Sustained-release opioid following open abdominal urologic surgery: A randomized controlled study

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ABSTRACT

Introduction: Despite increased risk of adverse events and overdose associated with sustained-release opioids, evidence is lacking to support the short-term use of a low-dose, sustained-release opioid for acute pain control in a monitored setting. Both immediate-release and sustained-release opioids are used clinically in postoperative analgesia. We hypothesized that short-term use of low-dose, sustained-release hydromorphone combined with immediate-release hydromorphone as required would facilitate earlier ambulation after major urologic surgeries compared to immediate-release opioid alone.

Methods: Following ethics approval and patient consent, patients undergoing elective open abdominal urologic surgeries were randomized into two groups: sustained-release

KEY MESSAGES

- The use of low-dose, short-term, sustained-release hydromorphone in the hospital setting for open abdominal urologic surgery did not offer clinical advantage in terms of early ambulation of patients with and without OSA.
- There was no difference regarding opioid consumption and pain score in the sustained-release hydromorphone when compared to patients who received only immediate-release hydromorphone in the immediate postoperative period.
- We did not find any significant difference in adverse effects between sustained-released or immediate-release hydromorphone.

hydromorphone on a regular basis for two days, with immediate-release hydromorphone available on an as-required basis; or immediate-release hydromorphone on an as-required basis only. The primary outcome measure was the time to get up and walk three steps.
Results: A total of 66 participants were included in the data analysis. There was no statistically significant difference in the time to first mobilization, opioid consumption, or pain scores at any time point between the two groups. There were trends toward more nausea on postoperative days 1, 2 and 3, as well as more severe loss of sleep the first night after surgery in the immediate-release group, although the differences did not reach statistical significance.
Conclusions: Our study showed that patients receiving short-term, low-dose, sustained-release hydromorphone immediately postoperatively did not mobilize sooner compared to those only receiving immediate-release hydromorphone. There was no difference in the pain score or opioid consumption.

INTRODUCTION

The use of both illegal and prescription opioids continues to contribute to the ongoing opioid crisis in Canada and the United States.[1-4] Canadians are among the world's largest consumers of prescription opioids.[5] The International Narcotics Control Board reported that between 2017 and 2019, the countries reporting the highest average consumption of opioid for pain management were the United States, Germany, Austria, Belgium and Canada.[6] Therefore, it is important to explore strategies that reduce opioid dosage without compromising pain control after major open abdominal surgery. Several studies suggest the implementation of Enhanced Recovery After Surgery (ERAS) protocols that limit the use of opioids during in-patient stays following major urological procedures was associated with a significant decrease in opioid prescription at discharge, a shift towards less potent opioids, and improved quality of life post-operatively.[7-9]

Compared to immediate-release opioids, sustained-release opioids may be associated with less fluctuation in drug plasma concentrations and an extended time in the therapeutic window, which may decrease periods of inadequate pain control.[10] Several studies also suggest sustained-release opioids are as effective as immediate-release opioids at managing pain in cancer and non-cancer patients, while having fewer adverse events.[11-14] In recent years, however, there has been a shift away from the use of sustained-release opioids for acute pain, largely due to their increased risk for overdose, addiction, and abuse, when used long-term for chronic pain.[15-16] Nonetheless, there is a lack of evidence for the short-term use of low dose sustained-release opioid in a monitored hospital setting to manage acute postoperative pain following painful open abdominal urologic surgeries. Our study aims to explore the short-term use of sustained-release opioids post-operatively in the hospital setting to reduce opioid consumption without compromising pain management and patient functionality after major

urologic surgery. We hypothesized that the use of a short-term, low dose sustained-release and immediate-release as needed opioid formulation would offer better pain control in the first 48 hours post-operatively and facilitate earlier ambulation, compared to immediate-release opioid alone in patients undergoing open abdominal urologic surgery.

