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Pain Management

(Abstracts)

Contents

HTX-011 Combined with Multimodal Analgesia as Pain Management after Total Knee Arthroplasty: Results from a Phase 3B Open-Label Study

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Introduction: Opioid medications are commonly prescribed for pain control following orthopedic surgery, but they can be associated with side effects, poor patient outcomes, and the potential for dependence and misuse.[1-3]

HTX-011 is a novel, extended-release, dual-acting local anesthetic (DALA) containing bupivacaine and low-dose meloxicam in a proprietary polymer allowing for controlled diffusion of active ingredients over 72 hours. In a prior phase 2b study (NCT03015532) in patients undergoing total knee arthroplasty (TKA), HTX-011 (400 mg bupivacaine/12 mg meloxicam) alone reduced pain, decreased opioid use, and reduced time to discharge readiness compared with bupivacaine hydrochloride or saline placebo.

The phase 3b study presented here (NCT03974932) was designed to assess pain control, opioid use, safety, and tolerability of intraoperative HTX-011 + perioperative scheduled non-opioid multimodal analgesia (MMA) in patients undergoing TKA.

Methods: Ethics approval was obtained from the local Research Ethics Board. Before surgery, patients received oral acetaminophen 1 g, celecoxib 200 mg, and pregabalin 300 mg. All patients underwent TKA with bupivacaine spinal anesthesia and received intraoperative HTX-011 400 mg bupivacaine/12 mg meloxicam administered via needle-free periarticular application. For 72 hours following surgery, patients received acetaminophen 1 g every 8 hours (q8h) and celecoxib 200 mg q12h (non-opioid MMA regimen). Opioid rescue medication was administered during the inpatient period only upon patient request. Following discharge at 72 hours, patients were to maintain a scheduled, oral, non-opioid, over-the-counter MMA regimen comprising acetaminophen 1 g q6h alternating with ibuprofen 600 mg q6h for 4 days. Patients returned for follow-up visits 10 and 28 days after surgery. The primary endpoint was the area under the curve (AUC) of visual analog scale (VAS) scores from 12-48 hours ($AUC_{12–48}$).[4]

Results: Fifty-one patients undergoing TKA received intraoperative HTX-011 + perioperative non-opioid MMA. Throughout the 72-hour inpatient period, mean pain scores remained in the mild pain range (VAS <4.4 cm, Figure).[5] The mean $AUC_{12–48}$ was 143.2 (SD, 93.5). 57% of patients never experienced severe pain (VAS ≥7.5 cm). Median opioid consumption was 22.5 mg of morphine milligram equivalents per patient through 72 hours (<5 oxycodone 10 mg pills). Most patients (75%) were discharged without an opioid prescription. The combination of HTX-011 with this scheduled non-opioid MMA regimen was well tolerated.

Conclusion: This phase 3b study demonstrated that intraoperative HTX-011 as the foundation of a scheduled non-opioid MMA regimen following TKA has the potential to eliminate severe pain in the majority of patients, maintain mean pain in the mild range, and reduce opioid consumption.

