Hydromorphone versus *morphine: a historical cohort study to evaluate the quality of postoperative analgesia*

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REPORTS OF ORIGINAL INVESTIGATIONS

Hydromorphone *versus* morphine: a historical cohort study to evaluate the quality of postoperative analgesia

Comparaison de l'hydromorphone à la morphine : une étude de cohorte historique pour évaluer la qualité de l'analgésie postopératoire

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Abstract

Purpose *Opioids are the most widely used therapy for pain during the postoperative period. It has been suggested by some that hydromorphone is clinically superior. Our primary objective was to determine if there is a difference in postoperative pain score ratings between adult patients receiving intravenous hydromorphone vs intravenous morphine on discharge from the post-anesthesia care unit (PACU).*

Methods *For this historical cohort study, convenience sampling was used to identify the first 605 patients ≥ 18 yr undergoing elective, non-cardiac surgery. Patients were categorized based on treatment in the PACU with hydromorphone (n = 326) or morphine (n = 279). Pain scores (scale of 0–10), nausea/vomiting (scale of 0–3), pruritis (scale of 0–3), and sedation (scale of 0–4), as well as total opioid dose administered from arrival in the PACU until readiness to discharge were evaluated.*

Results *For the primary outcome of pain reported at discharge from the PACU, there was no significant difference between the mean (standard deviation) hydromorphone numeric rating scale (NRS) [2.8 (1.6)] and the morphine NRS [2.5 (1.5)] after adjusting for potential confounders (adjusted mean difference, 0.10; 95% confidence interval, –0.21 to 0.42; P = 0.53). Similarly, there were no significant between-group differences in length of stay in the PACU, satisfactory analgesia, nausea/vomiting, and sedation.*

Conclusion *This study serves to help guide the decision-making process for selecting either morphine or hydromorphone for acute postoperative analgesia. Overall, we found no significant difference for analgesia or for common opioid-related adverse effects between these two opioids in the postoperative period at the time of discharge from the PACU. Furthermore, according to this data, the equipotency ratio of hydromorphone to morphine is closer to 1:6.5 rather than the commonly employed 1:5 ratio.*

Résumé

Objectif *Les opioïdes sont le traitement le plus fréquemment utilisé pour prendre en charge la douleur postopératoire. Certains auteurs suggèrent que l'hydromorphone est supérieure d'un point de vue clinique. Notre objectif principal était de déterminer s'il existait une différence dans les scores de douleur postopératoire entre des patients adultes ayant reçu de l'hydromorphone intraveineuse comparativement à de la morphine intraveineuse lors de leur congé de la salle de réveil.*

Méthode *Pour cette étude de cohorte historique, un échantillonnage de commodité a été utilisé pour identifier les premiers 605 patients ≥ 18 ans subissant une chirurgie*

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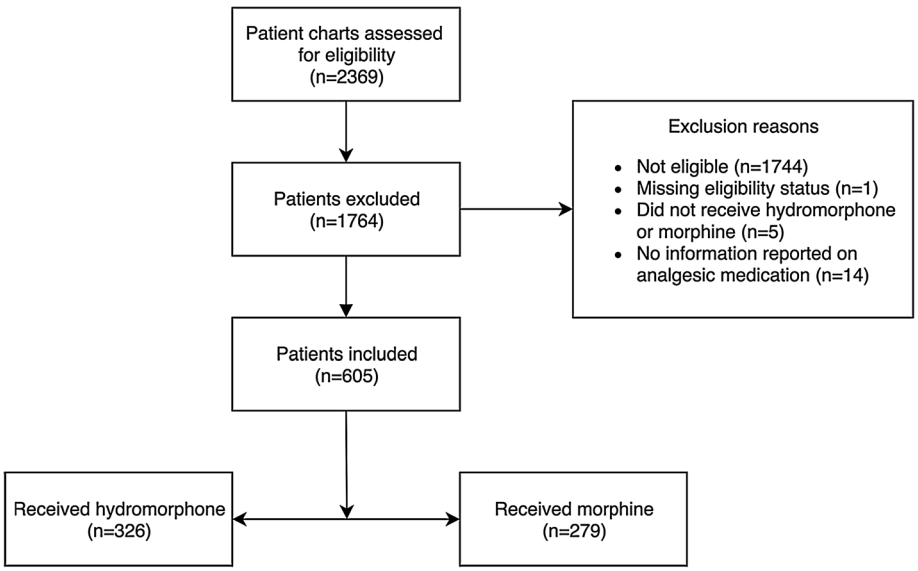

