ORIGINAL CLINICAL RESEARCH REPORT

CME

Intrathecal Hydromorphone Versus Intrathecal Morphine for Postcesarean Delivery Analgesia: A Randomized Noninferiority Trial

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BACKGROUND: Spinal anesthesia with intrathecal morphine is often the preferred anesthetic modality for elective cesarean delivery. Side effects and drug shortages, however, prompted researchers to look into intrathecal hydromorphone as an alternative. These studies established the effective analgesic dose for 90% of patients (ED90) for both opioids for postcesarean analgesia, yet failed to demonstrate the superiority of morphine over hydromorphone. Nonetheless, the noninferiority of hydromorphone has yet to be determined.

METHODS: In this noninferiority randomized blinded clinical trial, 126 patients undergoing elective cesarean delivery under spinal anesthesia received either morphine 150 µg or hydromorphone 75 µg (ED90). The primary outcome was the between-group difference of the mean Numeric Rating Scale (NRS) pain score (0–10) for the first 24 hours after cesarean delivery, with a preestablished threshold for noninferiority of 1. This 24-hour NRS pain score was defined as a single number obtained at the 24 hours postcesarean delivery interview, based on participant's recall of their overall pain experience during this period. Secondary outcomes included differences in NRS pain scores every 6 hours, cumulative 24 hour opioid consumption, time-to-first opioid request, quality of recovery as measured by the Obstetric Quality of Recovery Score-11 (ObsQoR-11), frequency of interventions for side effects, and Apgar scores.

RESULTS: The mean (standard deviation [SD]) of the 24-hour NRS pain score was 4.0 (1.7) for morphine and 3.6 (1.5) for hydromorphone (between-group difference –0.46 (95% confidence interval [CI], –1.0 to 0.1). Given that the upper limit of the 95% CI did not exceed 1, noninferiority of hydromorphone was established. No statistically significant differences were found in mean (SD) 24 hour oral morphine consumption (morphine: 4.2 mg (6.5) vs hydromorphone: 4.1 (8.0) mg; $P = .98$), median [interquartile range {IQR}] ObsQoR-11 score (morphine: score 87 [75–97.5] vs hydromorphone: score 90 [80–96.5]; $P = .51$), median [IQR] time to first opioid request (morphine: 10.2 [3.2–15.5] h versus hydromorphone: 6.2 [3.1–12.4] h; $P = .35$), or proportion of patients requiring interventions for opioid-related pruritus (morphine: 0.316 (variance 0.216) vs hydromorphone: 0.321 (variance 0.218) ($P = .96$) and opioid-related nausea and vomiting (morphine: 0.333 (variance 0.222) vs hydromorphone: 0.393 (variance 0.238) ($P = .51$).

CONCLUSIONS: Intrathecally, hydromorphone is noninferior to morphine for analgesia after elective cesarean delivery when using the previously established ED90 for both opioids (morphine: 150 µg versus hydromorphone: 75 µg); hydromorphone provides effective analgesia and may be a suitable alternative to morphine. (Anesth Analg 2026;142:19–27)

KEY POINTS

- **Question:** Is intrathecal hydromorphone noninferior to intrathecal morphine for postcesarean delivery analgesia?
- **Findings:** No significant differences between intrathecal hydromorphone and morphine in mean pain score at 24 hours, opioid consumption, time to first opioid request, quality of recovery, or opioid-related side effects.
- **Meaning:** Hydromorphone is noninferior to morphine for postcesarean delivery analgesia.

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Cesarean delivery is among the most frequently performed surgical procedures worldwide. In Canada, rates of cesarean delivery have steadily increased from 18.7% in 1997 to 31% in 2020, marking a significant 66% increase.[1] The preferred anesthetic technique for cesarean delivery involves spinal anesthesia combined with intrathecal morphine and a multimodal analgesic strategy.[2] Administration of morphine intrathecally is often promoted for postcesarean delivery pain management[3] due to its lasting pain relief and fewer side effects when compared to parenteral opioids.[4] However, intrathecal opioids are associated with a sizeable side effect profile, including nausea, vomiting, pruritus, and possibility of sedation and respiratory depression.[5] Moreover, the preferred use of morphine to provide postcesarean analgesia renders this practice susceptible to the escalating occurrence of insufficient supplies of preservative-free morphine, necessitating the exploration of other options. In contrast, there is limited literature on the use of intrathecal hydromorphone, which has primarily been utilized for chronic pain management, including cancer-related pain, intractable nonmalignant pain, and complex regional pain syndrome.[6–8] Furthermore, hydromorphone has been proposed for managing acute pain after gynecologic surgery.[9] Hydromorphone's favorable pharmacokinetic profile with higher lipid solubility results in faster onset than morphine, and similar pharmacodynamics as a potent mu opioid receptor agonist has led to its proposal as a reasonable alternative for postcesarean analgesia.[10–12] Despite these considerations, existing practice guidelines heavily lean towards intrathecal morphine, perhaps due to the limited research available on hydromorphone.[3] Recently, Sharpe et al.[13] did not find that morphine offers superior pain relief compared to hydromorphone 24 hours after cesarean delivery. Their findings, which showed no significant differences in pain scores, suggest that hydromorphone could be a reasonable substitute for morphine and warrant further investigation.

