ANESTHESIOLOGY

Intrathecal Morphine *versus* Intrathecal Hydromorphone for Analgesia after Cesarean Delivery

A Randomized Clinical Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intrathecal opioids provide effective analgesia after cesarean delivery.
- Both intrathecal hydromorphone and morphine are now used in the context of multimodal postcesarean pain management plans, although little information regarding comparative effectiveness is available.

What This Article Tells Us That Is New

- In a randomized, double-blinded trial, intrathecal hydromorphone and intrathecal morphine were compared in women receiving cesarean delivery using pain score at 24 h as the primary outcome.
- The analgesia provided by morphine was not superior to that provided by hydromorphone. In addition, breakthrough analgesic requirements were similar for the two groups.

ABSTRACT

Background: Intrathecal opioids are routinely administered during spinal anesthesia for postcesarean analgesia. The effectiveness of intrathecal morphine for postcesarean analgesia is well established, and the use of intrathecal hydromorphone is growing. No prospective studies have compared the effectiveness of equipotent doses of intrathecal morphine *versus* intrathecal hydromorphone as part of a multimodal analgesic regimen for postcesarean analgesia. The authors hypothesized that intrathecal morphine would result in superior analgesia compared with intrathecal hydromorphone 24 h after delivery.

Methods: In this single-center, double-blinded, randomized trial, 138 parturients undergoing scheduled cesarean delivery were randomized to receive 150 μg of intrathecal morphine or 75 μg of intrathecal hydromorphone as part of a primary spinal anesthetic and multimodal analgesic regimen; 134 parturients were included in the analysis. The primary outcome was the numerical rating scale score for pain with movement 24 h after delivery. Static and dynamic pain scores, nausea, pruritus, degree of sedation, and patient satisfaction were assessed every 6 h for 36 h postpartum. Total opioid consumption was recorded.

Results: There was no significant difference in pain scores with movement at 24 h (intrathecal hydromorphone median [25th, 75th] 4 [3, 5] and intrathecal morphine 3 [2, 4.5]) or at any time point (estimated difference, 0.5; 95% CI, 0 to 1; $P = 0.139$). Opioid received in the first 24 h did not differ between groups (median [25th, 75th] oral morphine milligram equivalents for intrathecal hydromorphone 30 [7.5, 45.06] *vs.* intrathecal morphine 22.5 [14.0, 37.5], $P = 0.769$). From Kaplan–Meier analysis, the median time to first opioid request was 5.4 h for hydromorphone and 12.1 h for morphine (log-rank test $P = 0.200$).

Conclusions: Although the hypothesis was that intrathecal morphine would provide superior analgesia to intrathecal hydromorphone, the results did not confirm this. At the doses studied, both intrathecal morphine and intrathecal hydromorphone provide effective postcesarean analgesia when combined with a multimodal analgesia regimen.

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Spinal anesthesia is the most commonly used anesthetic technique for cesarean delivery in the United States and across the world.[1] Intrathecal opioids are frequently administered with a local anesthetic during spinal anesthesia for postcesarean analgesia. Intrathecal morphine is the most widely used opioid for postcesarean analgesia, and its effectiveness is well established.[2–6] The prevalence of drug shortages has impacted the supply of preservative-free morphine in the United States, and alternative analgesic options have been explored. Retrospective studies have compared intrathecal morphine to intrathecal hydromorphone.[7,8] In addition, one randomized study compared epidural morphine with epidural hydromorphone.[9] Previous work by our group found the effective dose for postoperative analgesia in 90% of patients (ED90) after cesarean delivery is 75 μg for intrathecal hydromorphone and 150 μg for intrathecal morphine when used as part of a multimodal analgesic

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regimen.[10] There is a paucity of literature prospectively comparing the clinical effect or side-effect profiles of intrathecal morphine *versus* hydromorphone for analgesia after elective cesarean delivery at equipotent doses.

After intrathecal administration, opioid drug disposition depends on its lipid solubility. Because of morphine's hydrophilic nature, cerebrospinal fluid concentrations of it decline more slowly than that of more lipophilic drugs. This likely accounts for morphine's increased rostral spread, greater dermatomal analgesia, and longer duration of action when compared with more lipophilic opioids such as fentanyl and sufentanil. Although hydromorphone and morphine have similar molecular structures, hydromorphone is more lipid-soluble. This difference in lipid solubility results in a relative decrease in the spread of hydromorphone within the intrathecal space and may influence the duration of action with intrathecal administration.[11,12] These differences in lipid solubility between the two medications may influence their duration of action when administered in the intrathecal space. Specifically, this could reduce the duration of action of intrathecal hydromorphone when compared with intrathecal morphine. Retrospective studies have shown that the analgesic benefit for intrathecal hydromorphone appears to extend at least 12 h after cesarean delivery and may extend up to 24 h.[10,13]

The aim of the current study was to compare the effectiveness and side-effect profiles of intrathecal morphine *versus* intrathecal hydromorphone for analgesia after cesarean delivery. The primary outcome was pain score with movement at 24 h after delivery. Our hypothesis was that intrathecal morphine would result in superior analgesia compared with intrathecal hydromorphone at 24 h after delivery as measured by dynamic pain scores when using equipotent doses.

