Retrospective Analysis

Retrospective Review of Intrathecal Hydromorphone Dose Range and Complications

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Background: Optimal intrathecal dosing regimens for hydromorphone are not well established for analgesia after abdominal surgery.

Objectives: We reviewed intrathecal hydromorphone doses and complications because dosing variability has been observed among anesthesiologists. We hypothesized that increasing doses of intrathecal hydromorphone would be associated with improved postoperative analgesia, but with increased rates of opioid-related adverse events.

Study Design: Retrospective analysis.

Setting: A high-volume academic referral center in the United States.

Methods: A retrospective study was conducted of adults undergoing abdominal surgery under general anesthesia supplemented preoperatively with intrathecal hydromorphone for postoperative analgesia from May 5, 2018, through May 31, 2021. Patients were categorized into 3 hydromorphone dosing groups: low-dose (50-100 µg), middle-dose (101-199 µg), and high-dose (200-300 µg). Multivariable logistic regression models were used to assess rates of severe postoperative pain, severe opioid-related adverse events, oversedation, and pruritus in the postanesthesia care unit (PACU) and within 24 hours after PACU discharge.

Results: Of 1,846 patients identified, 1,235 (66.9%) were in the low-dose group; 321 (17.3%), middle-dose group; and 290 (15.7%), high-dose group. Patients receiving the 2 higher doses had more extensive procedures. An unadjusted analysis showed differing rates of severe pain in the PACU by group: 306 (24.8%) in the low-dose, 73 (22.7%) middle-dose, and 45 (15.5%) in the high-dose group ($P = 0.003$); these differences, however, were no longer significant after an adjusted analysis ($P = 0.34$). Ten severe opioid-related events occurred; all were recognized in the PACU. Five events each occurred in the low-dose and high-dose groups versus none in the middle-dose group ($P = 0.02$). No other differences were identified with adjusted analyses.

Limitations: Limitations of our study include its retrospective design and its conduct at a single center, along with the apparent, but difficult to characterize, treatment biases in hydromorphone dosing.

Conclusions: No dose response was observed between intrathecal hydromorphone dose and postoperative analgesia, a finding that may reflect treatment bias. Higher rates of severe opioid-related events were detected for patients receiving high-dose hydromorphone in the PACU, but all other safety outcomes were similar between dosing regimens.

Key words: Drug-related side effects, opioid analgesics, outcome assessment, postoperative pain, spinal injections

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Intrathecal administration of hydrophilic opioids is an attractive option to improve postoperative analgesia because a lower total dose of medication is needed to achieve effective analgesia than with systemic opioids (1,2). However, a feared complication of intrathecal opioid delivery is late-onset opioid-induced respiratory depression (3). Respiratory depression induced by opioids can result in permanent complications, such as anoxic brain injury or even death (4).

Morphine is the traditional hydrophilic opioid for intrathecal injections, but our practice has adopted intrathecal hydromorphone because of intermittent drug shortages and a perceived lower incidence of pruritus, a common adverse effect of neuraxial opioids (5). However, dose titration studies of intrathecal hydromorphone for surgical patients are sparse (6). They are mostly limited to the obstetric anesthesia literature regarding pain control after cesarean delivery (7-9). Because of this paucity of data, our institution has established a heterogeneous dosing practice of intrathecal hydromorphone to manage nonobstetric postoperative pain. This dosing practice provides a rare opportunity to examine whether associations exist between the intrathecal hydromorphone dose and a patient's postoperative pain level and opioid-related adverse events.

Administration of naloxone has been used as a surrogate marker for severe opioid-induced respiratory depression (10,11). Naloxone, however, is infrequently used on postoperative general care units (12), thus limiting the ability to establish the safety of hydromorphone in most retrospective cohort studies. Emerging evidence suggests that health care professionals are more adept at identifying sedation than respiratory depression before opioid-related respiratory arrests (4,13), a finding suggesting that postoperative sedation levels could also be used as a sensitive surrogate marker for opioid toxicity.