Figure Flowchart showing the participant inclusion and exclusion process. Patients were excluded for multiple reasons, including not receiving only one type of opioid (either hydromorphone or morphine) in the postanesthetic care unit (PACU) (n = 1,267), being on regular chronic opioid medication (n = 365), receiving patient-controlled analgesia (PCA) in the PACU or day surgery unit (DSU) (n = 171), not being extubated in operating room (OR) (n = 144), receiving extended-release opioid in the PACU (n = 136), having a hydromorphone or morphine allergy (n = 97), receiving a planned regional technique or nerve block other than local anesthesia infiltration (n = 90), emergency surgery (n = 32) or non-elective surgery (n = 25), and being < 18 yr of age (n = 6)

non cardiaque non urgente. Les patients ont été catégorisés en fonction du traitement reçu à la salle de réveil, soit hydromorphone (n = 326) ou morphine (n = 279). Les scores de douleur (échelle de 0-10), les nausées et vomissements (échelle de 0-3), le prurit (échelle de 0-3) et la sédation (échelle de 0-4), ainsi que la dose totale d'opioïdes administrés entre l'arrivée en salle de réveil et le moment de recevoir le congé ont été évalués.

Résultats *En ce qui touche à notre critère d'évaluation principal de douleur rapportée au moment du congé de la salle de réveil, aucune différence significative n'a été observée entre le score moyen (écart type) de l'hydromorphone sur l'échelle d'évaluation numérique (EEN) [2,8 (1,6)] et celui de la morphine [2,5 (1,5)] après avoir ajusté les valeurs pour tenir compte des facteurs de confusion potentiels (différence moyenne ajustée, 0,10; intervalle de confiance 95 %, -0,21 à 0,42; P = 0,53). De la même manière, aucune différence intergroupe significative n'a été observée en matière de durée de séjour à la salle de réveil, d'analgésie satisfaisante, de nausées et vomissements, et de sédation.*

Conclusion *Cette étude sert à guider le processus de prise de décision lors du choix de la morphine ou de l'hydromorphone pour l'analgésie postopératoire aiguë. Globalement, nous n'avons observé aucune différence significative dans l'analgésie procurée ou les effets secondaires néfastes liés aux opioïdes entre ces deux molécules en période postopératoire au moment du congé de la salle de réveil. En outre, selon ces données, le ratio d'efficacité équivalente de l'hydromorphone par rapport à la morphine est plus proche de 1:6,5 que du ratio fréquemment utilisé de 1:5.*

Keywords hydromorphone · morphine · postoperative analgesia · PACU · cohort study

There are several approaches to addressing pain in the postoperative period. These include the use of regional anesthesia, patient-controlled analgesia (PCA), and nurse-administered analgesic medications such as acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids. Hydromorphone and morphine are two of the most common opioids currently used. Hydromorphone, introduced in the 1920s, is a semi-synthetic morphine derivative. Structural differences cause hydromorphone to be approximately five to ten times more potent than morphine, allowing for enhanced cerebral distribution and easier titration.[1] Undesired effects of both hydromorphone and morphine include respiratory depression, nausea, emesis, and pruritus. Pruritus has been specifically linked to morphine because of histamine release.[2] Due to alterations in chemical structure, unlike morphine, hydromorphone does not form an active 6-glucoronide metabolite that is renally cleared, which may make hydromorphone better tolerated than morphine in renal failure patients.[1,3]