Materials and Methods

The study was approved by the Mayo Clinic Institutional Review Board in Rochester, Minnesota, and the protocol was registered at ClinicalTrials.gov (NCT02789410) on June 3, 2016, by H.P.S. This article adheres to the Consolidated Standards of Reporting Trials guidelines. The trial was conducted in accordance to the original protocol, which is available upon request. The study was a double-blinded, parallel group, randomized clinical trial conducted at a single academic institution, Mayo Clinic Hospital (Rochester, Minnesota). Eligible patients were recruited to the study by a member of the study team upon admission to the labor and delivery unit on the day of their scheduled cesarean delivery. Inclusion criteria included American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status II or III, term gestation (37 to 42 weeks), and desire for a spinal anesthetic for cesarean delivery. Exclusion criteria included contraindication to spinal anesthesia; history of intolerance or adverse reaction to opioid medications; chronic pain syndrome or current opioid use of more than 30 oral morphine mg equivalents per day; allergy or intolerance to acetaminophen, ketorolac, ibuprofen, or oxycodone; or body mass index greater than 50 kg/m^2.

Patients provided written, informed consent and were randomly allocated to one of two study groups: 150 μg of intrathecal morphine or 75 μg of intrathecal hydromorphone. Before study commencement, the study statistician (D.R.S.) created a computer-generated randomization schedule using blocks of size N = 4 to allocate study arm assignments. Using this randomization schedule, sealed, sequentially numbered, opaque envelopes were created that contained the treatment assignments. Patients, obstetricians, outcome assessors, and study investigators were blinded to the treatment arm. An anesthesia provider not involved in clinical care or performing postoperative patient assessments opened the envelope and prepared the study drug. The study medication (either 0.15 ml of 1 mg/ml concentration morphine sulfate preservative-free or 0.75 ml of 100 μg/ml concentration hydromorphone hydrochloride preservative-free) was drawn up in a 1-ml syringe, and sterile saline was added to make the total volume 1 ml.

After randomization, an intravenous catheter was placed, and the patient was transported to the operating room, where standard ASA monitors were placed and a fluid co-load with Lactated Ringer's was started. With the patient in a sitting position, a 25-gauge Whitacre (BD Biosciences, USA) needle was introduced into the subarachnoid space at the L2-3, L3-4, or L4-5 interspace in a standard sterile fashion. After return of clear cerebrospinal fluid, 12 mg of bupivacaine (1.6 ml of 0.75% bupivacaine in 8.25% dextrose), 15 μg of fentanyl, and the allocated study drug were administered. The parturient was then placed in the supine position with left uterine displacement and an IV phenylephrine infusion was initiated at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with further titration at the discretion of the anesthesiologist with a goal of maintaining blood pressure within 20% of baseline. After delivery of the baby, oxytocin was administered per hospital protocol, and all patients were given IV 0.1 mg of granisetron or IV 4 mg of ondansetron for nausea prophylaxis. Supplemental intraoperative analgesia with IV 50 to 100 μg of fentanyl was administered at the discretion of the covering anesthesiologist.

Postoperatively, all patients were treated with a standardized multimodal analgesia regimen, including scheduled 1,000 mg of acetaminophen orally every 6 h and 15 mg of ketorolac IV every 6 h for three doses, which was then replaced with 600 mg of ibuprofen orally. Oral oxycodone was administered every 4 h as needed based on numeric rating scale pain scores: no oxycodone was administered for pain scores less than 4, 5 mg was administered for pain scores rated 4 to 6, and 10 mg was administered for pain scores rated 7 to 10 in intensity. Up to two doses of 50 μg of IV fentanyl were administered for severe pain unresponsive to the aforementioned interventions. Nausea was treated with granisetron (0.1 mg IV) and/or droperidol (0.625 mg IV) as needed. Pruritus was treated with nalbuphine (5 mg

IV) every 4 h as needed. Naloxone (0.2 mg IV) was administered for a respiratory rate of less than 8 or Richmond Agitation Sedation Scale of −3, −4, or −5. The Richmond Agitation Sedation Scale, a validated sedation metric, measures sedation from +4 (combative) to −5 (unarousable) on an integer scale, with −3 and −4 being moderate and deep sedation, respectively.[14] Patients were monitored with continuous pulse oximetry for the first 24 h after neuraxial opioid administration. Respiratory rate, oxygen saturation, and sedation were monitored every hour for the first 12 h and every 2 h for the subsequent 12 h by nursing staff. Any serious adverse events were to be reported to the Medical Director of Obstetric Anesthesia at Mayo Clinic Hospital, Dr. Hans P. Sviggum.

