Poster #

Opioid-Free Recovery After Inguinal Hernia Repair With HTX-011 as the Foundation of a Non-Opioid, Multimodal Analgesia Regimen in a Real-World Setting

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BACKGROUND

- Despite the widespread use of multimodal analgesia (MMA), many patients are still prescribed opioids for pain management following herniorrhaphy[1]
  - Effective non-opioid medications are needed to adequately manage postoperative pain through the first 72 hours (when pain is often most severe) without opioid-associated side effects or risk of dependency
  - In addition, prescribing algorithms are needed to properly identify which patients may or may not require opioids for pain relief
- HTX-011 (ZYNRELEF™; Heron Therapeutics, San Diego, CA) is a dual-acting local anesthetic (DALA) formulation comprising bupivacaine and low-dose meloxicam in an extended-release polymer that controls the release of active ingredients over 72 hours, which results in enhanced and sustained analgesia and reduction in opioid use[2-4]
  - The nonsteroidal anti-inflammatory drug meloxicam in HTX-011 reduces surgery-related inflammation and normalizes the local pH, enhancing the penetration of bupivacaine into nerve cells and potentiating its analgesic effect[2]
- Helping Opioid Prescription Elimination (HOPE) Hernia is a two-part study of patients undergoing open inguinal herniorrhaphy
  - In part 1 of the HOPE Hernia study (HH-1), patients were randomized to one of two postoperative, over-the-counter, non-opioid MMA regimens; no differences between regimens were observed[6]
  - In part 2 of the HOPE Hernia study (HH-2), investigators could choose between the two non-opioid MMA regimens studied in part 1
    - HH-2 expanded the study to 17 new centers
  - Here, we present combined results from HH-1 and HH-2

OBJECTIVE

- The objectives of the HOPE Hernia study were to:
  - Identify which of two postoperative non-opioid MMA regimens (alternating or concurrent) resulted in the highest proportion of patients not requiring an opioid prescription at discharge (HH-1)
  - Examine the efficacy and safety of HTX-011, in combination with non-opioid MMA and a personalized opioid prescription algorithm, in a real-world setting (HH-1 and HH-2)

METHODS

Study Design and Patients

- HOPE Hernia is a two-part, phase 3b, open-label study of adult patients undergoing open inguinal herniorrhaphy with mesh (NCT03907176)
  - Patients with an American Society of Anesthesiologists physical status classification of I, II, or III were included
  - Patients were excluded if they had a known or suspected history of drug abuse or had taken any opioid within the past 24 hours
- Prior to surgery, all patients were shown a 5-minute educational video that summarized the HOPE Hernia study; set patient expectations for postsurgical pain; reviewed the potential side effects of ibuprofen, acetaminophen, and oxycodone; and discussed their scheduled postoperative MMA regimen
  - Patients received oral ibuprofen 400 mg and oral acetaminophen 1 g approximately 2 hours before surgery
- All patients received a single intraoperative dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam) via needle-free application to the surgical site prior to wound closure at the end of surgery (**Figure 1**)
  - In HH-1 (completed), patients were randomized to receive one of two postoperative, non-opioid MMA regimens[6]
    - Concurrent: oral ibuprofen 600 mg and oral acetaminophen 1 g; both were taken together every 6 hours for 5 days
    - Alternating: oral ibuprofen 600 mg and oral acetaminophen 1 g; each were taken every 6 hours, alternating so that one medication is taken every 3 hours for 5 days
  - In HH-2 (ongoing), investigators were allowed to choose either concurrent or alternating MMA for their patients
- Patients were discharged according to site practice; they returned for follow-up on days 15 and 29
- A personalized algorithm was used to determine whether a patient should receive an opioid prescription (10 tablets of oxycodone 5 mg) at discharge
  - Patients received an opioid prescription at discharge if they had a Numeric Rating Scale (NRS) pain intensity score of ≥6 at discharge and/or if they had received postoperative opioids at any time prior to discharge

Assessments and Endpoints

- The primary endpoint was the proportion of patients who did not require an opioid prescription from discharge through day 15
- Additional opioid-related endpoints included:
  - Proportion of patients receiving an opioid prescription at or after discharge
  - Patient-initiated callbacks (ie, patients who contacted the surgical site requesting additional pain medication)
  - Number of oxycodone pills taken between discharge and day 15
- Pain intensity at discharge was assessed via a 10-point NRS score, in which NRS score <4 indicates mild pain, NRS score ≥4 through <7 indicates moderate pain, and NRS score ≥7 indicates severe pain
- Patient satisfaction was assessed via the 9-question Treatment Satisfaction Questionnaire for Medication (TSQM-9)[7]
  - Domains of effectiveness, convenience, and global satisfaction were assessed
  - TSQM-9 scores range from 0 to 100, with higher scores indicating better patient experience
- Safety endpoints included the incidence of adverse events (AEs) and serious AEs