Objectives

We reviewed the practice of intrathecal hydromorphone where dosing variability was observed among anesthesiologists. We hypothesized that increasing doses of intrathecal hydromorphone would be associated with improved postoperative analgesia, but with increased rates of opioid-related adverse events. In this study, we evaluated whether differing dosing levels of intrathecal hydromorphone were associated with differences in rates of postoperative pain and opioid-related adverse events. We used opioid rescue (e.g., naloxone administration or mechanical respiratory support), level of postoperative oversedation, and pruritus severity as measures of opioid-related adverse events.

Study Design

This study is a retrospective review of all intrathecal hydromorphone administrations from May 5, 2018, through May 31, 2021. It was approved by the Mayo Clinic Institutional Review Board (protocol No. 20-013412, approval date January 15, 2021). Consistent with Minnesota Statute 144.295 (14), the included patients provided prior written authorization for research use of their electronic health records (EHRs). This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15).

Setting

This study took place in a high-volume surgical practice at a quaternary academic medical center, Mayo Clinic Hospital, in Rochester, Minnesota.

Study Patients

Patients were eligible for this study if they were aged 18 years or older and underwent abdominal surgery under general anesthesia supplemented with intrathecal hydromorphone at our institution from May 5, 2018, through May 31, 2021. Consecutive patients were included from the start of the current EHR system through the data retrieval. For patients who underwent multiple procedures, only the index procedure was included in the analysis. For eligible patients, we reviewed their EHRs, including surgical and anesthetic records.

Methods

Exposure

An attending anesthesiologist directed anesthetic care provided by an anesthesia resident, student nurse anesthetist, or Certified Registered Nurse Anesthetist. Intrathecal hydromorphone was administered preoperatively via prefilled one-mL vials of preservative-free solution containing 100 μg of hydromorphone. Intrathecal dosing of hydromorphone ranged from 75 μg to 300 μg, with the dose chosen by the attending anesthesiologist. The typical procedural sedation for intrathecal opioid injection is the intravenous administration of 2 mg midazolam and 100 μg fentanyl. Additional

analgesic medications were administered at the discretion of the anesthesia team.

For each patient, order sets were written that directed monitoring for postoperative pain, sedation, and respiratory depression after intrathecal hydromorphone administration during the 24 hours after discharge from the postanesthesia care unit (PACU). These order sets also included the option to prescribe diphenhydramine and/or nalbuphine to treat opioid-associated pruritus. Postoperative pain scores and sedation scores were measured and recorded in the EHR by the nursing teams in the PACU and hospital units.

Outcome Measures

Outcomes during recovery in the PACU and within the first 24 hours after PACU discharge were analyzed. The main outcomes were severity of postoperative pain and occurrence of opioid-related adverse events.

The pain outcome was assessed by the occurrence of severe pain, defined as a score of 7 or more on an 11-point numeric pain score where 0 indicated no pain and 10 indicated the worst pain imaginable.

Opioid-related adverse events were assessed by using 3 metrics. The first metric was severe opioid toxicity, defined as a life-threatening event requiring immediate intervention, such as application of noninvasive positive pressure ventilation, reintubation, naloxone administration, or intensive care unit (ICU) admission due to opioid toxicity. The second metric was postoperative oversedation, defined as light sedation or greater as determined by a Richmond Agitation-Sedation Scale (RASS) (16) score of -2 or lower. The third metric was pruritus requiring administration of diphenhydramine, nalbuphine, or both. All patients with any criteria for life-threatening events underwent a manual EHR review to determine whether the clinical circumstances would support an opioid overdose as the cause.

Data Abstraction

The EHRs, including surgical and anesthetic records, of study patients were abstracted for demographic information and procedural characteristics. Preoperative records were reviewed for the following variables: age; gender; body mass index; overall health determined by using the Charlson Comorbidity Index (17); preoperative obstructive sleep apnea determined by using a standard assessment screening tool, the STOP (snoring, tiredness during daytime, observed apnea, and high blood pressure) questionnaire (18); and long-term use of opioid analgesics.

Perioperative records were reviewed for the following variables: dose of intrathecal hydromorphone, surgical duration, incision classification (midline surgical wounds were categorized as upper abdominal incisions, lower abdominal incisions, both upper and lower abdominal incisions, or other, e.g., laparoscopic or robotic-assisted techniques and limited incisions for stoma closure), placement of a transversus abdominis plane block, and perioperative administration of an analgesic agent.