The patients were evaluated by study personnel every 6 h for the first 36 h after spinal administration. At each time point, the following were collected: pain score at rest, pain score with movement, highest pain score in the preceding 6 h, severity of nausea (none, mild, moderate, or severe), severity of pruritus (none, mild, moderate, or severe), and overall satisfaction with analgesia (satisfied, somewhat satisfied, neutral, somewhat dissatisfied, or dissatisfied). All pain scores were recorded on an integer 0 (no pain) to 10 (worst imaginable pain) numeric rating scale. Study personnel assessed the level of sedation and reviewed nurses' documentation for any episodes of respiratory depression. All assessments were done directly by study personnel, with the exception of any assessment occurring between 12:00 AM and 6:00 AM, which was usually the 18-h assessment. For this assessment, patients were asked to fill out a form with the above questions (except the sedation score) upon awakening as close to the scheduled assessment time as possible. Forms were collected by study personnel at the next scheduled assessment.

Maternal characteristics, including age, weight, height, ethnicity/race, gestational age, gravidity, parity, number of previous cesarean deliveries, and procedure length were recorded. Neonatal characteristics, including weight and Apgar scores, were collected. Additional information obtained from the electronic medical record included total opioid consumption at 24 and 36 h after study drug administration, medical treatments for nausea and pruritus in the first 24 and 36 h, and hospital length of stay. Opioid medications used were converted into oral morphine mg equivalents by multiplying by a factor of 0.3 for IV fentanyl, 15 for IV hydromorphone, 1.5 for oral oxycodone, and 0.1 for oral tramadol.[15] The data were entered into the Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, Tennessee) database.

The primary outcome was pain score with movement 24 h after spinal administration. Secondary outcomes included severity of opioid-related side effects, including pruritus, nausea, and sedation; total opioid consumption at 24 and 36 h; pain score at rest at each time point; and the number of treatments for nausea and pruritus at 24 and 36 h, postoperatively.

Statistical Analysis

Continuous variables are summarized using means ± SD or median (25th, 75th), and categorical variables are summarized using frequency counts and percentages. Only those subjects with data available at any given time point were included in the analysis. The primary outcome of interest was pain score with movement at 24 h after delivery. To accommodate skewed distributions, pain scores, the amount of opioid received, and hospital length of stay were compared between groups using the nonparametric Wilcoxon rank sum test. Opioid side effects were compared between groups using Fisher's exact test. For the primary outcome, the estimated difference between groups was quantified using the Hodges–Lehmann estimator. In all cases, two-tailed P values of <0.05 were considered statistically significant. The median time to first request for postoperative opioid was determined using the Kaplan–Meier method with data censored at 24 h for patients who did not request opioids in the first 24 postoperative hours. Time to first request for postoperative opioid was compared between groups using the log-rank test and also using proportional hazards regression with results summarized by presenting the point estimate and 95% CI for the hazard ratio for hydromorphone *versus* morphine. For this analysis, the assumption of proportional hazards was assessed by plotting the scaled Schoenfeld residuals *versus* the time of first opioid. Based on previous work by Sviggum *et al.*,[10] it was hypothesized that the SD of the numeric rating scale pain score at 24 h was 1.75 units. Under this assumption, it was determined that a sample size of n = 65/group would provide statistical power (two-tailed test, $\alpha = 0.05$) of approximately 90% to detect a difference between groups of 1.0 unit. Under the assumption that up to 5% of randomized subjects may be excluded for various reasons (*e.g.*, unable to place spinal) a total sample-size of N = 138 was used. All analyses were performed using SAS software (version 9.4, SAS Institute Inc., USA).

Results

From May 2016 through August 2017, 154 patients were approached about the study, and 138 were randomized to either the intrathecal hydromorphone group (n = 69) or the intrathecal morphine group (n = 69). Enrollment for the study ceased when the target sample size was obtained. A total of 134 women were included in the final analysis, with 66 women in the intrathecal hydromorphone group and 68 women in the intrathecal morphine group (fig. 1). Demographic and baseline characteristics were similar between study groups (table 1).

Pain Scores

At 24 h (primary outcome), there was not a significant difference between groups in pain with movement (table 2). There was no significant difference between pain scores with movement at