The relatively increased potency and favourable side effect profile of hydromorphone may guide the decision-making process towards choosing hydromorphone for postoperative analgesia. Nevertheless, a randomized-controlled trial (RCT) with a sample size of 402 compared morphine with hydromorphone for achieving satisfactory analgesia with minimal emesis within two hours after surgery and found no differences in analgesia and common side effects.[4]

This study, with a larger sample size of 605, was conducted as a retrospective cohort study. Since the primary outcome of the previously completed RCT was satisfactory analgesia with minimal emesis based on a pain score below or above a threshold on the numeric rating scale (NRS), the magnitude of analgesia was not analyzed in that study. Furthermore, the patients in this previous RCT must have had minimal postoperative nausea and vomiting (PONV) symptoms to be defined as having a positive outcome.

In this study, our primary objective was to instead identify differences in pain score ratings (using the NRS 0–10) between adult patients receiving intravenous (IV) hydromorphone *vs* IV morphine as postoperative analgesia at the time of discharge from the PACU. Additional objectives of this study were to determine the current practice pattern and prevalence of morphine and hydromorphone in the post-anesthesia care units (PACUs) in three tertiary care hospitals in Hamilton, and to test how the results of a large observation study compared with an RCT that was conducted in the same centre.

We hypothesized that pain scores would not be significantly different between patients who received hydromorphone *vs* morphine. Our four secondary objectives were to evaluate the following outcomes between patients receiving hydromorphone *vs* morphine: 1) satisfactory analgesia with minimal PONV; 2) total opioid dose; 3) occurrence of side effects (PONV, sedation, pruritis); and 4) length of stay in the PACU.

Methods

This retrospective observational cohort study was reported as per the guidelines in the STROBE statement for observational studies.[5] It was completed through a multi-site chart review of adult patients undergoing elective non-cardiac surgery at Hamilton Health Sciences (HHS). This study was conducted after local Research Ethics Board approval (Hamilton Integrated Research Ethics Board #1275-C).

Facilities

Hamilton Health Sciences comprises three tertiary care teaching hospitals affiliated with McMaster University. The three affiliated hospitals are the Hamilton General Hospital (HGH), McMaster University Medical Centre (MUMC), and Juravinski Hospital (JH). Postoperatively, patients are transferred from the operating room to the PACU. From there, PACU patients are either admitted to the appropriate surgical ward or transferred to the ambulatory surgical unit prior to discharge home the same day.

Patients

The inclusion criteria were as follows: age $\geq$ 18 yr; elective surgery performed between January and December 2014 (either same-day home, same-day overnight, or same-day admit); non-cardiac surgery; extubation at end of case; and only one opioid administered (i.e., hydromorphone or morphine only) in the PACU.

Exclusion criteria were as follows: allergy to morphine or hydromorphone; regular chronic opioid medication; planned regional technique or nerve block used (other than local anesthesia infiltration); PCA opioids administered in the PACU; extended-release opioid administered in the PACU; or emergency surgery. Lastly, patients who had missing data related to their opioid use and pain scores were excluded.

Convenience sampling was used to identify the first 605 patients who met inclusion criteria. Patients were identified through the HHS operating room database. This database records type of surgery, admission status, and demographic characteristics. The PACU flow sheet, included in the database, provided a record of medications given in the PACU along with assessment of discharge criteria. To ensure the accuracy of extracted data, two different reviewers manually reviewed each chart. Any discrepancy in data extraction was discussed and rectified by consensus.

Outcomes

The primary objective of our study was to determine if there is a difference in pain score ratings (using the NRS 0–10, where 0 is no pain and 10 is the worst pain imaginable)[6] between adult patients receiving IV hydromorphone *vs* IV morphine as postoperative analgesia at the time of discharge from the PACU. The primary study outcome was pain (at rest) at the time of discharge from the PACU.