To our knowledge, no previous studies have been specifically designed to assess whether intrathecal hydromorphone is noninferior to morphine for postcesarean delivery pain relief. Our hypothesis is that, when used alongside standardized multimodal pain management, an equivalent dose of hydromorphone will provide noninferior pain relief to morphine during the initial 24 hours after cesarean delivery.

METHODS

Study Design

This noninferiority, randomized, blinded controlled trial was performed at an academic tertiary care obstetric facility (London Health Sciences Centre, London, Ontario, Canada), and written informed consent was obtained from all subjects participating in the trial.

The trial's registration was completed through Clinicaltrials.gov (NCT03592992), while the Western University Research Ethics Board (#111264) and Health Canada (#220111) provided their approvals. These approvals were secured before initiating the study and after each protocol amendment. Inspections conducted by the Lawson Health Research Institute and Health Canada were found to be in compliance. The recruitment of study participants was conducted by a team member, and all participants provided written informed consent before becoming involved in any study-related activities.

Recruitment

Between November 2020 and July 2022, a total of 126 patients were enrolled in this study (Figure 1). Eligible subjects were 18 years of age or older, categorized as American Society of Anesthesiologist's physical status (ASA-PS) II or III, possessing a gestational age of at least 37 weeks, and undergoing an elective cesarean delivery under spinal anesthesia. Exclusion criteria included contraindication to spinal anesthesia, allergy or severe intolerance to opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, intraoperative conversion to general anesthesia, preexisting chronic pain syndrome, history of opioid use during pregnancy, and a body mass index (BMI) exceeding 40 kg/m^2.

Randomization and Blinding

The allocation of patients into either the intrathecal morphine or hydromorphone groups was executed using a computer-generated blocked randomization schedule (blocks of 2). A total of 126 participants were evenly allocated to receive either morphine or hydromorphone (Figure 1). Sequentially numbered opaque envelopes were prepared containing study identification number, data collection forms, and letters of informed consent. A member of our institutional clinical trials pharmacy assessed the randomization schedule and prepared the drugs for administration accordingly.

Intervention

On participant enrollment, a study team member communicated the study identification number to the clinical trials pharmacy. The pharmacy technician then cross-referenced this number with the randomization schedule in their possession to ascertain the allocated intervention. Sterile preparation of the assigned intervention occurred immediately before the administration of spinal anesthesia. Both morphine and hydromorphone interventions were

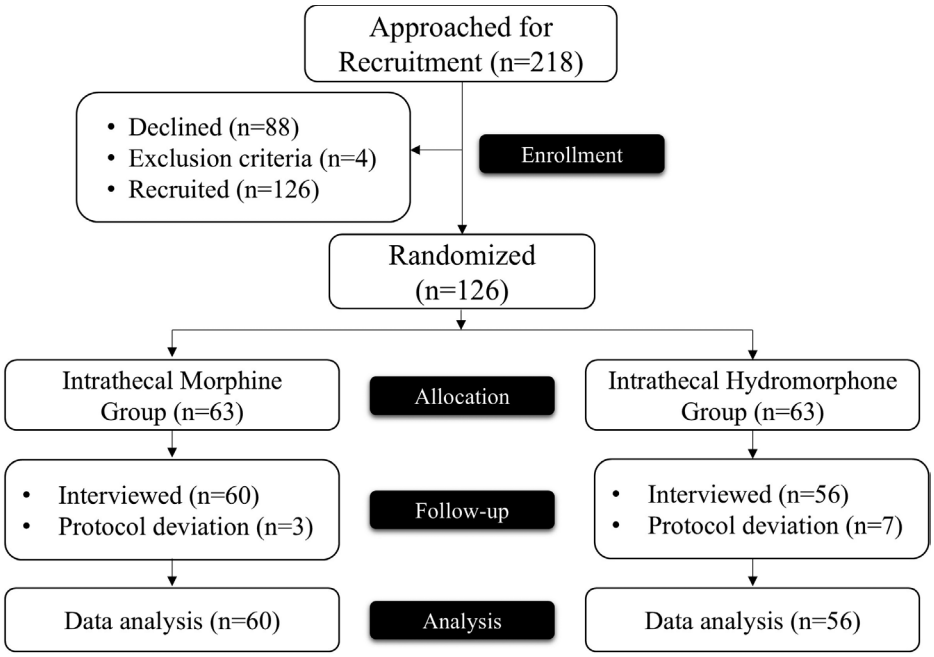

Figure 1. CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials.