METHODS

Following Ethics (IRB) approval (University of Alberta Human Subjects Research Ethics Board Approval: dated April 26, 2022, Pro00118895), and clinical trials registration [Clinicaltrials.gov protocol number NCT05375916], we conducted a randomized, double-blind, controlled trial. Patients meeting inclusion and exclusion criteria were enrolled into the study following written, informed consent. Inclusion criteria include assessing all adult patients (above 18 years old) undergoing elective open abdominal urologic surgeries with an American Society of Anesthesiologist physical status score of I to III. The exclusion criteria were patient refusal, history of chronic pain, patients with an allergy to hydromorphone, local anesthetic, or acetaminophen, severe post-operative nausea and vomiting, inability to swallow tablets, and patients with severe renal failure. The primary outcome was the time to achieve adequate pain relief to stand up and walk three steps following surgery (days post-operatively). Secondary outcomes included pain scores recorded in the Post-Anesthetic Care Unit (PACU), and 24/48/72 hours post-operatively, opioid consumption intraoperatively, in the PACU and 24/48/72 hours post-operatively, nausea, vomiting, loss of sleep, patient satisfaction, oxygen desaturation to below 93%, and other adverse events.

Using a computer-generated random number table with 1:1 allocation ratio, patients were randomly assigned into: Group 1 (SR group): Sustained-release hydromorphone (HM) on a regular basis for 2 days (HM 3 mg TID) with immediate-release HM available on an ‘as required’ basis or Group 2 (IR group): Immediate-release HM on an ‘as required’ basis only. Random number assignment was concealed in an opaque envelope until patient enrollment. All patients were given general anesthetic, 8 mg of dexamethasone, and intravenous opioid at the discretion of the anesthesiologist in the operating room. Prior to abdominal closure at the end of surgery, surgeons inserted bilateral rectus sheath catheters and injected 20 mL of 0.25% bupivacaine on each side. Both groups received local anesthetic infusion of 0.2% ropivacaine via rectus sheath catheters bilaterally for three days at a rate of 1 mL/hour and intermittent 15 mL bolus every four hours, as well as regular acetaminophen (975 mg by mouth [PO] every 6 hours). Group 1 received the first dose of sustained-release HM in PACU just prior to transfer to the ward. On the ward, group 1 continued to receive sustained-release HM on a regular basis for 6 doses (i.e., 2 days) and could ask for additional immediate-release opioid if necessary. Group 2 only received immediate-release opioid if required by asking the ward nurse. Oxygen saturation was continuously monitored on the ward and oxygen therapy via nasal cannula was administered if the oxygen saturation reduced below 93%.

Statistical analysis

The sample size for the study was based on a difference of 31% for the primary outcome of days to mobilization. Based on the previous study, the pain score (Visual Analogue Scale) was 55 for the sustained-released opioid arm and an improvement of 31% was assumed in the immediate-release opioid arm, which is approximately 42. A sample of 40 subjects in the sustained-release opioids group and 40 subjects in the immediate-release opioids provide 80% power to detect a 31% difference between the two groups with a two-sided significance level of 5%. The sample size calculation was conducted using t-test of proportions.

Descriptive statistics were used to describe the study variables. Mean and standard deviation (SD) were reported for normally distributed continuous variables; median and inter quartile range (IQR) were reported for non-normally distributed continuous data. Frequency and proportions were reported for categorical variables. Binary logistic regression was used to determine the factors associated with sustained-release opioids compared to immediate-release opioids. Odds ratio (OR) and the corresponding 95% confidence intervals were reported. The final multivariate model was chosen based on variables that were clinically and statistically significant. A p-value <0.05 was used for statistical significance. All statistical analysis were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) software.

RESULTS

A total of 66 patients were included in the final analysis. The CONSORT diagram (Figure 1) details the breakdown of patients included in the study. Of the 92 patients approached, 66 were included in the final analysis. The demographics of the patients in each group were summarized in Table 1 and the types of the open midline abdominal urologic surgeries are presented in Table 2.