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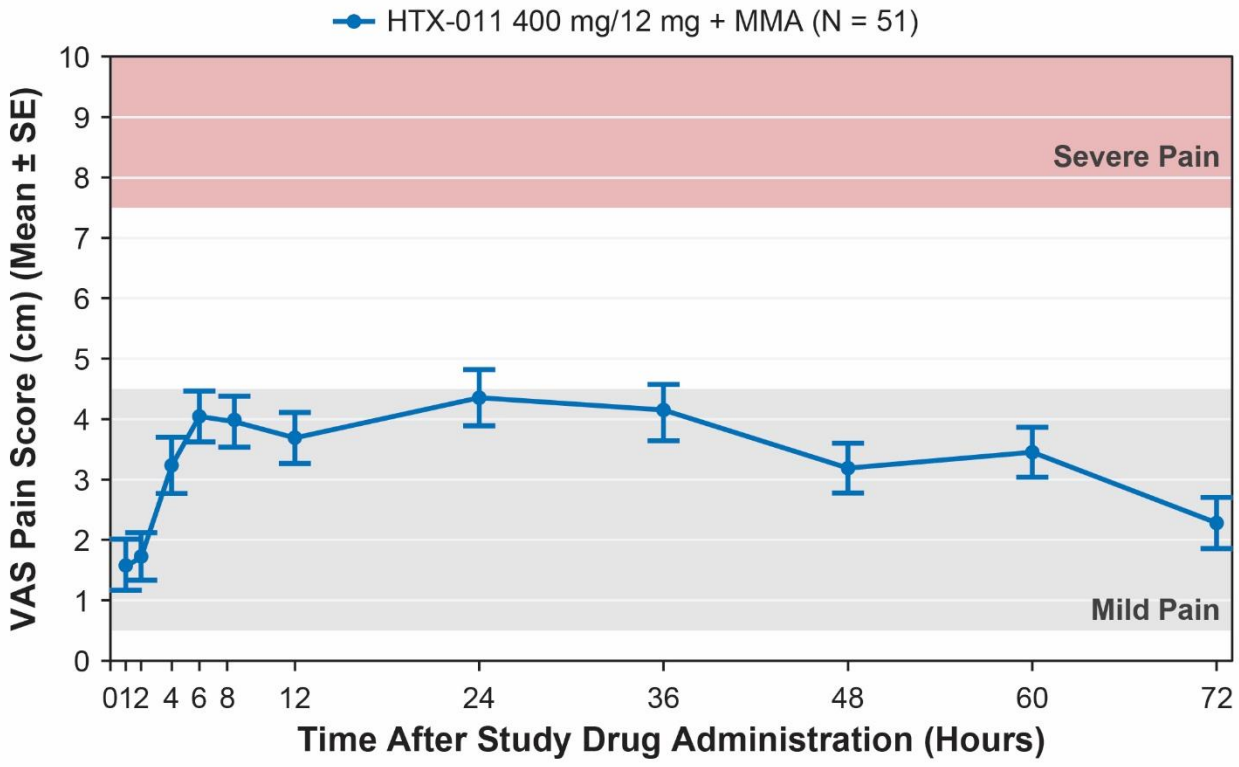
Figure. Mean Pain Intensity Through 72 Hours After TKA as Measured by Visual Analog Scale



MMA, multimodal analgesia; SE, standard error; VAS, visual analog scale.

Hydromorphone versus Morphine: A Historical Chart Review to Evaluate the Quality of Post-Operative Analgesia

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Introduction: Opioids are the most widely used therapy for pain during the postoperative period. Morphine and hydromorphone are among the most common opioids currently used.[1] A randomized control trial conducted by Shanthanna et al. (2019) compared morphine with hydromorphone for achieving satisfactory analgesia with minimal emesis within 2 hours after surgery. This study found no difference between morphine and hydromorphone regarding analgesia and common side effects.[2] Our study had a similar primary objective but was conducted as a retrospective cohort study with other differences in study design as well. Our primary objective was to determine if there was a difference in pain score ratings (using a numeric pain rating scale 0-10) between adult patients receiving intravenous (IV) hydromorphone versus morphine as post-operative analgesia at 2 hours of admission to the post-anesthesia care unit (PACU). Secondary outcomes included proportion of individuals with satisfactory analgesia without substantial postoperative nausea and vomiting (PONV), total equipotent opioid dose, proportion and severity of side effects (PONV, sedation, pruritis), and time until readiness for PACU discharge.

Methods: After ethics board approval, convenience sampling was used to identify the first 605 patients who met inclusion criteria. Patients >18 years old and undergoing non-cardiac surgery were identified through the Hamilton Health Sciences (HHS) operating room database. Data extraction from the anesthetic record included patient demographics, surgical procedure, length of procedure, type of anesthetic, and time of extubation. Patients were categorized based on treatment in the PACU with hydromorphone (n=326) or morphine (n=279). PACU flowsheets were used to determine pain scores (from 0-10), nausea/vomiting (scale of 0-3), pruritis (scale of 0-3) sedation (0-4), as well as total opioid dose administered from arrival in PACU until 2 hours or readiness to discharge. Total opioid dose was converted into morphine equivalents using a ratio of 1:5 of hydromorphone: morphine, respectively.[3,4]

Results: Regarding the primary outcome of pain reported at 2 hours from admission to PACU, there was no significant difference between hydromorphone and morphine (mean difference: 0.10; 95% CI: -0.21 to 0.42; p=0.53). Similarly, there were no significant differences between the groups' length of stay in PACU (p=0.82), achieving satisfactory analgesia (p=0.41), incidence of nausea/vomiting (p=0.08), and incidence of sedation (p=0.36). However, a lower equipotent dose of hydromorphone was required for analgesia (mean difference: -1.35; 95% CI: -2.03 to -0.68; p<0.001). There were not enough events to report differences in pruritus and respiratory depression.

