Opioid-Free Inguinal Hernia Repair with a Non-Opioid, Multimodal Analgesia (MMA) Regimen Including HTX-011 in a Real-World Setting

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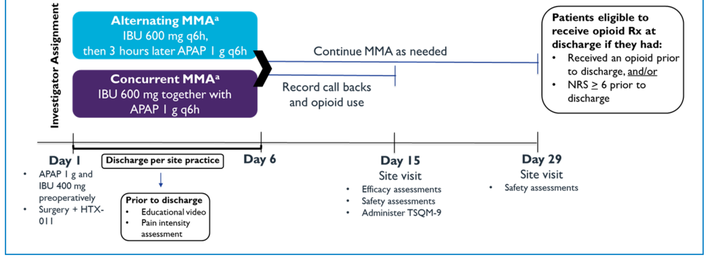
INTRODUCTION AND OBJECTIVES

- Despite use of multimodal analgesia and opioid-sparing protocols, opioids are still over-prescribed after surgery, possibly due to insufficient pain control and inability to predict which patients will need opioid-level analgesia[1]. New solutions are needed.
- HTX-011 (ZYNRELEF™) 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[2,3].
  - Meloxicam reduces surgery-related inflammation, thereby normalizing the local pH, which results in enhanced penetration of bupivacaine into the nerves[3]
- HTX-011 is administered via a needle-free Luer-lock applicator into the surgical site prior to closure
- The Helping Opioid Prescription Elimination (HOPE) project includes HOPE Hernia (HH)-1 (completed) and HH-2 (ongoing), both designed to evaluate HTX-011 as the foundation of non-opioid MMA in open inguinal herniorrhaphy in a real-world setting[4].
  - HOPE Hernia-1 (HH-1) was conducted in 7 research centers, where patients received HTX-011 and were randomized to one of two postoperative, over-the-counter, non-opioid MMA regimens. 90% of patients were discharged without an opioid prescription and 95% of patients reported an opioid-free recovery. Results were similar between MMA regimens[5].
  - The objective of HOPE Hernia-2 (HH-2), was to confirm the results of HH-1 in 17 new centers, with non-opioid MMA regimens assigned based on investigator/patient preference.

METHODS

- This was an interim analysis of HH-2, with results of HH-1 included for comparison.
- **Key Inclusion Criteria:** Adult patients undergoing unilateral open inguinal herniorrhaphy with mesh under deep sedation or general anesthesia with ASA I, II, III
- **Key Exclusion Criteria:** Planned concurrent surgical procedure, pre-existing painful condition expected to require analgesic treatment, opioid use for ≥ 7 days within 6 months, opioid use prior 24 hours
- **Study Endpoints:** Primary endpoint was proportion of patients who required no opioid prescription through Day 15. Secondary Endpoints included proportion of patients who received an opioid prescription at discharge or post-discharge through Day 15, number of oxycodone pills taken between discharge and Day 15, mean numeric rating scale (NRS) pain score at discharge, patient-initiated callbacks for pain management, mean Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores (patient satisfaction), and safety.
- **Treatment Assignments:**
  - All patients received preoperative oral ibuprofen 400 mg and oral acetaminophen 1 g, and a single intraoperative dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam) was administered via needle-free application to the surgical site in the inguinal canal and above the external oblique aponeurosis prior to closure at the end of surgery
  - Post-surgery, all patients received scheduled oral non-opioid MMA and were assigned into two cohorts of different MMA schedules based on investigator/patient preference (**Figure 1**)

Figure 1. HOPE Hernia-2 Study Design



APAP, acetaminophen; IBU, ibuprofen; MMA, multimodal analgesia; NRS, numeric rating scale of pain intensity; q6h, every 6 hours; TSQM-9, Treatment Satisfaction Questionnaire for Medication. [a]While patient is awake.