diluted with sodium chloride 0.9% to a final volume of 0.5 mL. To prepare the hydromorphone intervention, 0.15 mL (300 µg) of a hydromorphone 2 mg/mL vial (Sandoz Corp Ltd) was added to 1.85 mL of 0.9% sodium chloride, creating a concentration of 150 µg/mL. Similarly, the morphine intervention utilized 5 mg/ 5mL vials (Sandoz Corp Ltd) of preservative-free morphine that were diluted to 150 µg/0.5 mL. To prepare 2 mL of diluted solution, 0.6 mL (600 µg) of morphine was added to 1.4 mL sodium chloride 0.9%, creating a concentration of 300 µg/mL. Deidentified syringes containing the 0.5 mL allocated intervention (75 µg of hydromorphone or 150 µg of morphine) were dispensed to the study team by the clinical trials pharmacy, thus ensuring that patients, obstetricians, and all team members remained unaware of treatment assignments.

The chosen drug dosages at a 2:1 ratio (morphine: hydromorphone) were based on the previously established ED90[14] values for intrathecal morphine (150 µg) and intrathecal hydromorphone (75 µg) in the context of postcesarean delivery analgesia. Subsequently, the designated treatment was incorporated into the spinal anesthetic, which included fentanyl 15 µg and hyperbaric bupivacaine 0.75% at doses ranging from 10.5 to 12 mg. This range for bupivacaine dosage aligned with local practice which would enhance provider acceptance and, consequently, the study's feasibility.

The administration of spinal anesthesia was conducted with participants in a seated flexed position, using standard monitors and after lumbar antisepsis with chlorhexidine 0.5% W/V in 70% isopropyl alcohol. A 25-gauge Whitacre needle was introduced into the subarachnoid space at the L2–L3, L3–L4 or L4–L5 interspace until visual confirmation of clear cerebrospinal fluid was obtained, followed by administration of the preprepared spinal anesthetic mixture. Subsequently, participants were transitioned to the supine position with left uterine displacement. A phenylephrine infusion and coloading with crystalloid solution were initiated to sustain hemodynamic stability. On the establishment of motor block, the attending anesthesiologist assessed sensory levels to temperature, with a research team member recording the findings. After the delivery of the infant and cord clamping, an intravenous administration of 100 µg carbetocin took place.

Additionally, all participants received intraoperative intravenous administration of ketorolac (15 mg) and ondansetron (4 mg) in the operating room. Intravenous dexamethasone was not given due to potential impact on analgesia. On completion of surgery, participants were prescribed a standardized multimodal analgesic regimen, including acetaminophen (given first in PACU, then following the regimen), ketorolac (given first in OR, then following the regimen), as well as oral morphine available on request starting in the postanesthesia care unit (PACU) (Supplemental Digital Content 1, Supplemental Table 1, https://links.lww.com/AA/F323).

Data Outcomes

Demographic and surgical information including age, weight, number of previous cesarean deliveries, duration of surgery, neonatal Apgar scores at 1 and 5 minutes, tubal ligation, length of hospital stay, and ASA-PS scores were extracted from patient medical records by a member of the study team.

For the primary outcome of interest, study team members interviewed subjects 24 hours after delivery to collect data to calculate the mean 24-hour NRS pain scores. For this purpose, subjects were asked to rate, on a 0 to 10 NRS, the overall pain score they experienced in the period starting after the delivery of their child until the time of the interview. Our rationale for selecting this outcome was based on a study that has demonstrated that a single-item recall rating of pain over a 24-hour period is as reliable and valid for detecting treatment effects as composite pain scores created from multiple ratings of current pain while minimizing patient assessment burden.[15] At the same time, participants completed the Obstetric Quality-of-Recovery-11 (ObsQor-11) survey.[16]

In terms of secondary outcome assessment, study personnel directly assessed and collected NRS pain scores from participants for 2 of the time intervals (PACU and 24 hours), while pain scores for other time intervals (6, 12, and 18 hours) were retrieved from paper medical records filled by nursing staff. The question for pain with movement was standardized as "pain upon sitting or standing from a recumbent position." Side effects requiring treatment were extracted from the electronic medication administration record. Each medication administration for the purpose of nausea or vomiting and pruritus was counted as "one treatment." Subsequently, the proportion and variance of patients requiring treatments between each group was calculated. Additionally, patients were asked to rate their overall satisfaction on a Likert scale (1–5).

Secondary outcomes were collected by extracting data from medical records and nursing records at 6-hour intervals during the initial 24-hour period after the cesarean delivery. The following secondary outcomes were subjected to analysis: (1) difference in NRS pain scores (pain and movement) at 6, 12, 18 and 24 hours, (2) difference in opioid consumption (oral morphine in mg), for the first 24 hours after cesarean delivery, (3) time-to-first oral opioid analgesic request, measured in hours, (4) number of interventions for nausea and/or vomiting, (5) number of interventions for pruritus, (6) differences in respiratory rate and peripheral oxygen saturation, (7) neonatal Apgar scores at 1 and 5 minutes on a 1 to 10 scale, (8) patient satisfaction on a 1–5 Likert Scale, and (9) ObsQoR-11 survey scores.