Conclusion: There is limited literature comparing morphine to hydromorphone during the postoperative period. This study serves to increase information on prescribing practices, effective analgesia, and associated side effects. Overall, this study found that there is no statistically significant difference between the use of IV hydromorphone versus morphine to control pain in the post-operative period.

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Is Intrathecal Analgesia Associated with Reduced Post-Operative Pain in Laparoscopic Liver Resections?

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Introduction: In an era of Enhanced Recovery After Surgery (ERAS), intrathecal analgesia has been proposed as an alternative to epidural analgesia and patient controlled analgesia (PCA). Intrathecal analgesia have been recommended by the ERAS Society in laparoscopic colon resections and are also used in open liver resections; however, they have not been extensively studied in laparoscopic hepatobiliary surgeries. The primary objective of this study was to explore postoperative pain at 48 hours among patients who underwent laparoscopic liver resections (LLR), receiving either intrathecal analgesia with or without PCA versus PCA alone. Secondary objectives were to determine the association of treatment type with post-operative pain outcomes at 48 hours and surgical complications.

Methods: Ethics approval was obtained from the local REB. Patients who underwent LLRs between January 2016 and April 2019, and had intrathecal analgesia administration and/or PCA were included. To describe postoperative pain, descriptive statistics were completed for both treatment groups for each pain outcome. Postoperative pain outcomes included: cumulative opioid consumption, visual analog scale scores, length of time without requiring opioids, length of time unable to mobilize, and use of non-opioid pain-control medication (regional analgesia, acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, tramadol, lidocaine, and N-methyl-d-aspartate class of glutamate receptor antagonists).To describe the postoperative pain levels at 48 hours, descriptive statistics were presented by treatment group for each pain outcome. Unadjusted regression analyses were then performed to explore the association of treatment type with each pain and surgical complication outcome. Multivariable linear regression analysis was then conducted to determine other factors associated with increased cumulative postoperative opioid consumption at 48 hours.

Results: Out of 111 patients identified, 79 patients met the inclusion and exclusion criteria; 22 patients had intrathecal analgesia with or without PCA and 57 patients had PCA only. There were no statistically significant differences in baseline characteristics, use of non-opioid pain control, and post-operative complications between the two groups. Intrathecal analgesia use was associated with reduced post-operative opioid consumption, measured in oral morphine equivalents, compared to PCA alone (Mean Difference (95%CI)=-45.92 (-83.10, -8.75); p=0.016). In the multivariable regression analysis, it remained significant (p=0.036) along with age (p=0.005). Intrathecal analgesia were also associated with a greater length of time without requiring opioids post-operatively (Mean Difference (95%CI)=0.75(0.19, 1.31); p=0.010).

Conclusion: Intrathecal analgesia administration has the potential to decrease post-operative opioid use for patients undergoing LLRs. The findings from this study are consistent with the ERAS Society recommendations for laparoscopic colorectal surgery and offers support for the safety and efficacy of using intrathecal analgesia in the setting of LLRs for ERAS. This study is limited by its exploratory nature and small sample size; further research is necessary before recommending the use of routine intrathecal analgesia in LLRs.

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Table 1. Post-operative Pain Outcomes at 48 Hours

Postoperative Pain Outcomes	Intrathecal morphine with or without PCA (N=22)	PCA only (N=57)	Estimate(95%CI)p
Continuous outcomes	Mean(sd)	Mean(sd)	Mean Difference (95%CI)p
Cumulative opioid consumption within 48 hours using morphine equivalents (mg); mean(sd) Between 0-24 hours (Day 1) Between 24-48 hours (Day 2)	70.61(41.95) 27.57(19.99) 43.05(30.08)	116.54(83.35) 70.67(50.05) 45.86(49.39)	-45.92(-83.10,-8.75) 0.016
VAS Score at 48 hours; mean (sd)	3.23(1.93)	2.53(2.05)	-0.02(-0.17,0.12) 0.178[£]
	Median (Q1,Q3)	Median (Q1,Q3)	Mean Difference (95%CI)p
Length of time without requiring opioid (minutes); median (Q1,Q3)	70.00(45.00,378.00)	39.00(28.00,65.00)	0.75(0.19,1.31) 0.010[¥]
Length of time unable to mobilize (hours); median (Q1,Q3) Missing	26.68(21.00,48.78) 1	24.99(20.51,42.92) 1	0.07(-0.19,0.32) 0.601[¥] 1
Non-opioid pain-control medication	n(%)	n(%)	Odds Ratio (95%CI)p
Acetaminophen; n(%)	14(63.64)	28(49.12)	1.81(0.66,4.97) 0.249
Nonsteroidal anti-inflammatory drugs; n(%)	3(13.64)	10(17.54)	0.74(0.18, 3.00) 0.676
Gabapentinoids; n(%)	0	2(3.51)	Not enough events

[£]Adjusted for Pain at PACU arrival
[¥]Based on ln transformation of outcome
Comment: 0 events for regional analgesia, tramadol, lidocaine, and N-methyl-d-aspartate class of glutamate receptor antagonists.

