72 h				
Mean (SE)	73.6 (4.73)	68.4 (3.93)	64.4 (3.66)	24.8 (3.18)
Median	73.0	70.0	63.3	21.7
Min, max	10.0, 158.0	0.0, 147.5	2.5, 123.0	0.0, 118.3

Abbreviations: HCl, hydrochloride; max, maximum; min, minimum; MMA, multimodal analgesia; MME, morphine milligram equivalents; SE, standard error.

Table 3 Summary of AEs with an HTX-011–based MMA regimen

AE, n (%)	HTX-011 + MMA (N = 51)
At least 1 AE	42 (82.4)
Mild	17 (33.3)
Moderate	24 (47.1)
Severe	1 (2.0)
AE possibly related to study drug ^a	7 (13.7)
SAE	0
AE leading to study withdrawal	0
Most common AEs	
Nausea	29 (56.9)
Vomiting	14 (27.5)
Constipation	10 (19.6)
Dizziness	6 (11.8)

Abbreviations: AE, adverse event; MMA, multimodal analgesia; SAE, serious adverse event.

^aAEs reported by the investigator as possibly related to study drug were nausea, vomiting, dizziness, and intermittently elevated blood pressure.

patients undergoing TKA with other MMA protocols noted severe pain in up to 60% of patients.^{27,28} This is a meaningful observation because the potential consequences of severe, poorly controlled postoperative pain include delayed postoperative ambulation, an increase in cardiopulmonary complications, prolonged hospital stay, decreased patient satisfaction, and the development of chronic postoperative pain.^{29–31} In this study, the pain levels were lower compared

with the observed pain scores in the prior RCT in patients receiving HTX-011 without MMA undergoing primary TKA. Although differences in anesthesia (general anesthesia in the RCT and spinal anesthesia in the current study) contributed to lower initial pain scores in this study, subsequent pain scores remained lower for the HTX-011–based MMA regimen. Notably, opioid consumption was substantially lower as well. Over the 72-hour period, mean total consumption for HTX-011 with MMA was 24.8 MME (approximately one to two 10-mg oxycodone tablets per day) and the geometric mean was 3.7 MME (less than one-third of a 10-mg oxycodone tablet per day).

Despite the minimal use of opioids in the current study, HTX-011 with MMA provided sufficient pain control for early mobilization and was associated with high patient satisfaction. Adelani and Barrack surveyed prospective TKA patients and reported that 54.8% had concerns with pain control postoperatively.³² In this study, more than 88% of patients reported “good” or “excellent” pain control, and ~60% of patients were ready for discharge by 12 hours after surgery and up to 70% by 24 hours per the MPADSS.

A total of 39.2% of patients were discharged without an opioid prescription and did not call back to the study site to request additional pain medication between discharge at 72 hours and the day 11 follow-up visit. This result contrasts with data indicating that from 72 to 96% of patients receive an opioid prescription following TKA, with 86 to 126 oxycodone (5-mg) pills routinely prescribed.² Given that studies have found that up to 70% of prescribed opioids remain unused and available for misuse and abuse,^{10,11,33} the ability to avoid opioid prescriptions in nearly 40% of patients receiving HTX-011 and a scheduled MMA regimen will not only avoid opioid-related complications in individual

patients but could also have a profound societal impact by reducing the number of leftover opioid pills available for diversion and abuse.

Study treatment was well tolerated. HTX-011 with an MMA regimen had an overall safety profile similar to that for HTX-011 alone.^{19,34,35} The use of HTX-011 400 mg/12 mg in patients undergoing TKA with bupivacaine spinal anesthesia did not identify any safety concerns, and there was no evidence of NSAID-related toxicity, suggesting that MMA regimen did not impact the safety profile of HTX-011.

This study is not without limitations. No control arm was included in this current study, which was designed as a follow-on to an RCT of HTX-011 in TKA. However, the eligibility criteria and study assessments were similar to the prior RCT facilitating cross-study comparisons. General anesthesia was used in the RCT, while spinal anesthesia was used in this study, which may have contributed to differences in pain scores and the need for postoperative pain medications between studies. In addition, all patients were required to stay in the hospital for 72 hours following surgery to allow for data collection. This requirement contrasts with the recent shift toward outpatient TKA surgeries³⁶ and highlights the need for more real-world studies of postoperative pain and opioid use following TKA. It is possible that the number of opioid prescriptions provided at discharge may have differed from earlier patient discharge. Furthermore, the six study sites and eight surgeons in this study also participated in the RCT. In the RCT, pain scores for HTX-011-treated patients at the six sites were indistinguishable from those of the entirety of the HTX-011 group, supporting the use of the prior RCT as context when interpreting results from this follow-on study. Another limitation is that this study evaluated HTX-011 in combination with only one MMA regimen, although there are many postoperative MMA regimens currently in use for TKA. The MMA regimen selected for this study is commonly used and was evaluated in the phase 4 liposomal bupivacaine study (PILLAR study)²⁰ and, as in that study, did not include other periarticular infiltration medications or femoral and adductor canal blocks.³⁷ Further investigation will be needed to understand the benefits of HTX-011 in combination with the diverse options currently in place for MMA regimens used today. Finally, our study design excluded patients with recent prior opioid use. Additional studies that include patients with current and chronic opioid use are needed to see whether these patients will experience similar opioid reductions as observed in this study.

Conclusion

As TKA transitions to the outpatient setting, a pain protocol that is effective and well tolerated is critical to successful and safe patient discharge. HTX-011 and an MMA regimen provided substantial pain control, maintaining mean pain in the mild range after TKA, with only a minority of patients (<18%) experiencing severe pain at any individual time point through 72 hours. Notably, this effect was achieved with low opioid consumption, and nearly 40% of patients did

not require a discharge opioid prescription in this study. Pain scores and opioid consumption were lower than those observed in the prior RCT in which HTX-011 alone was superior to bupivacaine HCl. HTX-011 was well tolerated when used with bupivacaine-based spinal anesthesia and in conjunction with an NSAID-containing MMA regimen. These results suggest that HTX-011 in combination with an MMA regimen may be a promising new option for the management of postoperative pain in patients undergoing TKA.

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Conflict of Interest

G.-C.L. reports the following: Personal fees as a paid consultant from: Heron Therapeutics, Inc., Stryker, and Corin; research support as a principal investigator from: Smith and Nephew, Deeny, KCI Acelity, outside the submitted work; medical/orthopaedic publications editorial/governing board: *Journal of Arthroplasty*, *Clinical Orthopaedics and Related Research*, *Journal of Bone and Joint Surgery*, *Bone & Joint Journal*.

Board member: Knee Society - Technology Committee.

R.B. reports personal fees as a paid consultant and research support from Heron Therapeutics, Inc., during the conduct of the study and personal fees as a paid consultant from Baudax Bio and research support from Janssen outside the submitted work.

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J.H. reports personal fees from Heron Therapeutics, Inc. and stock options from Heron Therapeutics, Inc. during the conduct of the study.

A.R. reports personal fees as a paid consultant from Heron Therapeutics, Inc. during the conduct of the study.

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