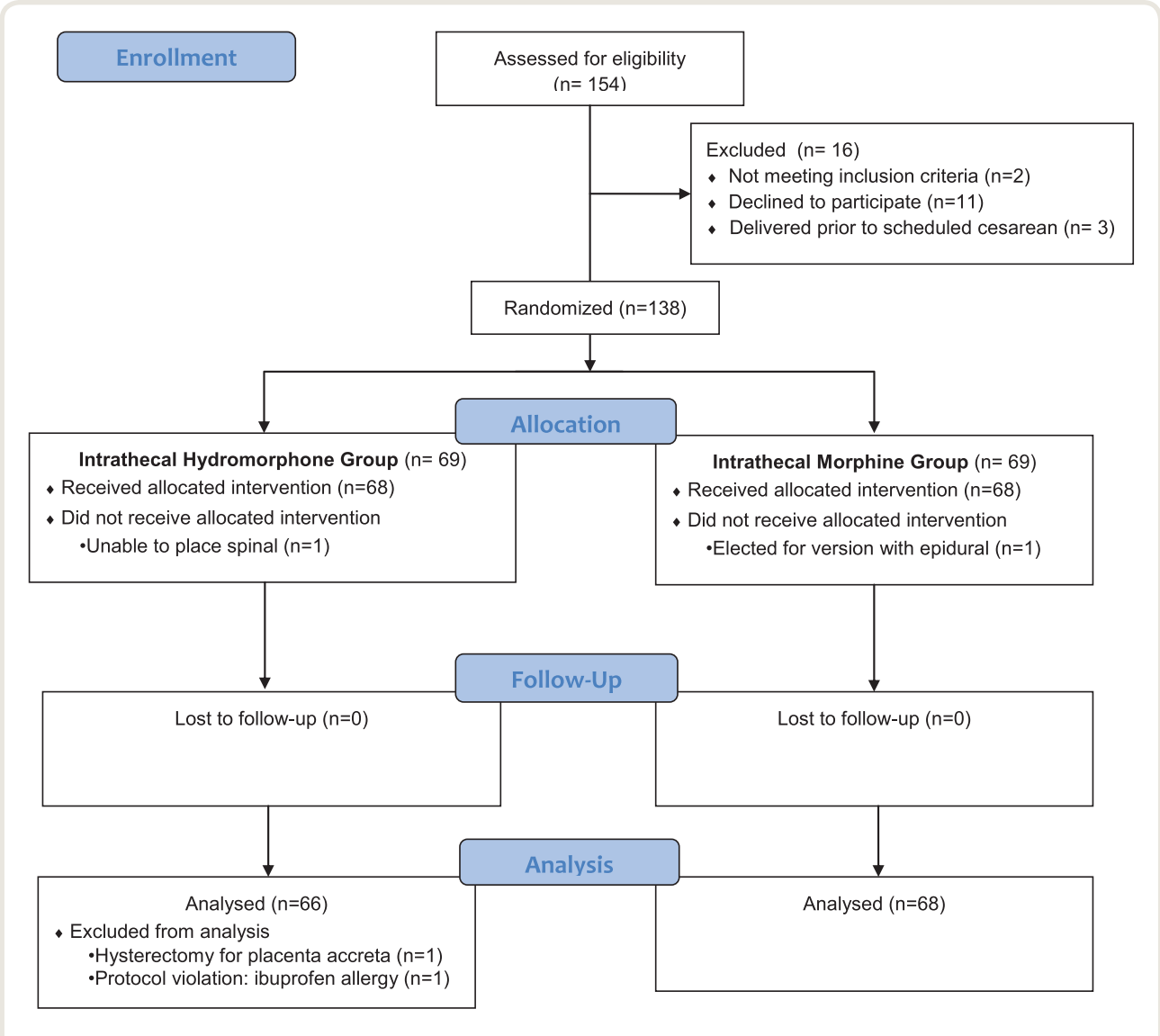

Fig. 1. Consolidated standards of reporting trials flow diagram.

any time point. Maximum pain scores did not differ between the two groups at any time point. There was a statistically significant decrease in pain scores at rest for the intrathecal morphine group at 18 h ($P = 0.035$; table 2). There was no significant difference between pain scores at rest at any other time point. For each of the three pain scores (pain at rest, pain with movement, and highest pain), the area under the curve over the first 36 h did not differ significantly between groups.

Opioid Use

Opioid use between the two groups was not significantly different (table 3). In the first 24 h, the percentage of parturients who received opioids was 71% (47 of 66) in the intrathecal hydromorphone group and 65% (44 of 68) in the intrathecal morphine group ($P = 0.463$). Among parturients who received opioids, the median (interquartile range) was 30.0 mg (7.5, 45.0) of oral morphine equivalents in the intrathecal hydromorphone group compared with 22.5 mg (15.0, 37.5) of oral morphine equivalents in the intrathecal morphine group ($P = 0.769$). There was no difference in the time to the first request for postoperative opioid between the groups (hazard ratio = 1.31; 95% CI, 0.87 to 1.97; fig. 2). From Kaplan–Meier analysis, the median time to the first opioid was 5.4 h for hydromorphone and 12.1 h for morphine (log-rank test $P = 0.200$).

Side Effects

There was no significant difference in the number of patients who reported moderate or severe symptoms and