Opioid-Free Recovery After Bunionectomy with HTX-011, an Extended-Release Local Anesthetic, in Combination with Non-Opioid Multimodal Analgesia

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Introduction: Opioid medications are commonly used for pain management in the postoperative setting, but they can be associated with side effects, poor patient outcomes, and the potential for dependence and misuse. Consequently, innovative and effective non-opioid pain management strategies are needed.

HTX-011, an extended-release, dual-acting local anesthetic (DALA) containing bupivacaine and low-dose meloxicam in a controlled-release polymer, has demonstrated superiority to bupivacaine hydrochloride through 72 hours in multiple surgical models.[1-3] In a previously conducted phase 3 study in bunionectomy with osteotomy and internal fixation (EPOCH 1), treatment with HTX-011 alone provided superior pain relief, reduced the incidence of severe pain, significantly reduced total opioid consumption and resulted in significantly more opioid-free patients through 72 hours than bupivacaine hydrochloride.[1]

The follow-on study presented here (NCT03718039) was designed to assess the efficacy and safety of HTX-011 as the foundation of a scheduled postoperative non-opioid multimodal analgesia (MMA) regimen in bunionectomy.

Methods: Ethics approval was obtained from the local Research Ethics Board. Patients undergoing bunionectomy with osteotomy and internal fixation using lidocaine Mayo block received intraoperative HTX-011 (up to 2.1 mL, ≤ 60 mg bupivacaine/1.8 mg meloxicam) via needle-free application. Throughout the 72-hour inpatient postoperative period, patients received a non-opioid MMA regimen of oral ibuprofen 600 mg every 6 hours (q6h) and oral acetaminophen 1 g q6h (alternating every 3h). Rescue opioids were available upon request. At discharge, patients were to use ibuprofen 600 mg q6h as needed and to add acetaminophen 1 g q6h if pain persisted. Only patients who received ≥10 mg oxycodone ≤12 hours before discharge were to receive an opioid prescription. Key efficacy assessments were pain intensity (on an 11-point [0-10] Numeric Rating Scale [NRS]) and opioid use. Safety assessments included adverse events (AE) and clinical laboratory tests.

Results: Thirty-one patients received HTX-011; all completed the study. Patient baseline characteristics were similar between the initial phase 3 study and this follow-on study. Mean pain intensity remained within the mild range (NRS ≤4) through 72 hours (Figure). Twenty-four patients (77%) required no opioids (ie, were opioid-free) through 72 hours, and all of these patients remained opioid-free through the 28-day recovery period. Only one patient required an opioid prescription at discharge. Twenty patients (65%) experienced an AE; the most common were nausea (23%) and vomiting (10%). No serious AEs were reported and there was no evidence of gastrointestinal, renal, or hepatic toxicity.

Conclusion: HTX-011, when administered alongside scheduled non-opioid over-the-counter ibuprofen and acetaminophen, resulted in opioid-free recovery in 77% of patients after bunionectomy. Average pain was maintained in the mild range through 72 hours. The regimen was well tolerated. HTX-011 has the potential to be the foundation of a non-opioid MMA regimen that effectively treats pain and achieves opioid-free recovery.