Eighty patients were recruited, and the final analysis included 32 patients in the sustained-release opioid group and 34 patients in the immediate-release opioid group. Fourteen patients were excluded from analysis after recruitment due to post-operative surgical complications, opioid sensitivity, severe vomiting, patient withdrawal or other clinical reasons unrelated to the study. There was no statistically significant difference in the primary outcome of time to first mobilization. The mean (SD) time to first mobilization in the sustained-release and immediate-release opioid groups were 0.86 (0.41) days and 0.94 (0.43) days, respectively. No significant difference was found in pain scores (Table 3) or opioid consumption (Table 3) at any time point between the two groups either. The average pain scores on a scale of 0-100 reported both at rest and with deep breathing were higher in the sustained-release opioid group, though not statistically significant.

There were trends toward more nausea in the immediate-release group in the PACU and on postoperative days one, two and three, as well as more severe loss of sleep the first night after surgery in the immediate-release group, although the differences did not reach statistical significance as shown in Table 4. Both groups reported similar levels of satisfaction with their

pain control. No other adverse effects were noted. The results of patient satisfaction are shown in Table 5.

DISCUSSION

Our study demonstrated that patients who received low dose, sustained-release hydromorphone in the hospital setting did not mobilize earlier than those who received only immediate-release hydromorphone in the immediate post-operative period following open abdominal urologic surgery. Opioid consumption and pain scores at rest and movement-evoked were comparable between groups at all time points. This refutes the concept of more stable analgesia and less frequent dosing with sustained-release opioids due to sustained plasma levels, as well as a previous study showing benefits of sustained-release opioids in early rehabilitation after arthroplasty surgery.[10, 17-18]

Available evidence surrounding the pharmacokinetics of immediate-release opioids compared to sustained-release opioids suggests that both formulations provide similar total systemic opioid concentrations and pain control when regular dosing is used with a fixed schedule.[11] Due to fewer peak-trough fluctuations, sustained-release opioids are associated with more stable plasma opioid concentration compared to immediate-release opioids. Although the maximal opioid concentration is lower for sustained-release opioids compared to immediate-release opioids, sustained-release opioids allow for the maximal concentration to be maintained for longer periods.[10] Therefore, theoretically, sustained-release opioid might offer advantages by reducing the frequency of patients requesting opioid from busy nursing staff on the ward, which often results in a delay in actually receiving the opioid in a timely fashion. As patients must be meticulous about the adherence to a frequent dosing at a fixed schedule to obtain stable opioid plasma levels and avoid end-of-dose failure.[10, 19-20] Patients receiving sustained-release opioid still reserve the ability to ask for additional immediate-release opioid when required. However, if patients can only request immediate-release opioid when required, they need to understand the rationale of requesting for medication earlier as there is a time lag for the onset of action. Furthermore, in practice, this form of analgesic administration is often dependent upon the availability of the nursing staff on the ward. Additionally, with both formulations, multimodal analgesia is important to obtain adequate pain control. In our study, all patients received intravenous dexamethasone intraoperatively, and regular acetaminophen with local anesthetic infusion via rectus sheath catheters during the postoperative period as part of the multimodal analgesic regimen.

Although there is concern around the use of sustained-release opioids for acute pain, evidence is lacking surrounding their role in the short term at a low dose in a monitored setting.[21] The use of sustained-release opioids for acute pain alone is discouraged, as it is challenging to make short-term adjustments and titrate as needed. Using immediate-release opioids for titration in combination with low-dose sustained-release opioids allows short-term adjustments to be made without compromising pain control, highlighting the importance of multimodal analgesia. Employing a multimodal approach to analgesia post-surgery can help to reduce pain, avoid side