Statistical Analysis

Data analysis was conducted using Stata version 17.0. Baseline characteristics were summarized using counts (percentages), means (standard deviation [SD]), or medians (interquartile range [IQR]) as appropriate.

The primary outcome was the between-group difference in the mean 24-hour NRS pain scores. The null hypothesis was that intrathecal hydromorphone would be inferior to morphine. The noninferiority margin was set a priori at 1 point on the NRS, as a previous study has demonstrated an NRS change of < 1.5 cm to be clinically significant.[17] This provided an effective noninferiority margin of 10%. Therefore, noninferiority would be declared if a 2-sided 95% confidence interval (CI) comparing NRS scores in the hydromorphone group to the morphine group excluded 1. A 2-sided CI was used so that a test of superiority could be conducted if noninferiority was declared. The sample size was calculated using a noninferiority margin of 1, an SD of 1.9, a power of 0.80, and a 2-sided alpha of 0.05, resulting in 114 subjects. This number was then inflated by 10% to account for deviations, yielding a final sample of 126 or 63 subjects per group (Figure 1).

Between-group comparisons for continuous secondary outcomes were done either using differences in medians or means, depending on the distribution of the variable. Ninety-five percent CIs for differences in medians were computed using bootstrapping and 10,000 repetitions. Pain scores at rest and with movement had both a group component (hydromorphone versus morphine) and a time component (baseline, 6 hours, 12 hours, 18 hours, and 24 hours – clustered within each patient). Therefore, a linear mixed-effects regression model (maximum likelihood estimation) was used in which the dependent variable was the pain score, and independent variables (fixed effects) were the group allocation and time period (main and interaction effects), while each patient was included in the random effects portion of the model. This controlled for the within-patient correlation of the repeated measures and allowed for a random intercept and slope for each patient in the regression model. An exchangeable correlation structure between pairs of within-patient measurements was assumed. Based on the statistical model, contrasts and 95% CIs for the contrasts were calculated for each measurement occasion both within-groups and between-groups. Contrasts of adjusted predictions were displayed graphically.

RESULTS

Patient Population

Among the initial cohort of 218 patients approached for potential inclusion, a total of 92 were deemed ineligible (Figure 1). Ultimately, 126 patients were subjected to randomization, with 63 participants each assigned to either group. Notably, 10 study participants were excluded due to protocol deviations, thereby resulting in the inclusion of 116 patients for the analysis—60 in the morphine group and 56 in the hydromorphone group.

There were no significant differences between groups in terms of patient demographics and clinical characteristics (Table 1).

Pain Scores

At 24 hours after cesarean delivery, participants rated their overall NRS pain scores as a single recall value over this period; subsequent mean (SD) calculations of these reported NRS pain scores revealed 3.6 (1.5) for hydromorphone and 4.0 (1.7) for morphine. The between-group difference was −0.46 (95% CI, −1.0 to 0.1, P = .12), as illustrated in Table 2. This statistical analysis establishes the noninferiority of intrathecal hydromorphone in relation to morphine (Figure 2). Notably, subsequent assessment to establish the superiority of intrathecal hydromorphone in comparison to morphine did not yield statistically significant differences (P = .12).

The secondary outcomes of mean pain scores for each assessed time point at rest and with movement are shown in Figure 3A and Figure 3B, respectively. In terms of pain scores at rest, there were no significant differences at any of the time points (Table 3). There were, however, statistically significant differences at 2 time points in terms of mean pain scores with movement, in different directions. Pain scores with movement were significantly lower (P = .02) for hydromorphone group 6 hours postcesarean delivery. In contrast, hydromorphone group pain scores were significantly higher (P = .01) at the 18-hour mark (Table 3).

Opioid Consumption

No differences were identified in terms of 24-hour opioid consumption in oral morphine (mg). This observation is valid for all the assessed time intervals (Supplemental Digital Content 2, Supplemental Table 2, https://links.lww.com/AA/F324). Furthermore, 75 of 116 patients (64.7%) did not receive any opioids: 38/75 (50.7%) were in the morphine group and 37/75 were in the hydromorphone group (49.3%). Supplemental Digital Content 3, Supplemental Table 3, https://links.lww.com/AA/F325 provides further analysis of opioid consumption between treatment groups in those who received postoperative opioids and those who did not. No statistically significant distinction in the median time elapsed until the first opioid rescue analgesia was administered between the 2 groups (10.2 hours for morphine and 6.2 hours for hydromorphone, P = .35, as presented in Supplemental Digital Content 4, Supplemental Table 4, https://links.lww.com/AA/F326).