Figure 1. HTX-011 (A) Product Packaging and (B) Instilled Into the Surgical Site and Surrounding Tissues Before Wound Closure[4]

A

B

RESULTS

- 192 patients (HH-1, 93; HH-2, 99) were included in this analysis
  - Overall, 96 patients (50%) received the concurrent MMA regimen and 96 patients (50%) received the alternating MMA regimen
- Patient characteristics were generally balanced between treatment groups (**Table 1**)

Table 1. Patient Demographics

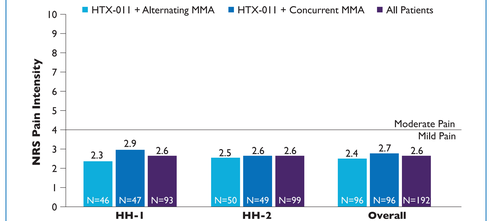
	Overall (HH-1 and HH-2)		
N (%)[a]	HTX-011 + Concurrent MMA N=96	HTX-011 + Alternating MMA N=96	All Patients N=192
Age, years, mean (SD)	55.1 (14.37)	54.5 (14.43)	54.8 (14.36)
Male	95 (99.0)	93 (96.9)	188 (97.9)
Ethnicity			
Hispanic or Latino	20 (20.8)	31 (32.3)	51 (26.6)
Not Hispanic or Latino	76 (79.2)	65 (67.7)	141 (73.4)
Race			
Asian	1 (1.0)	1 (1.0)	2 (1.0)
Black or African American	11 (11.5)	5 (5.2)	16 (8.3)
White	81 (84.4)	90 (93.8)	171 (89.1)
Multiple	1 (1.0)	0	1 (0.5)
Missing	2 (2.1)	0	2 (1.0)
BMI, kg/m², mean (SD)	28.0 (4.45)	26.9 (3.33)	27.5 (3.96)

BMI, body mass index; HH, HOPE Hernia; MMA, multimodal analgesia.
[a]Unless otherwise stated.

Pain Intensity and Discharge Time

- In general, results were similar between the two MMA regimens
- Mean (SD) time to discharge was 2.51 (2.33) hours after surgery
- Mean pain scores at discharge were mild (NRS score <4) (**Figure 2**)

Figure 2. Mean[a] NRS Pain Score at Discharge



HH, HOPE Hernia; MMA, multimodal analgesia; NRS, numeric rating scale of pain intensity.
[a]Mean of all patients in treatment group at a single time point.

Opioid Use

- 177 patients (92%) were discharged without an opioid prescription (**Table 2**)
  - Results were similar for the concurrent and alternating MMA regimens and between HH-1 and HH-2
  - No patients discharged without an opioid prescription called back with pain management concerns or to request an opioid prescription
- Only six patients took any oxycodone tablets between discharge and day 15
- 179 patients (93%) did not take any postoperative opioids (ie, remained opioid-free) through day 15
  - Two patients received an opioid prescription despite not meeting prespecified criteria; neither patient took an opioid at any time

Table 2. Opioid Use Summary

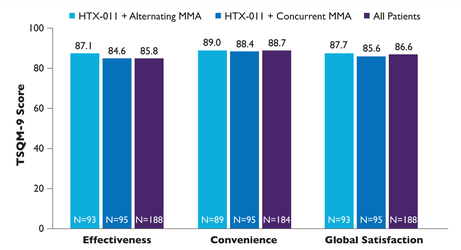
	Overall (HH-1 and HH-2)		
N (%)[a]	HTX-011 + Concurrent MMA N=96	HTX-011 + Alternating MMA N=96	All Patients N=192
Patients receiving an opioid prescription at discharge			
No[b]	87 (90.6)	90 (93.8)	177 (92.2)
Yes	9 (9.4)	6 (6.3)	15 (7.8)
Reason for prescription			
NRS score ≥6 at discharge	5 (5.2)	0	5 (2.6)
Received opioid rescue[c]	4 (4.2)	5 (5.2)	9 (4.7)
Both	1 (1.0)	0	1 (0.5)
Other[d]	1 (1.0)	1 (1.0)	2 (1.0)
Patients who took any opioids between discharge and day 15	4 (4.2)	2 (2.1)	6 (3.1)
Number of opioid pills taken, mean (SD)	12.8 (6.18)	11.5 (2.12)	12.3 (4.93)
Patients who did not receive an opioid prescription through day 15	87 (90.6)	90 (93.8)	177 (92.2)
Patients remaining opioid-free through day 15	88 (91.7)	91 (94.8)	179 (93.2)