Secondary outcomes included: 1) satisfactory analgesia (NRS $<$ 4) without substantial PONV (verbal descriptive

Table 1 Demographics

Demographics	Hydromorphone ($n = 326$)	Morphine ($n = 279$)	P
Age (yr); mean (SD)	55 (16.6)	46 (16.2)	<0.001
Female; *n* (%)	210 (64.4)	197 (70.6)	0.11
BMI; mean (SD)	29 (6.0)	30 (18.5)	0.77*
Missing	4	2	
Surgery class (type of surgery); *n* (%)			<0.001
ENT	14 (4.3)	46 (16.6)	
General surgery	93 (28.5)	55 (19.8)	
Gynecology	50 (15.4)	91 (32.7)	
Neurosurgery	18 (5.5)	6 (2.2)	
Orthopedic surgery	103 (31.6)	57 (20.5)	
Plastic surgery	36 (11.0)	16 (5.8)	
Vascular surgery	11 (3.4)	7 (2.5)	
Missing	1	1	
Allergy to NSAIDs; *n* (%)	14 (4.3)	9 (3.2)	0.49
Allergy to local anesthetics; *n* (%)	1 (0.3)	2 (0.7)	0.60†
Laparoscopic or open surgery; *n* (%)			0.003
Laparoscopic	92 (28.8)	91 (34.0)	
Open	139 (43.6)	80 (29.9)	
N/A	88 (27.6)	97 (36.2)	
Missing	7	11	
Local anesthetic infiltration; *n* (%)	232 (73.2)	172 (63.0)	0.01
Missing	9	6	
Intraoperative analgesia given within 30 min of surgical completion; *n* (%)	158 (48.5)	163 (58.8)	0.01
Missing	0	2	
Location; *n* (%)			<0.001
MUMC	51 (15.6)	173 (62.2)	
JH	112 (34.4)	35 (12.6)	
HGH	163 (50.0)	70 (25.2)	
Missing	0	1	

*Based on Fisher's exact test; remaining *P* values based on t test for age and Chi square test for categorical variables; †based on Mann–Whitney U test. BMI = body mass index; ENT = ears, nose and throat (otolaryngology); N/A = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs; MUMC = McMaster University Medical Centre; JH = Juravinski Hospital; HGH = Hamilton General Hospital

scale [VDS] < 2)[7] at the time of PACU discharge or within two hours after surgery, whichever came first; this was included to resemble the primary outcome of satisfactory analgesia with minimal emesis, NRS ≤ 4 and VDS < 2, included in the concurrently conducted and previously reported prospective RCT; 2) total equipotent opioid dose in morphine equivalents; 3) occurrence of side effects (PONV, sedation, pruritis); and 4) length of stay in the PACU between patients receiving hydromorphone and morphine. The eligibility time period differed between the previous RCT and our study to ensure patients were not in both studies.

Data collection

Data extracted from the anesthetic record included: patient demographics, surgical procedure, length of procedure, type of anesthetic, and time of extubation. The anesthetic record was also used to assess for intraoperative opioid within 30 min prior to surgical completion, as this may have impacted PACU pain scores. The planned postoperative disposition plan was determined from the operating room schedule list. The intraoperative nursing notes were used to determine whether local anesthetic was infiltrated prior to the completion of surgery.