Table 1. Demographic Distribution and Surgical Characteristics

Variable	Morphine (n = 60)	Hydromorphone (n = 56)
Age (y)	33.0 (5.0)	32.9 (4.5)
Height (cm)	164.8 (7.6)	164.8 (6.6)
Weight (kg)	81.0 (14.8)	81.6 (16.1)
BMI (kg/m^2)	29.8 (4.8)	30.0 (5.0)
Gestational age (wks)	38.6 (0.8)	38.8 (0.6)
Parity	1 [1–2]	1 [0–2]
Previous caesarean delivery	1 [0–1]	1 [0–1]
ASA (II/III) (%)	35/25 (58%/42%)	37/19 (66%/34%)
Duration of surgery (min)	50 [44–58]	48 [41–57]
Concurrent tubal ligation	14 (23%)	13 (23%)
Length of hospital stay (h)	49.3 [47.7–52.1]	51.1 [47.5–53.1]
Block height (thoracic dermatome level)	4 [4–4]	4 [3–4]
Local anesthetic dose (mL) of 0.75% bupivacaine	1.4 [1.4–1.5]	1.4 [1.4–1.5]

Mean (SD), median [IQR], or number (%). Percentages may not add to 100% due to rounding.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Side Effects and Quality of Recovery

Comparison of proportion and variance of patients requiring treatment for opioid-related side effects did not reveal any significant differences. The proportion of patients requiring intervention for opioid-related pruritus was 0.316 (variance 0.216) in the morphine group vs 0.321 (variance 0.218) in hydromorphone (P = .96). Regarding opioid-related nausea and vomiting, the proportion of patients requiring intervention was 0.333 (variance 0.222) in the morphine group vs 0.393 (variance 0.238) in hydromorphone (P = .51). Surveillance of respiratory rate and oxygen saturation was conducted at each designated time point. As mentioned above, these time points were at every 6 hours. Notably, no events of respiratory depression, as defined by a respiratory rate below 9, were documented (Supplemental Digital Content 5, Supplemental Table 5, https://links.lww.com/AA/F327).

In terms of quality of recovery, the assessment of median ObsQoR-11 scores yielded no significant differences (87 for morphine compared to 90 for hydromorphone, P = .51). Furthermore, patients rated their satisfaction of overall provided care on a numeric Likert scale ranging from 1 to 5. There were no statistically significant differences between the groups (Supplemental Digital Content 6, Supplemental Table 6, https://links.lww.com/AA/F328; Supplemental Digital Content 7, Supplemental Table 7, https://links.lww.com/AA/F329).

Analysis of Apgar scores at first and fifth minutes did not reveal significant difference between intrathecal hydromorphone and morphine groups (Supplemental Digital Content 1, Supplemental Table 8, https://links.lww.com/AA/F330).

DISCUSSION

Our blinded, randomized controlled, noninferiority trial identified that over the first 24 hours after cesarean delivery, intrathecal hydromorphone 75 µg was

Table 2. Mean Pain Scores for the First 24 h Postcesarean Delivery

	Morphine (n = 60)	Hydromorphone (n = 56)	Difference (95% CI of the difference)	*P* value
mean (SD)	4.0 (1.7)	3.6 (1.5)	−0.46 (−1.0 to 0.1)	.12
median [IQR]	4 [3–5]	3.5 [2–5]	−0.5 (−2.2 to 1.2)	.56

Difference is for intrathecal hydromorphone—morphine. *P* is 2-sided. 95% CI for difference in medians obtained by bootstrapping with 10,000 repetitions. NRS (0–10) pain scores were reported as a single recall value at 24 h for this overall period.
Abbreviations: CI, confidence interval; IQR, interquartile range; SD, standard deviation.

noninferior to morphine 150 µg with respect to mean 24-hour NRS pain scores, opioid consumption, and side effects when used as part of a multimodal analgesic regimen. The difference in the mean 24-hour NRS pain scores, as reported by the patients over a 24-hour period, was selected as the primary outcome due to the fact that perceived pain is considered a patient-oriented outcome. Surrogate outcomes, such as opioid consumption, are subject to several variables, including nursing and prescribing practices, as well as cultural disparities, therefore not necessarily reflective of patient's experienced discomfort.

Analysis of pain scores at 6-hour time intervals during the first 24 hours postcesarean delivery revealed no significant differences in pain scores at rest, for all time points. In contrast, 2 out of 4 time points revealed significant differences in pain scores with movement (NRS-M). The hydromorphone group had lower NRS-M at 6 hours and higher NRS-M at 18 hours. Albeit scarcely investigated, a previous retrospective study estimated the duration of analgesia as 14 hours for hydromorphone (60 µg) when compared to 17 hours for morphine (200 µg).[10] The explanation for this somewhat shorter duration relies on the pharmacokinetic properties of these 2 long-acting opioids. Hydromorphone, being more lipophilic, results in a reduced retention in the cerebrospinal fluid when compared to morphine.[11] Although this may suggest that hydromorphone does not last as long, it may also suggest that it results in an earlier, more intense onset of analgesia, which is reflected in the lower NRS-M during the initial 6 hours after cesarean delivery. The clinical importance of these findings remains to be determined.