Table 1. Baseline Characteristics of Patients by Treatment Group

Characteristic	Hydromorphone (N = 66)*	Morphine (N = 68)*	*P* Value
Age, yr	31.4 ± 4.3	31.9 ± 4.3	0.411
Height, cm	164.6 ± 7.2	165.4 ± 6.7	0.407
Weight, kg	77.8 ± 19.2	78.3 ± 18.2	0.735
Body mass index, kg/m^2	28.6 ± 6.4	28.5 ± 6.2	0.942
Gravidity			0.216
1	9 (14)	10 (15)	
2	25 (38)	34 (50)	
3	21 (32)	16 (24)	
≥4	11 (16)	8 (12)	
Parity			0.534
0	11 (17)	13 (19)	
1	33 (50)	35 (51)	
2	18 (27)	18 (26)	
≥ 3	4 (6)	2 (3)	
Previous cesareans			0.850
0	18 (27)	19 (28)	
1	35 (53)	37 (54)	
≥ 2	13 (20)	12 (18)	
Tubal ligation			0.313
No	53 (80)	59 (87)	
Yes	13 (20)	9 (13)	
Time of spinal placement			0.290
06:00–09:59	49 (74)	41 (60)	
10:00–13:59	15 (23)	24 (35)	
14:00–17:59	1 (2)	3 (4)	
18:00–21:59	1 (2)	0 (0)	
Duration of surgery, min			0.369
Median (25th, 75th)	59 (51, 69)	62 (50, 78)	
Minimum, maximum	35 to 111	30 to 204	
Gestational age, weeks			0.173
Median (25th, 75th)	39.0 (39.0, 39.2)	39.1 (39.0, 39.2)	
Range	37.0 to 40.4	37.0 to 40.3	
Fetal weight, g			0.393
Median (25th, 75th)	3,410 (3,070, 3,685)	3,460 (3,250, 3,730)	
Range	2,090 to 4,440	2,590 to 4,370	
Apgar at 1 min*			0.496
Median (25th, 75th)	8 (8, 9)	9 (8, 9)	
Range	1 to 9	3 to 9	
Apgar at 5 min*			0.044
Median (25th, 75th)	9 (9, 9)	9 (9, 9)	
Range	7 to 9	7 to 9	

The data are presented using means ± SD or median (25th, 75th) for continuous variables and n (%) for categorical variables. Tubal ligation was compared between groups using the chi-square test, and all other characteristics were compared between groups using the rank sum test.

*For the morphine group, the data are summarized for 67 newborns. The data are excluded for one subject who delivered twins.

no difference in those who required treatment for either nausea or vomiting (table 3). Nausea significant enough to require medication administration in the first 24 h occurred in 22 of 66 (33%) patients in the intrathecal hydromorphone group and 22 of 68 (32%) patients in the intrathecal morphine group ($P > 0.999$). There was no difference in the number of patients that required medical intervention for pruritus in the intrathecal hydromorphone group (7 of 66; 11%) compared with the intrathecal morphine group (13 of 68; 19%; $P = 0.226$). There were no episodes of respiratory depression in any patients in either group as indicated by respiratory rate less than 8 breaths/min or a desaturation event with oxygen saturation less than 92%. The sedation score did not differ between groups. The length of hospital stay did not differ between groups.

The percentage of patients who were not satisfied with their pain control at one or more time points (rated their satisfaction as "neutral," "somewhat dissatisfied," or "dissatisfied") did not differ between groups (intrathecal hydromorphone, 5 of 66 [8%]; and intrathecal morphine, 7 of 68 [10%]; $P = 0.764$). Among those patients who were not satisfied, 92% (11 of 12) received additional opioids postoperatively compared with 66% (80 of 122) of patients who were satisfied (which included patients reporting "somewhat satisfied" or "satisfied" only; $P = 0.065$). Among those who received additional postoperative opioids, those who were

Table 2. Pain Outcomes

Characteristic	Hydromorphone (N = 63†)	Morphine (N = 66†)	Estimated Difference* Estimate	95% CI	*P* Value
6 h					
Pain at rest	2 (1, 3)	2 (1, 2.5)	0.5	(0, 1)	0.371
Pain with movement	3 (2, 6)	4 (3, 5)	-0.5	(–1, 0)	0.183
Highest pain	4 (2, 6)	5 (4, 6)	-0.5	(–1, 0)	0.202
12 h					
Pain at rest	1 (0, 2)	1 (0, 2)	0.5	(0, 1)	0.227
Pain with movement	3 (2, 4)	3 (2, 4)	0	(–1, 1)	0.751
Highest pain	4 (3, 6)	4 (3, 5.5)	0	(–1, 1)	0.765
18 h					
Pain at rest	2 (1, 4)	2 (0, 2)	0.5	(0, 1)	0.035
Pain with movement	3.5 (3, 6)	4 (2, 4)	0.5	(0, 1)	0.137
Highest pain	4 (3, 6)	4 (3, 5)	0	(–1, 1)	0.596
24 h					
Pain at rest	2 (1, 2)	1 (0.5, 2)	0.5	(0, 1)	0.318
Pain with movement	4 (3, 5)	3 (2, 4.5)	0.5	(0, 1)	0.139
Highest pain	4 (3, 5)	4 (3, 6)	0	(–1, 1)	0.543
30 h					
Pain at rest	2 (1, 3)	2 (1, 3)	0.5	(0, 1)	0.241
Pain with movement	4 (3, 6)	4 (3, 5)	0.5	(0, 1)	0.155
Highest pain	5 (4, 6)	5 (3, 6)	0	(–1, 1)	0.839
36 h					
Pain at rest	2 (1, 3)	2 (1, 3)	0	(–1, 1)	0.941
Pain with movement	4 (3, 6)	4 (3, 5)	0.5	(0, 1)	0.526
Highest pain	5 (3.5, 6)	5 (4, 6)	0.5	(0, 1)	0.402
Area under the curve					
Pain at rest	1.8 (1.0, 2.7)	1.5 (1.0, 2.3)	0.25	(–0.17, 0.67)	0.173
Pain with movement	3.7 (2.8, 5.2)	3.8 (2.7, 4.8)	0.25	(–0.33, 0.83)	0.469
Highest pain	4.5 (3.2, 5.8)	4.5 (3.3, 5.3)	0.08	(–0.50, 0.67)	0.298

The data are summarized using median (25th, 75th) and compared between groups using the rank sum test.