Table 2 Outcomes

Outcome	HM ($n = 326$)	M ($n = 279$)	Unadjusted analysis		Adjusted analysis	
Primary outcome	Mean (SD)	Mean (SD)	Mean difference (HM–M) (95% CI)	*P*	Mean difference (HM–M) 95% CI	*P*
Pain at discharge from PACU (NRS) ($n = 524$)	**2.8 (1.6)**	**2.5 (1.5)**	0.31 (0.04 to 0.58)	$P = 0.02$	0.10 (− 0.21 to 0.42)	$P = 0.53$
Secondary outcomes	Mean (SD)	Mean (SD)	Mean difference (HM–M) (95% CI)	*P*	Mean difference (HM–M) 95% CI	*P*
Length of stay in PACU (minutes) (*n*=579)	114 (67)	98 (65)	15.75 (4.93 to 26.58)	$P \leq 0.01$	1.40 (− 10.74 to 13.54)	$P = 0.82$
Total opioid dose converted to IV morphine equivalents (mg) (*n*=601)	5.0 (3.6)	6.3 (3.4)	− 1.30 (− 1.87 to − 0.74)	$P \leq 0.001$	− 1.35 (− 2.03 to 0.68)	$P \leq 0.001$
	n (%)	*n* (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Satisfactory analgesia (NRS <4) with minimal PONV (VDS <2) (*n*=569)	170 (**55**)	164 (**64**)	0.69 (0.49 to 0.97)	$P = 0.03$	0.84 (0.56 to 1.27)	$P = 0.41$
Any side effect (*n*=601)	251 (**78**)	233 (**84**)	0.67 (0.45 to 1.02)	$P = 0.06$	1.02 (0.62 to 1.67)	$P = 0.95$
Side effects						
Nausea/vomiting (*n*=475)	71 (**29**)	43 (**19**)	1.79 (1.17 to 2.76)	$P = 0.01$	1.63 (0.95 to 2.80)	$P = 0.08$
Sedation (*n*=559)	235 (**80**)	230 (**87**)	0.61 (0.38 to 0.96)	$P = 0.03$	0.77 (0.44 to 1.34)	$P = 0.36$
Pruritus (*n*=396)	5 (**3**)	1 (**0**)	Not enough events		Not enough events	
Respiratory depression (*n*=593)	2 (**1**)	3 (**1**)	Not enough events		Not enough events	

Reference level is morphine for all regression analyses. The adjusted analyses took into account the impact of the following variables: age, sex, location, surgery class, type of surgery, local anesthetic infiltration administered, and intraoperative analgesia administered within 30 min of surgical completion. CI = confidence interval; HM = hydromorphone; IV = intravenous; M = morphine; NRS = numerical rating scale; OR = odds ratio; PACU = postanesthetic care unit; PONV = postoperative nausea/vomiting; SD = standard deviation; VDS = verbal descriptive scale

The PACU flow sheet was used to determine readiness to discharge as defined by a score of 8 or greater on the modified Aldrete scale.[8] PACU flowsheets were also used to determine total opioid dose (in morphine equivalents), as well as other analgesics administered from arrival in the PACU until readiness to discharge. Total opioid dose was converted into morphine equivalents using a factor of 1:5, hydromorphone:morphine. The literature provides a range for the conversion between morphine and hydromorphone as anywhere from 1:5 to 1:10.[1,9,10] A conversion factor of 1:5 hydromorphone:morphine was used to mirror the RCT conducted by Shanthanna *et al.*[4] Flow sheets allowed for abstraction of information regarding subjective pain scores (NRS 0–10), PONV (scale of 0–3), pruritis (scale of 0–3), sedation (scale of 0–4), and respiratory depression (respiratory rate ≤ 8 breaths·min^{-1}) (Appendix).

Demographics

The following demographic information was extracted from patient charts: age, sex, body mass index, surgery type, laparoscopic *vs* open surgery, local anesthetic infiltration, intraoperative analgesia given within 30 min prior to surgical completion, and location of surgery.

Measures to minimize bias

To limit selection bias, multivariable regression analyses were performed to adjust for potential confounders and imbalances between morphine and hydromorphone groups. Each chart was reviewed by two independent parties to ensure that data were accurate and free of errors. Additionally, a secure web application, REDCap, was used to extract the data from the patients' charts using a structured form.[11]

Statistical analysis

The objective of this study was to evaluate the treatment effect of hydromorphone *vs* morphine on postoperative pain, while adjusting for potential confounders. A target sample size of $n = 605$ was determined. This was justified based on the need to produce a stable model adjusting for eight variables (age, sex, body mass index, location, surgery class, type of surgery, local anesthetic infiltration administered, and intraoperative analgesia administered within 30 min of surgical completion) in a multiple linear regression model. By applying a rule of thumb of ten observations per degree of freedom—typically aimed at developing models for binary outcomes—we would need at least 150 observations.[12] We obtained a larger sample size of $n = 605$ in case more factors were to be included in the model. Since the primary outcome of this study is continuous, this sample size estimate is considered to be a conservative estimate.