effects, minimize rebound pain, and reduce overall opioid consumption.[22-24] In additional, guidelines suggest that opioid naïve patients should not be discharged on sustained-release opioids post-operatively, and that sustained-release opioid is thought to cause more opioid-related adverse effects compared to immediate-release opioid.[25] In the context of low dose, short-term sustained-release opioid in a hospital monitored setting for painful open abdominal surgeries, our study suggested that there was more nausea with immediate-release opioid alone, compared to in combination with sustained-release opioid immediately post-operatively, although did not reach statistical significance. Further, patients undergoing open abdominal urologic surgery often stay in the hospital for over a week, and sustained-release opioids were discontinued far in advance of being discharged. The dosage used in our study is relatively low and patients are monitored regularly within the hospital setting, which increases the safety profile.

Our study also showed that more severe loss of sleep on the first post-operative night in the immediate-release opioid group, however, did not reach statistical significance. This could be due to increased pain intensity during the night or the need to request analgesia more frequently. Nonetheless, neither the pain score at rest or movement-evoked at specific time points were different between groups.

Limitations

There are several limitations of the study which include the relatively small sample size in our study from attrition (17.5%), due to acute events and protocol violation rather than systematic bias: protocol violation (n=5), opioid sensitivity (n=2), surgical complications (n=2), withdrawal including from surgery (n=3), severe vomiting (n=2). We only performed a per-protocol analysis without intention-to-treat analysis. This contributes to the attrition bias and our remaining sample of patients represent a healthier and compliant sample which may affect the generalizability of our study findings. Nonetheless, our study could be underpower to detect smaller but potentially clinically meaningful differences and our effect estimates should be interpreted with caution.

The primary outcome of the ability to ambulate 3 steps could be subjected to other confounders such as drains and external tubes/lines, nursing availability, or patient factors (baseline functional status, hypotension, dizziness or motivation). We selected this as the primary outcome of our study as it is more patient-centered and aligning with the goal of enhance recovery after surgery. Although the selection of a 31% estimated difference in the primary outcome for our sample size calculation is based on statistics, it could be too high when considering the clinical relevance.

Furthermore, we did not evaluate the number of times patients were required to request immediate-release opioid during the night, or the time and value of the worst pain score, which could disturb sleep. Most patients on the ward received oxygen as the usual care, without actual titration to oxygen saturation which limits our ability to accurately ascertain the proportion of patients actually requiring oxygen due to a reduced oxygen saturation. Similar to clinical practice, we did not examine the time difference between when patients first request opioid, and

actually received it, which might have been delayed, depending on the availability of nursing staff on the ward.

CONCLUSIONS

Our randomized controlled study demonstrated that patients who received short-term, low dose, sustained-release hydromorphone in the hospital setting did not have clinical benefits in terms of ambulation, over those who received only immediate-release hydromorphone, with similar opioid consumption and pain score, in the immediate post-operative period following open abdominal urologic surgery. Although, there appears to be a trend towards more nausea and disturbed sleep in the immediate-release hydromorphone group immediately post-operatively, these did not reach significant difference. Our study serves as a preliminary investigation and study with larger sample size, perhaps including multicenter recruitment, is warranted to further investigate the use of sustained-release opioid on the quality of care following major open abdominal surgeries in a hospital setting.

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***Conflict of interests**:*

Dr. Ip is an editorial board member of the Canadian Journal of Anesthesia, and the Editor of Regional Anesthesia and Pain Medicine. Dr. Fairey has received a speaker honorarium from Stortz, and is currently one of the investigators in the MAST and TACT trials.

FIGURES AND TABLES

Figure 1. CONSORT diagram detailing the breakdown of patients included in and excluded from the study. NG: nasogastric, PO: by mouth; SC: subcutaneous.