Analgesics used were acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, ketamine, dexmedetomidine, and/or opioids calculated as intravenous morphine milligram equivalents (MMEs). Records from the PACU and for the first 24 hours after PACU discharge were reviewed for maximum pain score, minimum RASS score, opioid rescue interventions, and pharmacologic treatment of pruritus.

Statistical Analysis

Patient and procedural characteristics were summarized by using median (interquartile range [IQR]) for continuous variables and frequency counts and percentages for categorical variables.

Intrathecal hydromorphone doses were grouped into 3 categories: low (50-100 μg), middle (101-199 μg), and high (200-300 μg) doses. Comparisons of these characteristics across dose groups were performed with the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Outcomes of interest (severe pain, severe opioid-related adverse events) were summarized separately for the duration of the PACU stay and for the first 24 hours after PACU discharge. Unadjusted comparisons of outcomes across dose group were performed with the χ^2 test or the Fisher's exact test when the number of events was too low.

For oversedation, severe pain, and pruritus treatment, additional covariate-adjusted analyses were performed with multivariable logistic regression. For the covariate-adjusted analyses, the continuous covariates (age, body mass index, Charlson Comorbidity Index score, intraoperative intravenous MMEs, and surgical duration) were modeled by using restricted cubic splines with knots placed at the 5th, 50th, and 95th percentiles.

Findings from the covariate-adjusted analysis are presented as the odds ratio (OR) and 95% CI for the comparisons of the middle-dose group versus the low-dose group, and the high-dose group versus the low-dose group. The incidence rate of complications and CIs

were computed by using the adjusted Wald method. In all cases, 2-tailed *P* values were reported, with $P < 0.05$ considered to be significant. Analyses were performed with SAS version 9.4 (SAS Institute Inc).

Results

During the study time frame, we identified 1,846 unique patients who received intrathecal hydromorphone before abdominal surgery (Fig. 1). All doses ranged from 50 μg to 300 μg. Patients were categorized into 3 dosing groups: low, 1,235 patients (66.9%); middle, 321 patients (17.3%); and high, 290 patients (15.7%). The median dose (range) in the low-dose group was 100 μg (75-100 μg); middle-dose group, 150 μg (120-160 μg); and high-dose group, 200 μg (200-300 μg). Sixty-six patients (22.8%) received a 300-μg dose.

Patient and procedural characteristics are summarized in Table 1. Notable differences were that patients receiving high doses of hydromorphone were more often men and had significantly longer surgical durations, greater ketamine use, and greater dexmedetomidine use as well as a lower prevalence of obstructive sleep apnea, and less administration of nonsteroidal anti-inflammatory drugs and intraoperative opioids. Patients in the high-dose group were also more likely to receive transversus abdominus plane (TAP) blocks.

Table 2 summarizes outcomes in the PACU and the first 24 hours after PACU discharge. Although significant differences in severe pain between dose groups were detected with an unadjusted analysis, these differences were no longer significant with covariate-adjusted logistic regression. No differences in oversedation or pruritus were detected between groups.

During PACU stay, 10 episodes of severe opioid toxicity required intervention (incidence rate, 5.4 [95% CI, 2.6-10.0] per 1,000 patients). This rate differed significantly among dosing groups on unadjusted analysis: 5 episodes (incidence rate, 4.0 [1.3-9.4] per 1,000 patients) occurred in the low-dose group; 0, in the middle-dose group; and 5 (17.2 [5.6-40.2] per 1,000 patients) in the high-dose group ($P = 0.02$, Table 2). The limited number of events precluded a multivariate analysis. Clinical details of these 10 cases are summarized in Table 3.

No episodes of respiratory depression occurred in any group in the first 24 hours after PACU discharge. Three patients died while inpatients; all were due to multiorgan failure. Two additional patients died within 30 days postoperatively: one due to myocardial infarction and another due to acute gastrointestinal tract bleeding.

