Opioid-Free Recovery after Inguinal Hernia Repair with Bupivacaine and Meloxicam Extended-Release Solution (ERBMS) as the Foundation of a Multimodal Analgesia Regimen in a Real-World Setting

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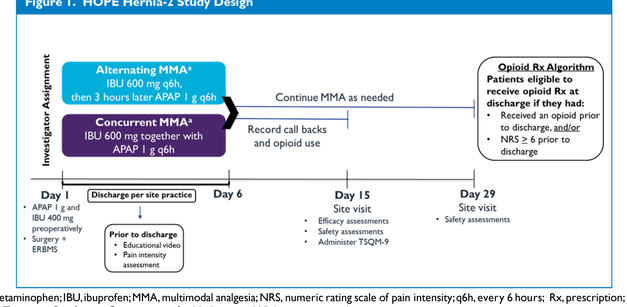
INTRODUCTION AND OBJECTIVES

- Despite use of multimodal analgesia and opioid-sparing protocols, opioids are still over-prescribed after surgery, possibly due to insufficient pain control and the inability to predict which patients will need opioid-level analgesia[1]. New non-opioid solutions and prescribing algorithms are warranted.
- ERBMS, or extended-release bupivacaine and meloxicam solution (ZYNRELEF®) is a dual-acting local anesthetic (DALA) formulation made up of an extended-release polymer that controls the release of active ingredients over 72 hours. The prolonged release of bupivacaine and meloxicam results in sustained analgesia, leading to a 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]
- ERBMS is administered via a needle-free Luer-lock applicator into the surgical site prior to closure.
- The Helping Opioid Prescription Elimination (HOPE) project included HOPE Hernia (HH)-1 and HH-2, both designed to evaluate ERBMS 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 ERBMS and were randomized to one of two postoperative, over-the-counter, non-opioid MMA schedules. 90% of patients were discharged without an opioid prescription and 95% of patients reported an opioid-free recovery. Results were similar between MMA schedules[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 schedules assigned based on investigator/patient preference.

METHODS

- This is the final analysis of HH-2.
- **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 tablets 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. In addition, a pain phenotyping questionnaire was conducted for analysis of baseline factors potentially predictive of opioid use.
- **Treatment Assignments:**
  - All patients received preoperative oral ibuprofen 400 mg and oral acetaminophen 1 g, and a single intraoperative dose of ERBMS 300 mg/9 mg (bupivacaine/meloxicam) was administered via needle-free application to the surgical site prior to closure at the end of surgery
  - Post-surgery, all patients were to receive 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; Rx, prescription; TSQM-9, Treatment Satisfaction Questionnaire for Medication. [a]While patient is awake.

RESULTS

Table 1. Patient Demographics

	ERBMS + Concurrent MMA N=60	ERBMS + Alternating MMA N=56	All Patients N=117
Age, years, mean (SD)	60.7 (14.6)	59.2 (15.3)	60.0 (14.8)
Sex, n (%)			
Male	59 (98.3)	54 (96.4)	114 (97.4)
Female	1 (1.7)	2 (3.6)	3 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	4 (6.7)	18 (32.1)	22 (18.8)
Not Hispanic or Latino	56 (93.3)	38 (67.9)	95 (81.2)
Race, n (%)			
Asian	1 (1.7)	0	1 (0.9)
Black or African American	6 (10.0)	0	6 (5.1)
White	52 (86.7)	55 (98.2)	108 (92.3)
Missing	1 (1.7)	1 (1.8)	2 (1.7)
BMI, kg/m², mean (SD)	27.2 (4.5)	26.4 (3.3)	26.8 (4.0)

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

Demographics

- 117 patients were treated with ERBMS and 116 received MMA (concurrent, n=60; alternating, n=56). Two patients were lost to follow-up prior to study completion. Patient demographics were consistent with the surgical population **(Table 1).**

Efficacy

- Mean time to discharge was between 2 and 3 hours and mean numeric rating scale (NRS) for pain at discharge was 2.4, in the mild range (NRS <4).
- Overall, 109/117 (93.2%) patients were discharged without an opioid prescription, 54/60 (96.4%) and 54/56 (90%) in the ERBMS + alternating MMA and ERBMS + concurrent MMA arms, respectively **(Table 2).**
- 8 patients received a discharge opioid prescription in HH-2; algorithm criteria are listed in **Table 2.**
  - Of these 8 patients, 4 took an opioid (5, 9, 10, and 22 oxycodone 5-mg tablets through Day 15)
- Of the patients discharged without an opioid prescription, 1 patient called the site back for pain management and received a prescription for oxycodone 5 mg tablets. This patient stopped taking MMA medications on Day 4 and consumed 20 tablets from discharge to Day 15.
- Across cohorts, 106/117 (90.6%) patients had an opioid-free recovery **(Figure 2)**.
- No relationship was discerned between pain phenotyping factors, postoperative opioid consumption, or discharge opioid prescriptions.
- Patients indicated high satisfaction per TSQM-9, as 110/117 (94%) patients indicated they were either satisfied, very satisfied, or extremely satisfied (8.5%, 28.2%, 57.3%, respectively). Overall TSQM-9 scores were similar between cohorts.