Means and standard deviations (SD) were used for normally distributed continuous variables, while counts and percentages were used for categorical variables. To identify any baseline differences between individuals receiving hydromorphone and morphine, t-tests were performed for continuous variables and Chi square tests for categorical variables.

The effect of the type of opioid used (hydromorphone *vs* morphine) on each primary and secondary outcome was first investigated using univariable regression analyses and then with multivariable regression analysis. Linear regression was performed on continuous outcomes: i) pain at discharge from PACU, ii) time until discharge (minutes), and iii) total equipotent opioid dose in morphine (mg). Results are presented using mean differences, 95% confidence intervals (CIs), and *P* values. Logistic regression was performed on binary outcomes: i) satisfactory analgesia, ii) nausea/vomiting, iii) sedation, iv) itching, and v) respiratory depression. Results are presented using odds ratios (OR), 95% CIs, and I values.

Potential confounders adjusted for in the multivariable analyses included age, sex, location (HGH, JH, MUMC), surgery class (general surgery, gynecology, orthopedic surgery, plastic surgery, ear/nose/throat surgery), type of surgery (laparoscopic, open, not applicable), local anesthetic infiltration administered (yes/no), and intraoperative analgesia administered within 30 min of surgical completion (remifentanil excluded) (yes/no).

Results

From a total of 2,369 patients, patients were excluded if they were not eligible ($n = 1744$), had a missing eligibility status ($n = 1$), received something other than hydromorphone or morphine for analgesia ($n = 5$), or did not have any information reported for analgesic medication ($n = 14$). This left a total of 605 eligible patients for analysis (Figure). Seventy-two of the 279 patients who received morphine and 150 of the 326 patients who received hydromorphone were admitted overnight as inpatients.

The demographic characteristics of the sample are shown in Table 1, which lists all the factors included in the multivariable analyses. Most of the patients underwent orthopedic, gynecologic, or general surgery. Unadjusted analyses comparing hydromorphone and morphine groups revealed significant differences in baseline characteristics of patients' age, surgery class, surgery type (laparoscopic or open), use of local anesthetic infiltration, intraoperative analgesia administered within 30 min of surgical completion, and location (Table 1). Specifically, patients treated with morphine were significantly younger, had more otolaryngologic and gynecologic surgeries, had fewer open surgeries, had less frequent intraoperative local anesthetic infiltration, more often received analgesic medications within 30 min of surgical completion, and were more often treated at MUMC—a centre for women and children and ambulatory day surgeries for adults.

Regarding the primary outcome of pain reported at discharge from the PACU, no significant difference was observed between the mean (SD) hydromorphone NRS [2.8 (1.6)] and the morphine NRS [2.5 (1.5)] after adjusting for potential confounders (adjusted mean difference, 0.10; 95% CI, − 0.21 to 0.42; $P = 0.53$). Similarly, for the secondary outcomes, our adjusted analyses revealed no significant differences between the groups' lengths of stay in the PACU, reports of satisfactory analgesia without substantial PONV, incidence of PONV, and incidence of sedation. Nevertheless, a significantly lower total equipotent dose of morphine was administered to individuals in the hydromorphone group compared with those in the morphine group based on the 1:5 conversion ratio used (mean difference, − 1.35; 95% CI, − 2.03 to − 0.68; $P < 0.001$). There were not enough events to investigate differences in our secondary outcomes of pruritus and respiratory depression (Table 2).