HH, HOPE Hernia; MMA, multimodal analgesia; NRS, numeric rating scale of pain intensity.
[a]Unless otherwise stated.
[b]Three patients in HH-2 received opioid rescue medication but did not receive an opioid prescription at discharge.
[c]Opioid rescue medication was provided per institutional standard of care only upon patient request for pain control.
[d]Two patients were given an opioid prescription at discharge despite not meeting prespecified criteria.

Patient Satisfaction

- At day 15, patients reported high scores (mean domain scores >85/100) for all TSQM-9 domains assessed (**Figure 3**); data are combined from HH-1 and HH-2
  - Responses were similar in both treatment arms for all domains

Figure 3. Mean TSQM-9 Scores at Day 15[a]



HH, HOPE Hernia; MMA, multimodal analgesia; TSQM-9, 9-question Treatment Satisfaction Questionnaire for Medication.
[a]Data shown are combined from HH-1 and HH-2. Similar results were observed when analyzed separately.

Safety

- Overall, 52 patients (27%) experienced ≥1 AE (**Table 3**)
  - Results were similar between the concurrent and alternating MMA regimens and between HH-1 and HH-2
  - One serious AE was reported, but was not related to study treatment
  - 2.6% of AEs were possibly related to HTX-011 and included constipation (2 patients), tinnitus, insomnia, and nausea (1 patient each)
- There were no new safety signals observed with scheduled ibuprofen and acetaminophen when used with HTX-011

Table 3. Safety Summary

	Overall (HH-1 and HH-2)		
N (%)	HTX-011 + Concurrent MMA N=96	HTX-011 + Alternating MMA N=96	All Patients N=192
Patients with ≥1 AE	29 (30.2)	23 (24.0)	52 (27.1)
AE possibly related to study drug	5 (5.2)	0	5 (2.6)
AE possibly related to MMA regimen	7 (7.3)	2 (2.1)	9 (4.7)
Patients with ≥1 SAE	0	1 (1.0)	1 (0.5)
SAE possibly related to study drug	0	0	0
SAE possibly related to MMA regimen	0	0	0
ORAE[a]	14 (14.6)	8 (8.3)	22 (11.5)
AEs (≥1.0%)			
Nausea	8 (8.3)	5 (5.2)	13 (6.8)
Constipation	6 (6.3)	2 (2.1)	8 (4.2)
Vomiting	2 (2.1)	3 (3.1)	5 (2.6)
Headache	2 (2.1)	2 (2.1)	4 (2.1)
Testicular swelling	2 (2.1)	2 (2.1)	4 (2.1)
Dizziness	0	2 (2.1)	2 (1.0)
Hematoma	1 (1.0)	1 (1.0)	2 (1.0)
Hypotension	0	2 (2.1)	2 (1.0)
Insomnia	2 (2.1)	0	2 (1.0)
Scrotal swelling	1 (1.0)	1 (1.0)	2 (1.0)

AE, adverse event; HH, HOPE Hernia; MMA, multimodal analgesia; ORAE, opioid-related adverse event; SAE, serious adverse event.
[a]ORAEs include the preferred terms of nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.

CONCLUSIONS

- No differences were observed between concurrent and alternating MMA regimens
  - HTX-011 provided similar pain control and limited the need for opioid use when combined with an alternating or concurrent non-opioid MMA regimen
- HTX-011, when used in combination with a scheduled non-opioid MMA regimen and a personalized opioid prescription algorithm, has the potential to:
  - Eliminate the need for opioid prescriptions after herniorrhaphy in most patients
  - Reduce or prevent patient callbacks for additional pain management
  - Effectively manage postoperative pain
  - Provide high patient satisfaction
  - Minimize unnecessary prescribing of postoperative opioids

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DISCLOSURES

TBD

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HERON THERAPEUTICS

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