RESULTS

Table 1. Baseline Characteristics

	HOPE Hernia-1			HOPE Hernia-2		
	Cohort 1 HTX-011 + Alternating MMA N=46	Cohort 2 HTX-011 + Concurrent MMA N=47	Total N=93	Cohort 1 HTX-011 + Alternating MMA N=50	Cohort 2 HTX-011 + Concurrent MMA N=49	Total N=99
Age, mean (SD)	50.0 (12.4)	49.0 (11.1)	49.5 (11.7)	58.5 (15.1)	61.0 (14.8)	59.8 (14.9)
Sex						
Female, n (%)	1 (2.2)	0	1 (1.1)	2 (4.0)	1 (2.0)	3 (3.0)
Male, n (%)	45 (97.8)	47 (100)	92 (98.9)	48 (96.0)	48 (98.0)	96 (97.0)
Race, n (%)						
Asian	1 (2.2)	1 (2.1)	2 (2.2)	0	0	0
Black or African American	5 (10.9)	5 (10.6)	10 (10.8)	0	6 (12.2)	6 (6.1)
White	40 (87.0)	39 (83.0)	79 (84.9)	50 (100)	42 (85.7)	92 (92.9)
BMI (kg/m^2), mean (SD)	27.3 (3.3)	29.1 (4.0)	28.2 (3.8)	26.6 (3.3)	27.0 (4.7)	26.8 (4.0)

MMA, multimodal analgesia; SD, standard deviation; BMI, body mass index

Demographics

- In HH-2, 99 patients were treated with HTX-011 and MMA (alternating, n=50; concurrent, n=49)
- Most patients in HH-2 were male (97.0%) and white (92.9%); mean (SD) age was 59.8 (14.9) years and BMI 26.8 (4.0) kg/m^2 **(Table 1).**

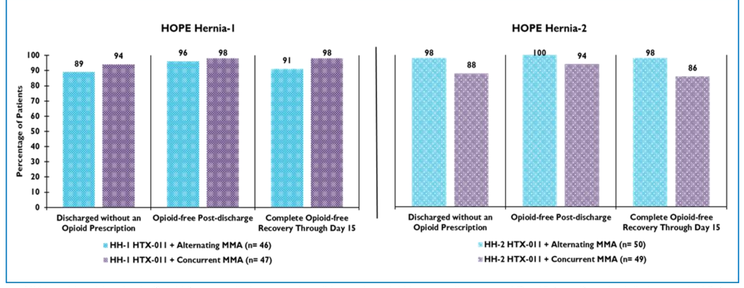
Efficacy

- Efficacy results (including pain levels, opioid consumption, and patient satisfaction) were similar between HH-1and HH-2 and also between cohorts in each study.
- In both studies, mean time to discharge following surgery was between 2 and 3 hours and mean pain at discharge was in the mild range (NRS <4).

Opioid Consumption

- In HH-2, overall 93% of patients did not receive an opioid prescription at discharge through recovery Day 15 (**Figure 2**)
- 7 patients received a discharge opioid prescription in HH-2; algorithm criteria are listed in **Table 2**
  - Only 3 patients took an opioid (a total of 22, 10, and 9 oxycodone 5-mg tablets through Day 15, respectively)
- Of the patients discharged without an opioid prescription, there were no callbacks (in either study) for pain management

Figure 2. Postoperative Opioid Utilization



MMA, multimodal analgesia; Opioid-free post-discharge= patient did not take opioid between discharge and Day 15 (even if received discharge opioid Rx); Complete opioid-free recovery through Day 15= patient did not take opioid in hospital or after discharge (even if received discharge opioid Rx)

Patient Satisfaction

- Results of TSQM-9 were slightly higher in HH-2 compared to HH-1. On a 0-100 scale for each domain, mean scores in HH-2 were the following:
  - Effectiveness: 90 for both alternating and concurrent MMA regimens vs. 85 and 79 in HH-1, respectively
  - Convenience: 89 and 90 for alternating and concurrent MMA regimens vs. 89 and 86 in HH-1, respectively
  - Global satisfaction: 90 and 89 for alternating and concurrent MMA regimens vs. 86 and 82 in HH-1, respectively