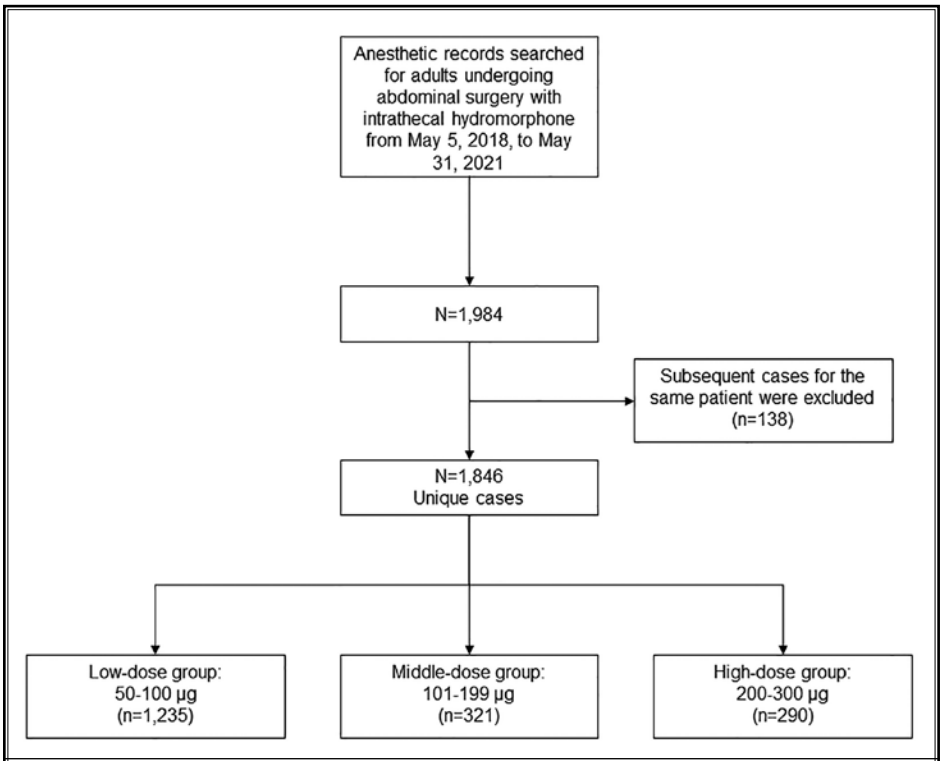

Fig. 1. *Consolidated Standards of Reporting Trials (CONSORT) diagram of records included in the study.*

Discussion

The main finding of this study is that increasing doses of intrathecal hydromorphone given for postoperative analgesia were not associated with increasing rates of postoperative sedation or pruritus. However, the rate of severe respiratory depression in the PACU was highest in the high-dose group. No episodes of respiratory depression occurred in the first 24 hours after PACU discharge. An unadjusted analysis detected differing rates of severe pain among

dosing regimens, but these differences were no longer significant after covariate-adjusted logistic regression.

Postoperative Pain

Severe pain in the PACU and during the first postoperative 24 hours was not significantly different among the groups. This lack of dose response was unexpected. However, the substantial heterogeneity of patients in our cohort complicated dose-response comparisons, even after adjustment for confounders. We hypothesize that the dose of hydromorphone selected was, in part, dependent on the nature of the surgical procedure (higher doses were selected for more extensive procedures) and on the clinician's intuition (higher doses for patients expected to have more pain), both of which mitigated a dose-response effect.

Dosing studies of intrathecal hydromorphone have been mostly limited to the obstetric anesthesia literature (7,8). Lee, et al (19) did conduct a dose titration study for arthroscopic knee surgery by using an intrathecal injection of 6 mg of hyperbaric bupivacaine and increasing doses of hydromorphone (0, 2.5, 5, and 10 μg); they reported improved analgesia with higher doses. However, that study is not comparable to our current study because the doses used were substantially less, were coadministered with a local anesthetic, and were used in a different surgical model.