Discussion

This study showed that were no significant differences in postoperative pain scores, satisfactory analgesia, and length of stay between patients administered hydromorphone *vs* morphine in the postoperative period until discharge from the PACU. Morphine has previously been shown to be associated with increased pruritis and

other side effects especially in renal failure populations, but our results showed a similar incidence of common side effects between both opioids.[1–3] Our demographic analysis showed that there were differences in age, type of surgery, choice of laparoscopic *vs* open surgery, intraoperative analgesics received, and surgery location between those who received morphine *vs* hydromorphone. These can be attributed to differences in resources and medication-ordering practices among providers and hospitals, as well as the potential impact of surgical and patient characteristics on the choice of postoperative opioids. Our study did show that the morphine group required a significantly higher dose of opioid compared with the hydromorphone group accounting for morphine equivalent dosages. The RCT by Shanthanna *et al*. had a similar finding where the morphine group required a higher dose of opioid than the hydromorphone group (2019).[4] This suggests that the conversion ratio of 1:5 selected among the reported ratios of 1:5 to 1:10 have underestimated the potency of hydromorphone.[1,8,9] Given the mean difference of -1.35 mg (95% CI, -2.03 to 0.68; $P < 0.001$) needed to achieve this based on 1:5 potency ratio, we estimate that the actual potency of hydromorphone could be between six to seven times that of morphine.

Opioids are the leading medication for controlling moderate to severe pain in the postoperative period, but their side effects often limit analgesic therapy.[13] There is a limited amount of existing literature about the choice of long-acting opioids to be used in the PACU. Our trial serves to increase the evidence base that hydromorphone is not superior to morphine for providing analgesia or in relation to its side effects.[10] Our findings complemented the results of the RCT conducted by Shanthanna *et al*. That study showed no differences between morphine and hydromorphone with regard to satisfactory analgesia with minimal emesis, which was a dichotomous outcome defined as a pain score ≤ 4 on the NRS scale and a PONV score < 2 on the VDS.[4] Our study similarly showed no differences with both our primary outcome of pain measured as a continuous outcome using the 0–10 NRS in addition to our secondary outcome of satisfactory analgesia without substantial PONV measured as a dichotomous outcome using an NRS < 4 and VDS < 2. Randomized-controlled trials are considered the gold standard methodology for a study and higher than observational studies in the hierarchy of evidence. Further, it is thought that observational studies lead to larger treatment effects compared with RCTs. Our observational study's results were similar to those of the previous RCT in terms of the direction and magnitude of the results. A study by Benson *et al*. compared the results of observational studies and RCTs among 136 studies.[14] The studies included 19 different treatments, and among those treatment effects, only two showed that the results of observational studies were significantly different from the results of RCTs. These findings lend credence to the value that observational studies have in the body of evidence and that they may be a reasonable choice to evaluate some treatments where an RCT is not feasible.

Contrary to our results, others have found that hydromorphone provided better analgesia outcomes. We hypothesize that these differences in findings can be attributed to methodological differences across studies such as sample sizes and outcome measurements. A meta-analysis showed that hydromorphone was favoured over morphine for producing lower visual analogue scale (VAS) scores for acute pain.[1] The analyzed studies included patients in non-OR environments as well, such as acute pain in the emergency department. While our study included patients who received multiple doses of opioids from PACU staff as necessary, this meta-analysis included patients who received single-bolus administrations and PCA using equipotency ratios of 1:6.66 and 1:5, respectively. Another finding that contrasted our study's results was shown in a small randomized trial of patients undergoing total hysterectomy, which showed that patients who received hydromorphone had lower VAS scores and a lower incidence of severe PONV compared with those who received morphine.[15] These findings are applicable to a more specific population since the participants included 80 patients undergoing a hysterectomy procedure. Opioids were also administered to all patients at the same predetermined dosages using a 1:5 equipotency ratio, which we found to underestimate the potency of hydromorphone.