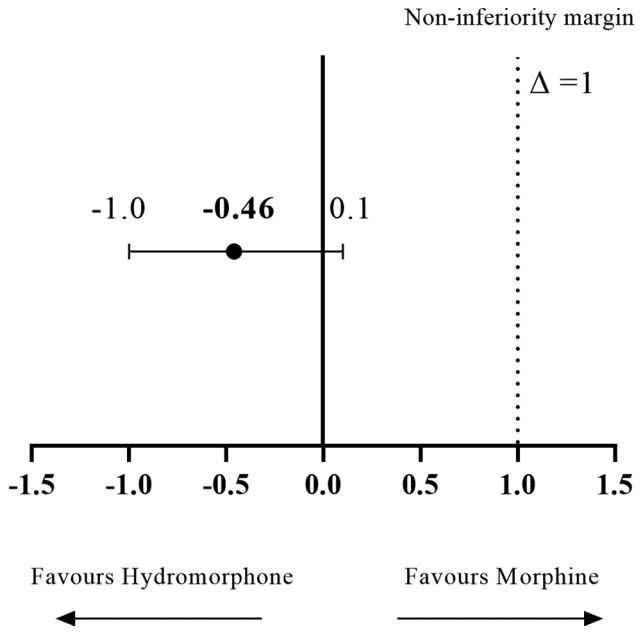

Figure 2. Between-group difference in the mean 24-h patient reported pain scores (NRS 0–10). NRS indicates Numeric Rating Scale.

In our study, although we found that hydromorphone had significantly higher NRS-M at 18 hours, both groups reported relatively low, satisfactory NRS-M, with the general trend increasing over the 24-hour period. Interestingly, at the 24-hour mark, pain scores with movement were the same for both intervention groups suggesting that, at this time point, analgesia effects were potentially related to the multimodal analgesia regimen.

Although this study did not find significant differences in side effects requiring treatment such as nausea, vomiting, pruritus, or sedation and respiratory depression, it is important to consider the interplay between risk of adverse effects and duration of action of morphine and hydromorphone.

For rescue analgesia, oral morphine (mg) was prescribed every 4 hours, and administered on an as-needed-basis. There were no significant differences in terms of total opioid consumption (mg) or time-to-first opioid request for the first 24 hours after cesarean delivery. However, the intrathecal hydromorphone group requested opioid analgesia at a median time of 6.2 hours after cesarean delivery, while the morphine group requested at 10.2 hours; this is similar to the findings of a previously published randomized controlled trial (RCT) comparing both opioids at the same ED90 doses in which median time to first opioid request was 5.4 hours for hydromorphone and 12.1 hours for morphine.[13] Although not statistically significant, 1 could argue that needing supplemental analgesia 4 hours earlier is a clinically significant disadvantage of hydromorphone, as this may impact rest and recovery. Interestingly, there was not a significant increase in total opioid use. Our findings are similar to that of Sharpe et al.[13] suggesting a shorter duration of intrathecal hydromorphone compared to morphine, but not an increase in pain requiring additional analgesia.