Severe Opioid Toxicity

In this cohort, all events meeting the criteria for severe opioid toxicity occurred during the PACU stay, with an incidence rate of 5.4 per 1,000 patients. Five

Table 1. *Patient and perioperative characteristics.*

Characteristic	Intrathecal Hydromorphone Dose Group			*P* Value[a]
	Low (n = 1,235)	Mid (n = 321)	High (n = 290)	
Age, y, median (IQR)	60.0 (48.0-69.0)	56.0 (44.0-65.0)	57.0 (46.0-65.0)	< 0.001
Gender, no. (%)				< 0.001
Women	641 (51.9)	110 (34.3)	109 (37.6)	
Men	594 (48.1)	211 (65.7)	181 (62.4)	
BMI, median (IQR)	26.7 (22.8-30.9)	26.8 (24.1-30.7)	28.0 (23.9-31.1)	0.02
CCI score, median (IQR)	4.0 (2.0-6.0)	3.0 (2.0-5.0)	4.0 (2.0-6.0)	0.01
OSA, no. (%)	443 (35.9)	104 (32.4)	68 (23.4)	< 0.001
Home use of opioids, No. (%)	213 (17.2)	40 (12.5)	40 (13.8)	0.06
Location of abdominal incision, no. (%)				< 0.001
Lower	283 (22.9)	41 (12.8)	20 (7.0)	
Upper	187 (15.1)	79 (24.6)	34 (11.7)	
Upper and lower	552 (44.7)	167 (52.0)	214 (73.8)	
Other	213 (17.2)	34 (10.6)	22 (7.6)	
TAP block, no. (%)	345 (27.9)	116 (36.1)	132 (45.5)	< 0.001
Perioperative analgesic, No. (%)				
Acetaminophen	914 (74.0)	241 (75.0)	251 (86.6)	< 0.001
NSAIDs	537 (43.5)	172 (53.6)	78 (26.9)	< 0.001
Gabapentinoid	413 (33.4)	118 (36.8)	27 (9.3)	< 0.001
Ketamine	385 (31.2)	123 (38.3)	163 (56.2)	< 0.001
Dexmedetomidine	16 (1.3)	9 (2.8)	58 (20.0)	< 0.001
Intraoperative opioids, IVMME, mg, median (IQR)	10.0 (5.0-15.0)	10.4 (5.0-20.0)	9.5 (0-15.0)	< 0.001
Surgical duration, h, median (IQR)	4.4 (3.4-5.7)	5.1 (4.0-6.8)	7.5 (5.2-10.1)	< 0.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCI, Charlson Comorbidity Index; IVMME, intravenous morphine milligram equivalents; NSAIDs, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnea; TAP, transversus abdominis plane.

[a] Comparisons of characteristics across dose groups were performed by using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.

Table 2. *Postoperative outcomes after abdominal surgery with differing doses of intrathecal hydromorphonea.*

	Unadjusted Analysis				Adjusted Analysisa		
	Low Dose (n = 1,235), No. (%)	Middle Dose (n = 321), No. (%)	High Dose (n = 290), No. (%)	P value[b]	Middle vs Low Dose, OR (95% CI)	High vs Low Dose, OR (95% CI)	*P* Value[b]
Severe pain							
PACU	306 (24.8)	73 (22.7)	45 (15.5)	0.003	0.85 (0.62-1.17)	0.76 (0.51-1.15)	0.34
First 24 hours	562 (45.5)	149 (46.4)	156 (53.8)	0.04	0.84 (0.64-1.11)	0.97 (0.69-1.35)	0.46
Severe opioid toxicity[c]							
PACU	5 (0.4)	0 (0)	5 (1.7)	o.02[d]	NA	NA	NA
First 24 hours	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
Oversedatione							
PACU	269 (21.8)	69 (21.5)	67 (23.1)	0.87	0.95 (0.69-1.30)	1.06 (0.72-1.57)	0.87
First 24 hours	277 (22.4)	75 (23.4)	74 (25.5)	0.53	0.99 (0.73-1.36)	1.02 (0.70-1.50)	0.99
Pruritus[f]							
PACU	67 (5.4)	22 (6.9)	10 (3.5)	0.17	1.43 (0.83-2.44)	0.74 (0.34-1.62)	0.24
First 24 hours	272 (22.0)	73 (22.7)	61 (21.0)	0.88	1.11 (0.81-1.52)	0.90 (0.61-1.34)	0.64