Our study has several strengths. It is a moderately sized observational study exploring the analgesic and side effect profiles of IV morphine and hydromorphone in the context of acute postoperative pain. We analyzed clinically important primary and secondary outcomes. Quantifying pain on the NRS from 0 to 10 for our primary outcome and as satisfactory or non-satisfactory analgesia for one of our secondary outcomes, in addition to analyzing a variety of factors indirectly related to analgesia, facilitated a strong analysis of analgesia as an outcome. To ensure our sample was representative of its population, we only included patients with minimal missing data and loss to follow-up and captured potential confounding factors such as intraoperative local anesthetic infiltration and opioid administration.

Our study has several limitations. First, the equipotency conversion factor of 1:5 may have underestimated the potency of hydromorphone and as a result contributed to the differences found in required doses. Second, although we recorded and controlled for many demographic characteristics, intraoperative analgesics administered

prior to 30 min of surgical completion, intraoperatively administered anti-emetics, and the specific amount of local anesthetic infiltration by the surgeons were not controlled for. Non-opioid analgesics administered in the PACU such as ketorolac were also not accounted for, which may have impacted postoperative pain and side effects. Third, a prospective design would have facilitated data collection on other risk factors for postoperative pain and side effects not routinely part of the preoperative patient questionnaire. Our retrospective design also meant that pain was quantified at unstandardized timepoints, weakening internal validity. Fourth, in regard to the patient population, because of our stringent inclusion and exclusion criteria, the findings of our study cannot be extrapolated to the following populations: pediatric, emergency surgery, cardiac surgery, patients with chronic pain, and patients who received a nerve block in the perioperative period. A majority of the patients selected underwent orthopedic, general, and gynecologic surgery, with relatively little representation of patients undergoing vascular or neurosurgery. Fifth, our patient population was also gathered via non-random sampling, which may have led to selection bias.[16]

These results are consistent with the hypothesis of no differences between the hydromorphone and morphine groups. Like all clinical research, it would be helpful to see whether the results can be replicated in other centres or settings.

Future larger studies are required to evaluate the effectiveness of morphine and hydromorphone delivered through other routes such as PCA, oral, and intrathecal. A historical cohort study showed that the usage of PCA with morphine decreased the length of stay in hospital compared with hydromorphone.[17] Nevertheless, other small RCTs have shown no significant differences in analgesia or side effect profiles with PCA morphine *vs* hydromorphone.[18,19] A meta-analysis investigating adverse effects of opioids administered via PCA similarly showed that there were no differences in side effects between morphine and hydromorphone.[13] Trials comparing intrathecal morphine and hydromorphone after Cesarean delivery showed similar analgesia and side effects, although one study found that morphine resulted in a longer time to first opioid.[20,21] There are currently no studies published that have investigated both the analgesic properties and side effects of oral morphine *vs* hydromorphone.

Conclusions

In summary, this retrospective observational study showed that the analgesic properties and side effect profile of hydromorphone was not significantly different to those of morphine for postoperative analgesia purposes within the postoperative period at the time of discharge from the PACU. Future studies should focus on developing a more accurate equipotency ratio between hydromorphone and morphine. In addition, future investigations should compare the usage of morphine *vs* hydromorphone through other routes such as PCA and oral.

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Appendix Post-anesthesia care unit flowsheet data

Pain at admission

- Scale of 0–10

Nausea/vomiting at admission

- Nausea/vomiting/pruritus scale:

  0 = None
  1 = Mild, no prescription needed
  1 = Mild, no prescription needed
  2 = Moderate, prescription effective
  3 = Severe, prescription ineffective

Sedation at admission

- Sedation scale used in the postanesthesia care unit:

0 = Alert
1 = Occasional drowsy, easy to rouse
2 = Frequently drowsy, easy to rouse
3 = Normal sleep, easy to rouse
4 = Somnolent, difficult to rouse

Itching at admission

- Nausea/vomiting/pruritus scale:

0 = None
1 = Mild, no prescription needed
2 = Moderate, prescription effective
3 = Severe, prescription ineffective

Respiratory depression at admission

- Respiratory depression defined as respiratory rate ≤ 8 breaths·min^{-1}

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