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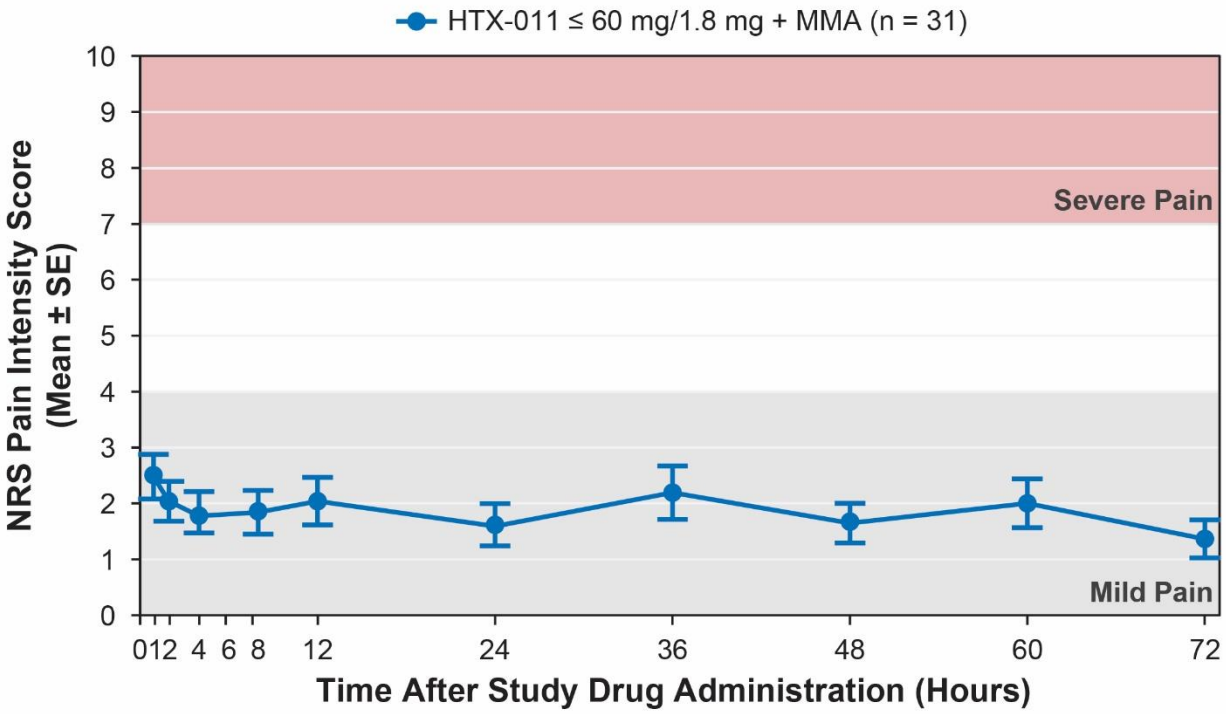
Figure. HTX-011 With a Non-Opioid MMA Regimen Maintained Pain Scores in the Mild Range Through the 72-Hour Postoperative Period After Bunionectomy



MMA, multimodal analgesia (ibuprofen and acetaminophen); NRS, numeric rating scale of pain intensity; SE, standard error.

The Effect of Intra-Operative Use of Ketamine and Lidocaine in DIEP Flap Reconstruction on Post Operative Pain

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Introduction: DIEP flap reconstruction surgery is considered as a major surgery with a substantial post-operative pain[1,2]. The use of multimodal analgesia decreases the post-operative opioid usage and its related side effects[2,3].

Method: We conducted a descriptive, retrospective study of DIEP flap reconstruction over a period of 5 years (September 2013-September 2018). The study was approved by our institution's Research Ethics Board. We included adult female patients who had no history of a significant chronic opioid usage. Data was obtained from the hospital Electronic Medical Record (EMR) and patients' charts. The collected data included patient's demographic information, duration of surgery, duration of hospitals stay, perioperative analgesic medications/interventions, postoperative pain scores and opioid related side effects. A two-tailed Welch's t-test was used for analysis.

Results: During the study period, 106 patients were identified. One patient was excluded for using more than 80 mg of oral morphine equivalent per day. Data of 105 patients (53.33% bilateral) were included in the analysis. The mean age of 51.24 years (± 0.90) and mean weight 78.98 kg (±1.30). The mean duration of the surgical procedure was 561.19 min (±12.26). Post operatively, the 2-hour mean visual analogue scores (VAS) at rest 2.82 (±0.22) and activity 3.53 (± 0.24). The 24-hour mean visual analogue scores (VAS) at rest 2.86 (±0.22) and activity 4.13 (± 0.24). Intraoperatively, lidocaine infusion (0.5-2 mg /kg/hr) was used in 10 patients (9.52%), ketamine (5-12 mg/hr) was used in 32 patients (30.47%), both lidocaine and ketamine used in 25 patients (23.30%) and opioid only analgesia used 38 patients (36.19%). A two-tailed Welch's t-test was performed to compare post operative VAS these groups at 2 and 24 hours (Table1). The combination of intraoperative lidocaine and ketamine analgesia reduced the 24-hour post operative pain during activity when compared to no intraoperative adjuvant analgesia ($p=<0.05$). The standard post operative analgesia includes opioid-PCA and oral multimodal analgesia. The mean length of hospital stay (days) for the four groups as follow; opioid only 5.75(± 0.21), ketamine 5.15 (± 0.16), lidocaine 5.6 (±0.22) and both lidocaine and ketamine 5.16 (±0.12). The use of ketamine and/or a mixture of lidocaine and ketamine, but not lidocaine alone, causes a significant reduction in hospital stay ($p< 0.05$). The use of intraoperative analgesia did not show a significant reduction in first postoperative day opioid related side effects (nausea, vomiting and pruritus) OR 0.9-1.0 (95% CI).