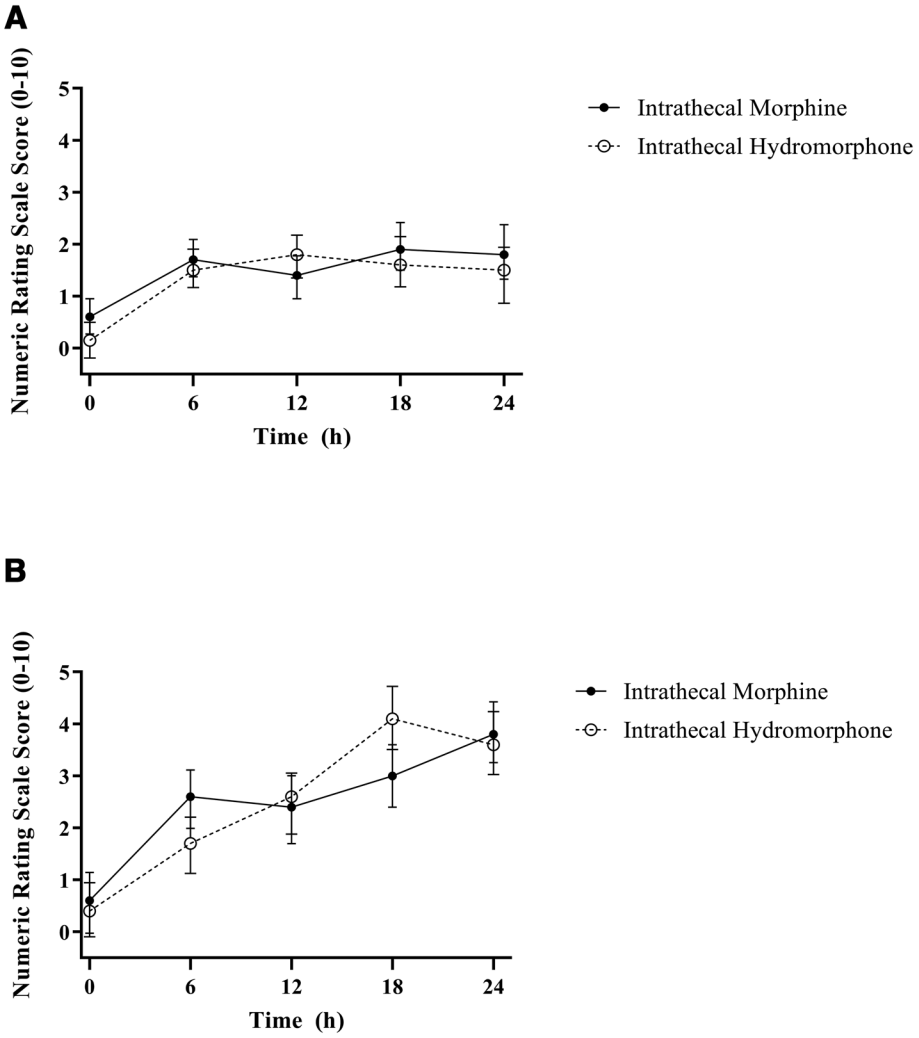

Figure 3. Pain scores (NRS 0–10) (A) at rest and (B) with movement for the first 24 h postcesarean delivery. NRS indicates Numeric Rating Scale.

One of the main limitations of the RCT mentioned above[13] is that they used the difference in NRS pain scores at 24 hours as a single time point as their primary outcome. As a strength of our study, we assessed reported mean NRS pain scores for the entire 24-hour period, which provides a more comprehensive evaluation. Another strength of our study lies in the fact that we chose a noninferiority design with a conservative

Table 3. Mean Pain Scores (Rest and Movement) Every 6 h Postcesarean Delivery

Time	Morphine	Hydromorphone	Adjusted difference (95% CI of the difference)	*P* value
0 h (PACU)				
Pain at rest	0.6 (1.5)	0.15 (0.6)	–0.4 (–0.9 to 0.04)	.07
Pain with movement	0.6 (1.8)	0.4 (1.1)	–0.3 (–1.0 to 0.5)	.51
6 h				
Pain at rest	1.7 (1.8)	1.5 (1.7)	–0.2 (–0.7 to 0.3)	.44
Pain with movement	2.6 (1.9)	1.7 (1.6)	–0.9 (–1.7 to –0.1)	.02
12 h				
Pain at rest	1.4 (1.6)	1.8 (2.0)	0.4 (–0.2 to 1.0)	.18
Pain with movement	2.4 (1.7)	2.6 (2.6)	0.3 (–0.6 to 1.2)	.53
18 h				
Pain at rest	1.9 (1.8)	1.6 (1.5)	–0.3 (–1.0 to 0.4)	.37
Pain with movement	3.0 (1.8)	4.1 (2.7)	1.1 (0.2 to 1.9)	.01
24 h				
Pain at rest	1.8 (1.9)	1.5 (1.7)	–0.2 (–0.9 to 0.6)	.69
Pain with movement	3.8 (1.9)	3.6 (1.8)	–0.2 (–1.0 to 0.6)	.66

Mean (SD). Difference is for intrathecal hydromorphone—morphine. The adjusted differences and *P* values are from the mixed effects model (see Methods for details).
Abbreviations: CI, confidence interval; PACU, postanesthesia care unit; SD, standard deviation.

a priori margin of 1. It has been previously demonstrated that the minimum clinically important difference (MCID) for acute pain scores range from 0.8 to 4 (0–10 cm) and analgesic interventions that provide a change of 10% in pain scores result in a clinically important effect.[18,19]

Our study has several limitations. First, we acknowledge the possible recall bias of our primary outcome of patient's self-reported pain score over 24 hours. Nevertheless, patients were clearly informed on enrollment of our main objective. In addition, we did not select a validated measure of global health score as a primary outcome, such as the Obstetric Quality of Recovery-11 (Obs-QoR11).[16] This survey is a validated measure of recovery after cesarean delivery, and assesses numerous metrics including shivering, dizziness, mobility, breastfeeding, personal hygiene, and sense of self-control.[16] At the time of study initiation, the cutoff for difference between poor and good recovery as per the ObsQoR-11 was not clearly established. After the study had initiated data collection, the ObsQoR-11 tool was subjected to a slight modification combining moderate and severe pain in 1 item (ObsQoR-10); however, we decided to continue with the ObsQoR-11 to preserve our internal validity. The Obs-QoR11 revealed no significant differences in recovery scores between treatment groups.