*For the hydromorphone group data were available for 64 subjects at 12 and 36 h and 65 subjects at all other time points. For the morphine group data were available for 66 subjects at 36 h, 67 subjects at 18 and 30 h, and 68 subjects at all other time points. The area under the curve was calculated for subjects who had data available for all time points (N = 63 and N = 66 for hydromorphone and morphine, respectively). †Hodges–Lehmann estimated difference between groups (hydromorphone – morphine).

not satisfied with their analgesia at one or more time points received significantly ($P = 0.023$) higher doses of opioids in comparison with those who were satisfied (median [25th, 75th]: 45 mg [33, 75] oral morphine equivalents for those who were unsatisfied *vs.* 22.5 mg [7.5, 37.5] oral morphine equivalents for those satisfied with their analgesia).

Discussion

The main finding of this randomized clinical trial was that pain scores with movement at 24 h were not different between patients receiving intrathecal morphine and intrathecal hydromorphone as part of a multimodal analgesic regimen for scheduled cesarean delivery. In addition, there were no differences in pain with movement or maximum pain at any time point from 6 to 36 h after delivery. Side effects including nausea, pruritus, and respiratory depression also did not differ. Of note, the median time to first opioid was 5.4 h for intrathecal hydromorphone and 12.1 h for intrathecal morphine. Although not statistically different, this difference may be clinically relevant.

The gold standard for analgesia after cesarean delivery is neuraxial morphine. Our group previously determined the ED90 for intrathecal morphine to be 150 μg and that for intrathecal hydromorphone to be 75 μg based on pain scores measured 12 h after administration.[10] An additional study by Lynde[16] determined the ED50 of hydromorphone for postoperative analgesia after cesarean delivery to be 4.6 μg based on pain scores measured 12 h after administration. However, the duration of analgesia and side-effect profiles of the two medications had not been prospectively compared. Beatty *et al.*[7] retrospectively compared parturients who received 100 μg of intrathecal morphine and 40 μg of intrathecal hydromorphone and did not find a statistically significant difference in median total opioid consumption and pain scores in the first 24 h. However, Marroquin *et al.*[8] retrospectively compared both epidural and intrathecal morphine and hydromorphone and found that 60 μg of intrathecal hydromorphone had a shorter duration of analgesia than 200 μg of intrathecal morphine. They were unable to collect pain scores in their study. Neither of these aforementioned studies likely utilized the two drugs in equipotent doses.[7,8]

Table 3. Other Outcomes

Characteristic	Hydromorphone (N = 66)	Morphine (N = 68)	*P* Value*
In the first 24 h			
Opioid†			
Any received	47 (71)	44 (65)	0.463
Amount received‡, mg	30.0 (7.5, 45.0)	22.5 (15.0, 37.5)	0.769
Nausea			
Self-report or treatment§	30 (45)	32 (47)	0.864
Treatment	22 (33)	22 (32)	> 0.999
Pruritus			
Self-report or treatment§	41 (62)	41 (60)	0.861
Treatment	7 (11)	13 (19)	0.226
Sedation‖	1 (2)	3 (4)	0.321
Unsatisfied with analgesia	5 (8)	7 (10)	0.764
Hospital length of stay, days			0.814
1	1 (2)	1 (1)	
2	23 (35)	23 (34)	
3	42 (64)	43 (63)	
4	0 (0)	1 (1)	

All values reported as n (%) except as noted.

*The amount of opioid received and the hospital length of stay are compared between groups using the rank sum test. Other characteristics are compared between groups using Fisher's exact test. †Does not include intraoperative fentanyl. ‡Only those who received opioids are included (N = 47 and N = 44 for hydromorphone and morphine respectively), reported as medians (25th, 75th). Reported in oral morphine milligram equivalents. §Defined as reporting symptoms as moderate or severe or receiving pharmacologic treatment for symptoms. ‖Defined as any negative score on the Richmond Agitation Sedation Scale.

Unfortunately, guidelines for the equianalgesic conversion of intrathecal morphine to hydromorphone are not yet established, leaving clinicians to rely on expert opinion, clinical experience, and data in parenteral dosing studies. Given the different mechanism of action of intrathecal opioids from parenteral opioids, common parenteral conversion factors may not translate to the intrathecal route.[17] Rathmell *et al.*[12] report that 100 to 200 μg of intrathecal morphine produces similar analgesia to 50 to 100 μg of intrathecal hydromorphone, suggesting an approximate 2:1 morphine:hydromorphone ratio. The two prospective dose-finding studies by Lynde[16] and Sviggum *et al.*[10] and three retrospective studies[7,8,13] utilized a wide dose range of intrathecal hydromorphone from 4.6 to 100 μg. Given these limited data, we chose to evaluate intrathecal morphine to intrathecal hydromorphone at a 2:1 ratio based chiefly on our previously published work evaluating equipotency in a similar patient population.[10]

Our hypothesis was that at these previously established equipotent doses, intrathecal morphine would result in superior analgesia at 24 h than intrathecal hydromorphone, but our results did not confirm this. We found no statistically significant difference in reported pain scores with movement at 6, 12, 18, 24, 30, and 36 h. Curiously, there was a single time point at 18 h where pain scores at rest were significantly lower in the intrathecal morphine group. However, given the lack of statistical difference with movement at this time point and the lack difference in pain scores at any other time point, this statistical finding has unclear significance.