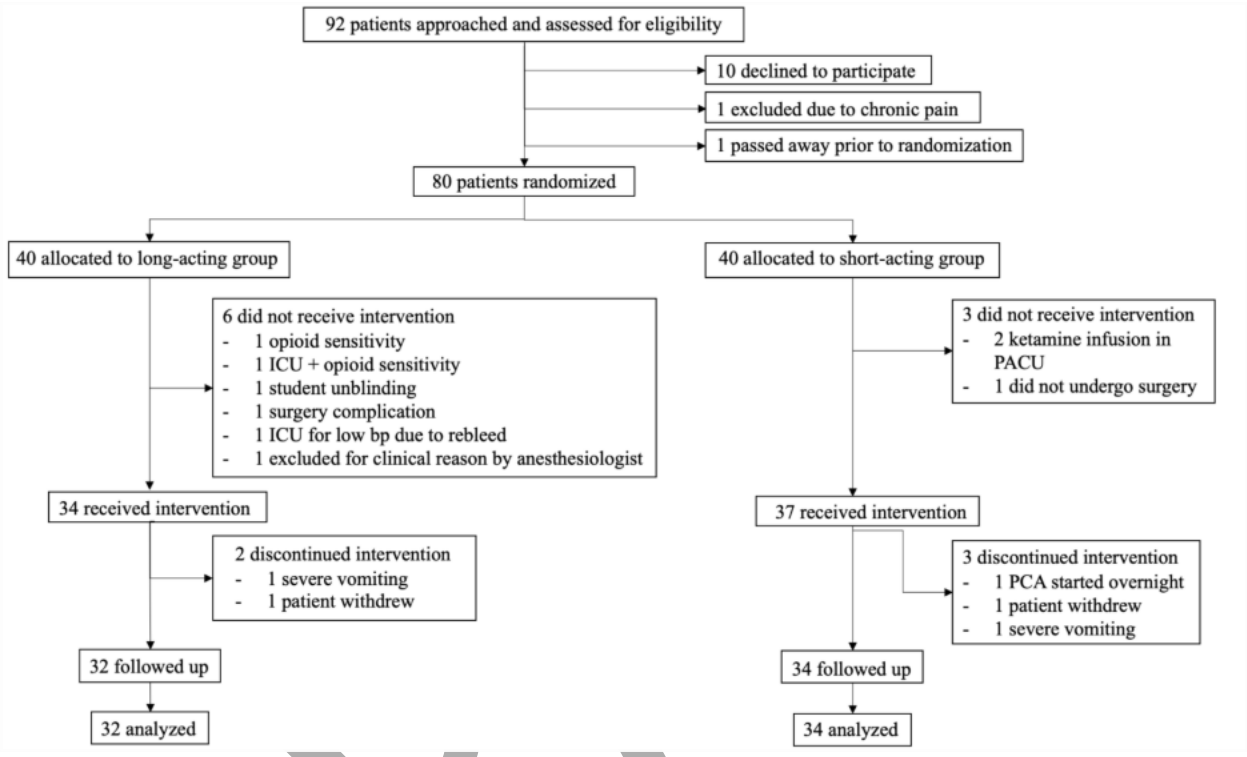

Table 1. Demographics of patients in the sustained-release + immediate-release as-needed opioid group (SR) and the immediate-release only opioid group (IR)			
Demographic		**SR (n=32)**	**IR (n=34)**
Sex	Male	24 (75%)	27 (79%)
	Female	8 (25%)	7 (21%)
Age	18–40	4 (12%)	4 (12%)
	41–60	8 (25%)	7 (21%)
	61–80	15 (47%)	21 (62%)
	>80	5 (16%)	2 (6%)
BMI	20.0–24.9	8 (25%)	12 (35%)
	25.0–29.9	8 (25%)	9 (26%)
	30.0–34.9	11 (34%)	11 (32%)
	35.0–39.9	5 (16%)	2 (6%)