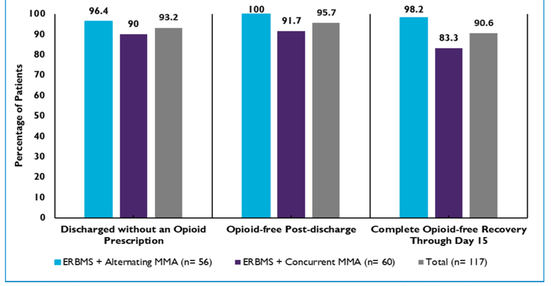
Table 2. Opioid Prescription Algorithm

	ERBMS + Concurrent MMA N=60	ERBMS + Alternating MMA N=56	All Patients N=117
Patients who did not receive opioid prescription at discharge, n (%)	54 (90)	54 (96.4)	109 (93.2)
Initiated contact with the site post-discharge to discuss postoperative pain, n (%)	1 (1.7) [a,b]	0	1 (0.9) [a,b]
Patients who received opioid prescription at discharge, n (%)	6 (10)	2 (3.6)	8 (6.8)
NRS-R ≥6 at discharge	1 (1.7)	0	1 (0.9)
Received rescue opioid	1 (1.7)	2 (3.6)	3 (2.6)
Both NRS-R ≥6 and rescue opioid[c]	3 (5)	0	3 (2.6)
Other[d]	1 (1.7)	0	1 (0.9)
Patients who took any opioids between discharge and day 15, n (%)	5 (8.3)	0	5 (4.3)
Mean number of oxycodone 5 mg pills taken (range)	13.2 (5-22)	0	13.2 (5-22)

[a]1 patient who did not receive an opioid discharge Rx and contacted the site on Day 4 to request additional pain medication. The patient received an Rx for ten 5 mg oxycodone tablets, then contacted the site again on Day 7 and received an Rx for twenty 5 mg oxycodone tablets. They consumed 20 tablets total from discharge to Day 15 (had stopped taking MMA medications on Day 4). [b]1additional patient who did receive an opioid discharge Rx contacted the site on Day 13 to request additional pain medication and received twelve 5 mg tramadol tablets (considered a protocol deviation). [c]1 of whom also expressed concern about pain management plan. [d]Patient request due to potential travel.

RESULTS

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)

Safety

- Both MMA regimens comprising ERBMS, PO ibuprofen, and PO acetaminophen were well-tolerated. There was no evidence of local anesthetic systemic toxicity (LAST) or NSAID-related toxicity, and there were no clinically meaningful mean changes in vital signs. The most common adverse events (>2%) were testicular swelling and constipation **(Table 3).**

Table 3. Safety Summary

	ERBMS + Concurrent MMA N=60	ERBMS + Alternating MMA N=56	All Patients N=117
Patients with ≥ 1 AE, n (%)	12 (20)	12 (21.4)	25 (21.4)
AE possibly related to study drug	2 (3.3)	0	2 (1.7)
AE possibly related to MMA regimen	4 (6.7)	1 (1.8)	5 (4.3)
Patients with ≥ 1 SAE, n (%)	0	0	0
ORAE[a]	3 (5)	1 (1.8)	5 (4.3)[a]
NSAID-related AEs[b]	1 (1.7)	6 (10.7)	7 (6)
AEs (>2%)			
Constipation	2 (3.3)	1 (1.8)	3 (2.6)
Testicular swelling	1 (1.7)	2 (3.6)	3 (2.6)

AE, adverse event; MMA, multimodal analgesia; SAE, severe adverse event; ORAE, opioid-related adverse event
[a]Opioid-related AEs were prespecified as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention. The 5 reported included constipation (3 patients), nausea (1 patient), urinary retention (1 patient).
[b]NSAID-related AEs were identified using a customized list of NSAID toxicity-related preferred terms (>1,800) derived from Essex MN, et al.[6] The 7 reported NSAID-related AEs included 1 of each of the following: scrotal swelling, hypotension, angioedema, hepatic cirrhosis, liver injury, palatal edema, peptic ulcer hemorrhage, and swelling.

SUMMARY AND CONCLUSIONS

- HH-2 confirmed that ERBMS with a non-opioid MMA regimen plus an opioid prescription algorithm resulted in >90% of patients discharged without an opioid prescription.
- 91% of patients experienced an opioid-free recovery and only 1 patient discharged without an opioid prescription called back for pain management.
- ERBMS with NSAID-containing MMA was well-tolerated and patients reported high treatment satisfaction.
- In a real-world setting of hernia repair, ERBMS as the foundation of a non-opioid MMA regimen effectively manages postoperative pain, minimizes opioid use, and eliminates unnecessary prescribing of opioids.

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