Although the difference in median time to first opioid use (5.4 h intrathecal hydromorphone *vs.* 12.1 h intrathecal morphine) was not statistically significant, it is arguably clinically relevant. In addition, the median oral morphine equivalents between the groups (30 mg of intrathecal hydromorphone *vs.* 22.5 mg of intrathecal morphine) may be considered clinically relevant. It is possible that our study was underpowered to detect a subtle superiority of intrathecal morphine over intrathecal hydromorphone in terms of postoperative opioid use. Additional study is required to further explore these associations.

Although effective in reducing pain, intrathecal opioids are associated with side effects including pruritus, nausea, and respiratory depression. A meta-analysis reviewing 28 studies that investigated intrathecal morphine *versus* placebo demonstrated moderately increased incidences of pruritus, nausea, and vomiting.[3] In fact, the incidence of nausea with intrathecal morphine has been reported to be up to 52%[3,18,19] with increased nausea or vomiting with increasing dose. The differences in pharmacokinetics between morphine and hydromorphone may result in differences in side-effect profiles. Hydromorphone has less hydrophilicity than morphine and less rostral spread, which theoretically could result in less pruritus and nausea. Although some studies have found that neuraxial hydromorphone produces fewer side effects (including pruritus) than morphine,[20,21] most obstetric studies have not found a difference.[7–9] This study also found no difference between these two medications.

Although nausea and pruritus are two of the most common side effects of intrathecal opioids, sedation and respiratory depression are the most concerning. In this study, sedation scores did not differ between the two groups, and there were no cases of respiratory depression in either group. Recently, the Society for Obstetric Anesthesia and Perinatology (Milwaukee, Wisconsin) published a consensus statement on monitoring and treatment for neuraxial opioid-induced respiratory depression.[22] This statement states that "hydromorphone has not been studied as thoroughly and lacks the track record of safety that neuraxial morphine has, and therefore if available, intrathecal morphine is the preferred single-shot intrathecal opioid in this setting."[22] Because clinically significant respiratory depression is a rare event, it will be necessary to report the sedation and respiratory depression outcomes for a large number of patients to evaluate the safety of neuraxial hydromorphone for this side effect. The results of the current study add to previous studies of intrathecal hydromorphone for postcesarean analgesia that have reported no cases of respiratory depression.[7,8,10,13]

Drug shortages are an ongoing problem worldwide. A study of Canadian anesthesiologists found approximately 66% of survey respondents had experienced a shortage of one or more anesthesia or critical care medications, and