BMI: body mass index

Table 2. Table showing the types of open urologic surgeries		
	Sustained-release opioid	**Immediate-release opioid**
Anterior pelvic exenteration, cystectomy, ileal conduit creation	9/32 (28.1%)	5/34 (14.7%)
Radical cystoprostatectomy	10/32 (31.3%)	12/34 (35.3%)
Open nephrectomy	8/32 (25%)	8/34 (23.5%)
Open nephroureterectomy	1/32 (3.1%)	5/34 (14.7%)
Retroperitoneal lymphadenectomy	4/32 (12.5%)	4/34 (11.8%)

Table 3. Average number of days to mobilization, and other secondary outcomes, including pain scores, and opioid consumption, for the sustained-release + immediate-release as-needed opioid group (SR) and the immediate-release only opioid group (IR)			
Outcomes (average)	**SR**	**IR**	**T-test (p<0.05)**
Days to mobilization	0.9 (0.21)	0.9 (0.43)	0.42
Pain score at rest in PACU (0–100), mean (SD)	44.4 (27.5)	61.5 (30.7)	0.02
Pain score at rest 24 hours post-op (0–100), mean (SD)	57.5 (21.7)	61.9 (24.7)	0.45
Pain score at rest 48 hours post-op (0–100), mean (SD)	36.1 (22.7)	28.8 (21.7)	0.19
Pain score at rest 72 hours post-op (0–100), mean (SD)	28.4 (19.2)	26.8 (19.3)	0.81
Pain score with deep breathing in PACU (0–100), mean (SD)	51.6 (29.3)	71.8 (26.4)	0.01
Pain score with deep breathing 24 hours	69.7 (19.9)	64.1 (25.8)	0.33

post-op (0–100), mean (SD)			
Pain score with deep breathing 48 hours post-op (0–100), mean (SD)	59.4 (19.6)	55.7 (24.2)	0.51
Pain score with deep breathing 72 hours post-op (0–100), mean (SD)	46.9 (21.2)	42.9 (21.0)	0.45
Opioid consumption intraoperatively (OME mg), mean (SD)	22.3 (17.0)	19.7 (5.7)	0.41
Opioid consumption in PACU (OME mg), mean (SD)	20.0 (21.4)	10.9 (8.8)	0.03
Opioid consumption 0–24 hours post-op (OME mg), mean (SD)	96.4 (47.5)	82.6 (53.4)	0.12
Opioid consumption 24–48 hours post-op (OME mg), mean (SD)	74.2 (33.1)	64.9 (49.4)	0.29
Opioid consumption 48–72 hours post-op (OME mg), mean (SD)	38.2 (40.1)	37.7 (36.9)	0.89

OME: oral morphine equivalent; SD: standard deviation.

Table 4. Percentages of patients in the sustained-release + immediate-release as-needed opioid group (SR) and the immediate-release only opioid group (IR) that reported experiencing nausea (yes or no) and very severe loss of sleep (scale of 1–4)

Adverse event	SR	IR	Chi-squared test
Nausea POD1	8/32 (25%)	14/34 (41%)	0.20
Nausea POD2	12/32 (38%)	16/34 (47%)	0.47
Nausea POD 3	9/32 (28%)	16/34 (47%)	0.14
Very severe loss of sleep POD0	4/32 (13%)	14/34 (41%)	0.07
Very severe loss of sleep POD1	2/32 (6%)	1/34 (3%)	0.88
Very severe loss of sleep POD2	1/32 (3%)	4/34 (12%)	0.58

POD: postoperative day

Table 5. Percentages of patients in the sustained-release + immediate-release as-needed opioid group (SR) and the immediate-release only opioid group (IR) that reported satisfaction

Patient satisfaction with pain control	SR	IR
Ranked satisfaction 1/5 (unsatisfied)	2/32 (6%)	0/34 (0%)
Ranked satisfaction 2/5	1/32 (3%)	1/34 (3%)
Ranked satisfaction 3/5	4/32 (13%)	1/34 (3%)
Ranked satisfaction 4/5	14/32 (44%)	21/34 (62%)
Ranked satisfaction 5/5 (extremely satisfied)	11/32 (34%)	11/34 (32%)