Abbreviations: NA, not applicable; OR, odds ratio; PACU, postanesthesia care unit.
[a] Multivariable logistic regression analyses were performed for each outcome, with covariates included for all characteristics listed in Table 1.
[b] Unless otherwise indicated, χ^2 test.
[c] Severe opioid toxicity was defined as a life-threatening episode that required immediate intervention with noninvasive ventilation, reintubation, naloxone administration, or intensive care unit admission due to opioid toxicity.
[d] Fisher's exact test; the number of events was too low to allow covariate-adjusted logistic regression.
[e] Oversedation was defined as a Richmond Agitation-Sedation Scale score of ≤ -2.
[f] Pruritus requiring treatment with diphenhydramine, nalbuphine, or both.

Table 3. *Clinical details of rescue events during anesthesia recovery for life-threatening opioid toxicity.*

Patient No.	IT Hydromorphone Dose, µg	Abdominal Incision/ Surgical Duration, min	Volatile Agent	Anesthetic Adjunct	Perioperative Opioid Dose, IVMME, mg	Rescue Interventions
Low dose of IT hydromorphone						
1	75	Lower/399	Sevoflurane	None	31.9	NIPPV
2	100	Upper/300	Sevoflurane	Gabapentin	40.0	Naloxone
3	100	Upper/202	Isoflurane	Gabapentin	20.0	Naloxone, ICU admission
4	100	Upper and lower/238	Sevoflurane	Gabapentin	40.0	NIPPV, ICU admission
5	100	Upper/353	Isoflurane	None	15.0	NIPPV
High dose of IT hydromorphone						
6	200	Upper and lower/778	Desflurane	Dexmedetomidine, ketamine	25.0	Naloxone
7	200	Lower/223	Isoflurane	Ketamine	30.0	Naloxone
8	200	Upper and lower/820	Sevoflurane	Dexmedetomidine, ketamine	15.0	Reintubation (due to respiratory depression), ICU admission
9	200	Upper/741	Desflurane	Dexmedetomidine, ketamine	25.0	Naloxone, ICU admission
10	300	Upper/570	Isoflurane	Ketamine	10.0	ICU admission due to somnolence

Abbreviations: ICU, intensive care unit; IT, intrathecal; IVMME, intravenous morphine milligram equivalents; NIPPV, noninvasive positive pressure ventilation.

of these 10 cases (0.3% of the entire cohort) included the administration of naloxone. This incidence rate of 2.7 naloxone administrations per 1,000 patients is similar to the rate of 2.5 naloxone administrations per 1,000 patients shown in a previous study of naloxone administration in the PACU for adults after general anesthesia (20). In these 10 cases, whether the opioid toxicity resulted from the intrathecal hydromorphone administration or the effects of residual anesthesia was unclear. No episodes of severe opioid toxicity occurred after PACU discharge.

All patients at our institution who are administered neuraxial hydrophilic opioids are continuously monitored with pulse oximetry, monitoring that has been shown to reduce postoperative rescue events and ICU transfers after PACU discharge (21). We also suspect that the anesthesiologists adjusted the hydromorphone dose if a patient had any relevant comorbid conditions that could increase sensitivity to the adverse effects of opioids, as evidenced by significant baseline differences of patient characteristics (e.g., Charlson Comorbidity Index score) among the 3 dosing regimens.

Opioid-related respiratory depression is a potential complication of all opioid analgesics, and the definition of respiratory depression influences the prevalence (4). Using hydrophilic intrathecal opioids has been associated with respiratory depression that is not initially apparent and may be delayed by several hours (1). Gwirtz, et al (22) reported a series of almost 6,000 patients who underwent abdominal surgery who received intrathecal morphine (0.2-0.8 mg) administered for postoperative pain control. They reported a 3% rate of respiratory depression as defined by the need for naloxone administration. Why patients in the cohort described by Gwirtz, et al (22) had a rate of naloxone administration higher than in our cohort (0.5%) is unclear.