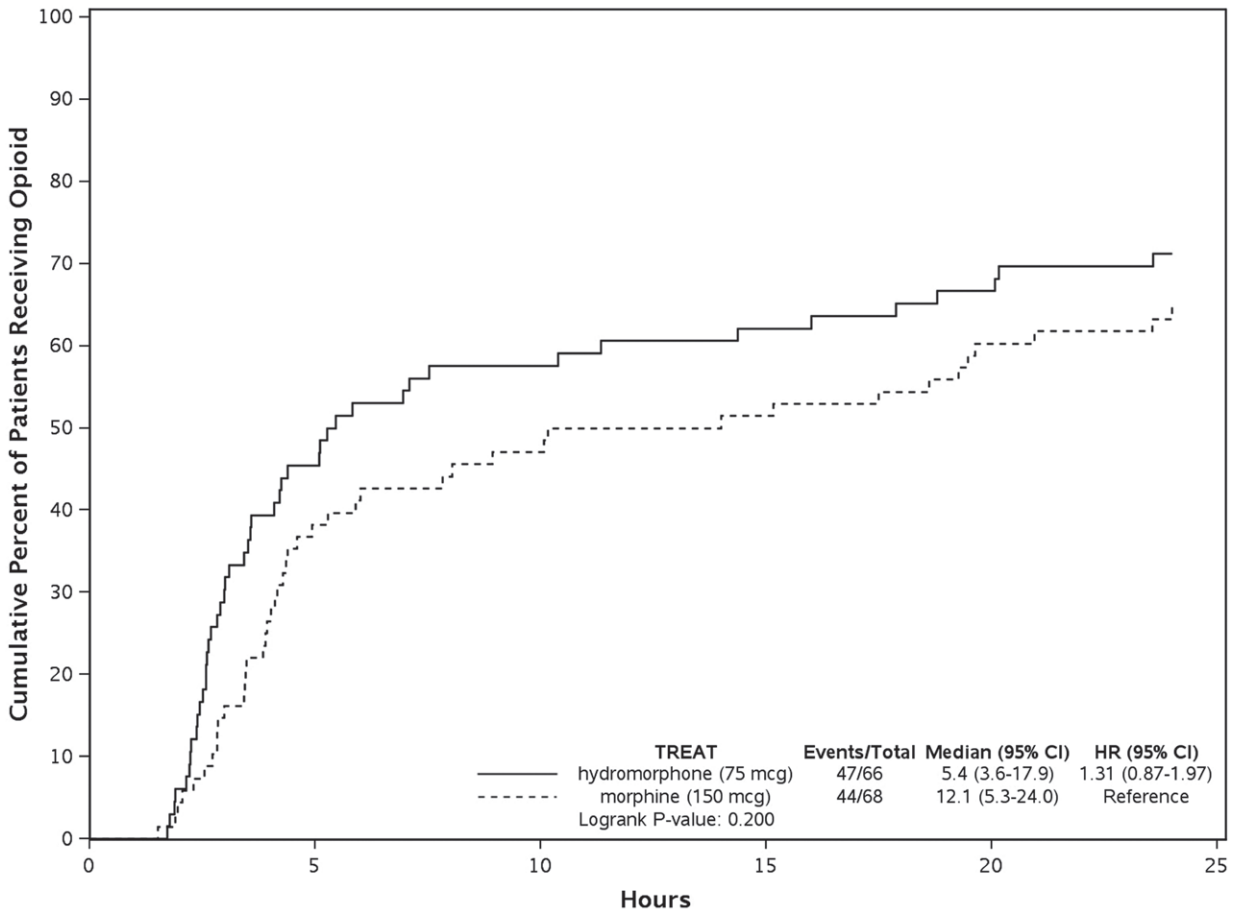

Fig. 2. Cumulative incidence of postoperative opioid use. Kaplan–Meier plot showing the cumulative incidence of postoperative opioid use over the first 24 h according to the treatment group. The median time to the first opioid was 5.4 h for hydromorphone and 12.1 h for morphine (log-rank test $P = 0.200$). HR, hazard ratio.

15.2% had experienced a shortage of an opioid medication in the prior year. Additionally, 49% of respondents believed that as a result of drug shortages, they had given an inferior anesthetic, and 30% were giving medications with which they were unfamiliar.[23] Recently, there has specifically been a shortage of preservative-free morphine in the United States. The results of this study should provide reassurance to anesthesiologists that intrathecal hydromorphone could be a reasonable substitute with similar clinical effect and side-effect profile to intrathecal morphine.

This study has a few limitations. Notably, pain scores during movement at 24 h may not be the most ideal endpoint for determining the effectiveness of analgesic medications. This primary endpoint was chosen based on the expected duration of analgesia of the medications, its importance to patient satisfaction, and the clarity of data collection and comparison. Using a different primary endpoint (*e.g.*, opioid consumption) or coprimary endpoints might have altered the results. Second, the use of multimodal analgesia, including intrathecal fentanyl, although appropriate in clinical practice, potentially limits the observed difference in pain scores between groups. It is possible that eliminating scheduled acetaminophen, nonsteroidal anti-inflammatory drugs, and intrathecal fentanyl could have changed the observed pain scores and analgesic use in such a way that group differences would have been apparent. Third, we did not employ a standardized methodology for obtaining pain scores with movement, which could have confounded the reported scores. The ED90 for intrathecal hydromorphone and intrathecal morphine were based on achieving a pain score of 3 or less at 12 h in our prior study.[10] The 2:1 ratio of morphine to hydromorphone used in this study resulted in no statistically significant differences in postoperative analgesia. Using a different ratio of intrathecal morphine to intrathecal hydromorphone (*e.g.*, 3:1) may have created clinical outcome differences in postcesarean analgesia and likely side effects. Functional recovery measures, although more difficult to obtain, may provide a more holistic view

of patient well-being. Additionally, although we powered our study to have a 90% probability of detecting a statistically significant difference in the numeric pain rating scale of 1 or more points (two-tailed test, $\alpha = 0.05$), this study may have been underpowered to detect clinically significant differences in our secondary outcomes. For example, the estimated median time to first request for postoperative opioids was 5.4 h *versus* 12.1 h for patients receiving hydromorphone *versus* morphine, and based on the 95% CI for the hazard ratio (0.87 to 1.97), our study cannot rule out the possibility that outcome occurs substantially sooner for those receiving hydromorphone. The results of the present study may not be generalizable to patients with chronic pain or opiate use. Last, although considerable effort was made to collect data at multiple meaningful time points, it is possible that meaningful differences might have been apparent if an alternative timing of data collection had been used.

In conclusion, this study demonstrates that the use of 75 μg of intrathecal hydromorphone for cesarean delivery produces postoperative analgesia of similar effectiveness at 24 h as that produced by 150 μg of intrathecal morphine when used as part of a multimodal analgesic regimen. Additionally, the side-effect profile between these medications is similar. Anesthesia providers should feel comfortable administering either intrathecal hydromorphone or intrathecal morphine as part of a multimodal analgesic regimen to care for patients undergoing cesarean delivery.

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Competing Interests

The authors declare no competing interests.

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