Discussion: Our data suggests that the use of a combination of lidocaine and ketamine intra-operatively reduced the 24-hour post-operative pain during activity in this group of patients. More prospective, well designed studies are needed to determine the effect of intra-operative lidocaine and ketamine on acute post-DIEP flap pain.

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2-hour VAS (rest)					**2-hour VAS (Activity)**		
Adjuvant analgesia	Mean	Variance	P value		Mean	Variance	P value
Lidocaine	2.6	2.93	0.61		3.9	5.87	0.83
Ketamine	2.78	4.75	0.76		3.43	5.60	0.64
Lidocaine and ketamine	2.80	6.75	0.83		3.48	7.09	0.73
None	2.94	6.32			3.71	6.80	
24-hour VAS (rest)					**24-hour VAS (Activity)**		
Adjuvant analgesia	Mean	Variance	P value		Mean	Variance	P value
Lidocaine	3.50	2.27	0.44		4.70	2.67	0.95
Ketamine	2.81	6.15	0.70		3.87	5.01	0.13
Lidocaine and ketamine	2.48	5.26	0.35		3.32	8.06	**0.048**
None	3.02	5.10			4.73	6.36	

Table 1: The comparison between the visual analogue scores of the use of adjuvant analgesics with opioid only analgesia by using Welch's t-test.

Understanding Opioid Prescribing versus Opioid Consumption in the Postoperative Period

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Introduction: In the past twenty-five years, opioid related deaths have increased four-fold in Ontario, and opioid related emergency department visits have tripled between 2008 and 2016 in the Niagara region alone. Despite vast media coverage of the opioid crisis, opioid prescriptions continue to rise. Indeed, a significant number of overdose deaths have been linked to opioid prescriptions in the postoperative period. There is great variability in post-surgical opioid prescriptions across procedures at the time of discharge. Given that overprescribing of narcotics by physicians could further contribute to the opioid crisis, it is timely to understand opioid prescribing in the postoperative setting. This study aims to improve opioid prescription strategies postoperatively at the Niagara Health System (NHS) by identifying and, ultimately, mitigating the discrepancy between the amount of opioids prescribed by physicians and the proportion of prescribed opioids consumed by patients.

Methods: Ethics approval was obtained from the local REB. This prospective study included patients undergoing one of eighteen elective, day surgeries across eight surgical specialities, which had been examined for opioid overprescribing practices in the literature. Exclusion criteria included patients <18 years of age, non-English speaking, pregnant, or those with a history of opioid use or chronic pain. Patients from all three NHS sites (Welland Hospital, Greater Niagara General Hospital, St. Catharine's General Hospital) were included. Participants who provided consent were given a questionnaire to establish pre-operative prescription use, and copies of discharge opioid prescriptions were obtained from chart retrieval. Patients were contacted by phone on post-operative day ten to fourteen to establish the amount of postoperative narcotic prescription consumed. If they could not be reached after three attempts, they were deemed lost to follow-up. Data was collected from March – June 2019.

Results: A total of 255 patients, from the eighteen surgeries included in the study, consented to the study and met inclusion criteria. For simplicity, all opioid prescriptions were converted to morphine equivalents (ME) for data analysis. It was found that on average, only 35.7% + 19% opioids prescribed were used postoperatively to achieve adequate pain control (see Figure 1).

Conclusion: Our results demonstrate that patients across multiple surgical specialties are overprescribed narcotics in the elective, day surgery postoperative setting. This is one of the first studies in Canada to examine opioid prescribing habits in conjunction with patient use on a large scale, though our results echo what has been found in the American literature. Following the results of our study, multidisciplinary education sessions were held to disseminate

information and gather feedback from all stakeholders. Patient education handouts on multimodal analgesia, appropriate opioid use, and opioid disposal have been implemented following the results of the study. Perioperative order sets are also being changed to reduce overprescribing in the postoperative period. We will continue to monitor the use of postoperative opioid prescribing for elective day surgery patients, with the intent of minimizing opioid overprescribing.

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