Another potential criticism point of our study lies in the selection of the primary outcome, in which we chose mean pain scores as rated by subjects instead of the area under the curve (AUC) for pain scores at the selected time intervals. AUC is a reasonable alternative for assessment of variables evaluated at equal time intervals. Nevertheless, we chose to use a linear mixed-effects regression model as per the description on the statistical analysis section of this manuscript, thus negating the need to calculate the AUC. In addition to this point, our primary end point was chosen to be 24 hours, while our interventions were dosed based on ED90 studies at 12 hours.

Furthermore, we excluded subjects with class III obesity, limiting the generalizability of our data. More importantly, we excluded subjects with a history of chronic pain and those using opioids during pregnancy. The incidence of opioid use in our obstetric cohort is low, therefore including them would likely have led to inadequate power to draw any conclusions; however, this exclusion may limit generalizability and present a missed opportunity to study an important population.

In summary, our RCT studied the noninferiority of intrathecal hydromorphone when compared to morphine for postcesarean analgesia. Our study findings support the use of 75 µg hydromorphone as an alternative to 150 µg morphine in this clinical scenario as part of a spinal anesthetic and multimodal analgesic regimen. We suggest consideration of use of hydromorphone when morphine cannot be used due to shortages, patient allergy to morphine, or significant previous side effect profile with morphine such as pruritus or nausea. Further studies looking at the superiority of intrathecal hydromorphone when compared to morphine, especially in patients suffering from opioid use disorder are warranted. ■

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DISCLOSURES

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REFERENCES

1. Gu J, Karmakar-Hore S, Hogan ME, et al. Examining cesarean section rates in Canada using the modified Robson classification. *J Obstet Gynaecol Can*. 2020;42:757–765.
2. Juang J, Gabriel R, Dutton R, Palanisamy A, Urman R. Choice of anesthesia for cesarean delivery: An analysis of the national anesthesia clinical outcomes registry. *Anesth Analg*. 2017;124:1914–1917.
3. Bauchat J, Weiniger C, Sultan P, et al. Society for obstetric anesthesia and perinatology consensus statement: Monitoring recommendations for prevention and detection of respiratory depression associated with administration of neuraxial morphine for cesarean delivery analgesia. *Anesth Analg*. 2019;129:458–474.
4. Rathmell J, Lair T, Nauman B. The role of intrathecal drugs in the treatment of acute pain. *Anesth Analg*. 2005;101:S30–S43.
5. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: A meta-analysis. *Anaesthesia*. 2009;64:643–651.
6. Ackerman L, Follett K, Rosenquist R. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symptom Manage*. 2003;26:668–677.
7. Du PS, Du PA, Hillyer J. Intrathecal hydromorphone for intractable nonmalignant pain: a retrospective study. *Pain Med*. 2006;7:10–15.
8. Deer T, Smith H, Burton A, Cousins M, et al. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician*. 2011;14:283–312.
9. Gajarawala S, Wells A, Watkins E, Rust B, Archambault M. Intrathecal hydromorphone as an analgesia option for gynecology patients. *JAAPA*. 2020;33:33–37.
10. Marroquin B, Feng C, Balofsky A, et al. Neuraxial opioids for post-cesarean delivery analgesia: Can hydromorphone replace morphine? A retrospective study. *Int J Obstet Anesth*. 2017;30:16–22.

11. Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage*. 2005;29:57–66.
12. Bujedo BM. Spinal opioid bioavailability in postoperative pain. *Pain Pract*. 2014;14:350–364.
13. Sharpe E, Molitor R, Arendt K, et al. Intrathecal morphine versus intrathecal hydromorphone for analgesia following aesarean delivery: A randomized clinical trial. *Anesthesiology*. 2020;132:1382–1391.
14. Sviggum H, Arend K, Jacob A, et al. Intrathecal hydromorphone and morphine for postcesarean delivery analgesia: Determination of the ED 90 using a sequential allocation biased-coin method. *Anesth Analg*. 2016;123:691–697.
15. Jensen MP, Hu X, Potts SL, Gould EM. Single vs composite measures of pain intensity: Relative sensitivity for detecting treatment effects. *Pain*. 2013;154:534–538.
16. Ciechanowicz S, Setty T, Robson E, et al. Development and evaluation of an obstetric quality-of-recovery score (ObsQoR-11) after elective caesarean delivery. *Br J Anaesth*. 2019;122:69–78.
17. Kendrick D, Strout T. The minimum clinically significant difference in patient-assigned numeric scores for pain. *Am J Emerg Med*. 2005;23:828–832.
18. Olsen MF, Bjerre E, Hansen MD, et al. : Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med*. 2017;15:35.
19. Myles PS, Myles DB, Galagher W, et al. Measuring acute postoperative pain using the visual analog scale: The minimal clinically important difference and patient acceptable symptom state. *Br J Anaesth*. 2017;118:424–429.