Bai, et al (23) compared outcomes of neuraxial anesthesia with or without 100 μg of intrathecal morphine for arthroplasty in a large cohort of adults with obstructive sleep apnea and observed no differences in postoperative pulmonary outcomes. This finding most likely reflects an increased safety margin with "lower" dosing regimens. To our knowledge, no case series with more than 124 patients receiving intrathecal hydromorphone have been reported outside an orthopedic or obstetric setting.

Postoperative Oversedation

Postoperative oversedation is being recognized as a potential precursor for severe respiratory depression (4,13). In the current study, we examined whether postoperative oversedation was associated with the hydromorphone dose. Our definition of oversedation was a RASS score of -2 or lower, a score that should prompt medical intervention for hospitalized patients on general care units.

Our rate of oversedation ranged from 22.4% to 25.5% after PACU discharge. Although this high rate is concerning, these rates were not significantly associated with the hydromorphone dose. Our data cannot determine whether the administration of hydromorphone (regardless of dose) contributed to this high frequency of oversedation or whether other factors (deteriorating health, nonopioid sedating medications) contributed. Regardless, these findings support recommendations to monitor patients administered neuraxial opioids by continuous assessment of respiratory effort and oxygenation after discharge from the PACU (24).

Pruritus

Pruritus is an infrequent complication of oral or intravenous opioid therapy, but is common with neuraxial administration of opioids (25,26).Pruritus risk can be mitigated by decreasing the intrathecal opioid dose. Pruritus is treated with a 5-HT3 receptor antagonist, an opioid partial agonist (e.g., nalbuphine), an antagonist (e.g., naloxone), or an antihistamine (26-28).

Our practice for treating neuraxial opioid-induced pruritus is to administer nalbuphine, diphenhydramine, or both. Because pruritis documentation in the EHR was inconsistent, we used administration of either of these medications as a surrogate marker for this complication. This approach undoubtedly did not account for mild, untreated pruritis cases, or cases for which symptoms were treated nonpharmacologically. Therefore, our incidence is probably an underestimate. Our pruritis rates after PACU discharge ranged from 21.0% to 22.7%. These rates were higher than the 11% pruritis rate requiring treatment reported by Sharpe et al (8); however, their study patients were parturients undergoing cesarean delivery, and the dose of intrathecal hydromorphone was only 75 μg.

Our patient cohort differs substantially from the obstetric population. A more similar cohort to ours, reported by Ding, et al (29), consisted of patients undergoing hepatectomy with administration of 100 μg of intrathecal hydromorphone; their reported postoperative pruritus rate was 19%, a rate more in line with ours. Lee, et al (19) reported a 13% pruritus rate after intrathecal hydromorphone injection for arthroscopic

knee surgery; however, the doses used in that study were substantially less than in our cohort (2.5 μg -10 μg). Of interest is that we did not find a difference in the pruritis rate among our treatment groups. This finding suggests that at these dosing ranges, no dose-related response occurs for this complication.

Limitations

This study has several important limitations, including its retrospective design. The lack of a protocol-based approach for decisions regarding intrathecal hydromorphone dosing may have led to the introduction of bias. The differences among the dosing groups were most likely related to treatment biases, which may differ among clinicians. Furthermore, the surgical cases were heterogeneous, which may have introduced bias unaccounted for in our multivariable model. Additionally, because our definitions of severe opioid toxicity and pruritus depended on treatment, untreated cases were not accounted for. However, the clinical administration of potentially life-saving therapies (e.g., naloxone, noninvasive ventilation), escalation of care (transfer to ICU), or both in cases of suspected severe opioid toxicity is a reasonable surrogate for this complication. Finally, these results are from a single-center academic institution and may not be generalizable.

Conclusion

In this retrospective study of 1,846 patients receiving anesthesia with preoperative intrathecal hydromorphone for postoperative analgesia, we did not observe an association between dose and postoperative analgesia or opioid toxicity. These results may reflect unaccounted-for biases in selecting the hydromorphone dose or a relatively flat response curve at the specific doses studied. The results of this study should be interpreted carefully and should be used as a hypothesis for generating prospective trials.

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