RESULTS

Table 2. Opioid Prescription Algorithm

	HOPE Hernia-1			HOPE Hernia-2		
	Cohort 1 HTX-011 + Alternating MMA N=46	Cohort 2 HTX-011 + Concurrent MMA N=47	Total N=93	Cohort 1 HTX-011 + Alternating MMA N=50	Cohort 2 HTX-011 + Concurrent MMA N=49	Total N=99
Patients who received an opioid prescription at discharge, n (%)	5 (10.9)	3 (6.4)	8 (8.6)	1 (2.0)	6 (12.2)	7 (7.1)
Criteria:						
NRS-R ≥6 at discharge	0	2 (4.3)	2 (2.2)	0	3 (6.1)	3 (3.0)
Received rescue opioid*	4 (8.7)	1 (2.1)	5 (5.4)	1 (2.0)	3 (6.1)	4 (4.0)
Both NSR-R ≥6 and rescue opioid	0	0	0	0	1 (2.0)	1 (1.0)
Other	1 (2.2)	0	1 (1.1)	0	1 (2.0)	1 (1.0)

MMA, multimodal analgesia; *3 patients in HH-2 received opioid rescue medication but did not receive an opioid prescription at discharge

Safety

- The most common adverse events (AEs) (≥3%) in HH-2 were testicular swelling and constipation. There were no severe AEs reported and no patients withdrew from the study due to an AE **(Table 3).** One serious AE was reported in Cohort 1 and was a peptic ulcer hemorrhage. This was determined as unlikely related to study drug or MMA, and likely due to the patient's underlying ulcer disease (patient had pre-existing cirrhosis and history of coagulopathy).

Table 3. Summary of Adverse Events

	HOPE Hernia-1			HOPE Hernia-2		
	Cohort 1 HTX-011 + Alternating MMA N=46	Cohort 2 HTX-011 + Concurrent MMA N=47	Total N=93	Cohort 1 HTX-011 + Alternating MMA N=50	Cohort 2 HTX-011 + Concurrent MMA N=49	Total N=99
Any AE	12 (26.1)	18 (38.3)	30 (32.3)	11 (22.0)	11 (22.4)	22 (22.2)
Severe AE	0	0	0	0	0	0
Serious AE	0	0	0	1 (2.0)	0	1 (1.0)
AE leading to study withdrawal	0	0	0	0	0	0
Opioid-related AE*	7 (15.2)	11 (23.4)	18 (19.4)	1 (2.0)	3 (6.1)	4 (4.0)
Most common AEs (≥3%)						
Insomnia	0	0	0	0	2 (4.1)	2 (2.0)
Headache	2 (4.3)	2 (4.3)	4 (4.3)	0	0	0
Dizziness	2 (4.3)	0	2 (2.2)	0	0	0
Nausea	5 (10.9)	7 (14.9)	12 (12.9)	0	1 (2.0)	1 (1.0)
Constipation	1 (2.2)	4 (8.5)	5 (5.4)	1 (2.0)	2 (4.1)	3 (3.0)
Vomiting	3 (6.5)	2 (4.3)	5 (5.4)	0	0	0
Testicular swelling	0	1 (2.1)	1 (1.1)	2 (4.0)	1 (2.0)	3 (3.0)

AE, adverse event; MMA, multimodal analgesia;
*Opioid-related AEs were prespecified as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.

SUMMARY AND CONCLUSIONS

- In HH-2, HTX-011 with a scheduled non-opioid MMA regimen plus an opioid prescription algorithm achieved opioid prescription elimination after open inguinal hernia repair in 93% of patients, with no call-backs for pain management.
- 92% of patients experienced an opioid-free recovery, treatment regimens were well-tolerated, and patients reported high satisfaction.
- Results from HH-2 were similar to HH-1, which confirmed the HH-1 findings in a broader patient population.
- In a real-world setting of hernia repair, HTX-011 as the foundation of a non-opioid MMA regimen effectively manages postoperative pain, minimizes opioid use, and eliminates unnecessary prescribing of postoperative opioids.

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