REPORTS OF ORIGINAL INVESTIGATIONS

The median local analgesic dose of intrathecal bupivacaine with hydromorphone for labour: a double-blind randomized controlled trial

La dose médiane de bupivacaïne intrathécale avec hydromorphone comme analgésique local pour le travail obstétrical: une étude randomisée contrôlée à double insu

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Abstract

Purpose Neuraxial hydromorphone has been reported to provide rapid onset of labour analgesia, effective segmental pain relief, and a longer duration of action than commonly used lipophilic opioids. This study was conducted to test the hypothesis that intrathecal hydromorphone reduces the dose requirement for intrathecal bupivacaine to induce rapid analgesia for women in the first stage of labour.

Methods In this double-blind randomized controlled sequential allocation trial, 88 labouring parturients received combined spinal-epidural analgesia at 2-6 cm cervical dilation. Participants received intrathecal bupivacaine alone or bupivacaine plus hydromorphone 100 μg with the bupivacaine dose determined using up-down sequential allocation. An effective dose was defined as a visual analogue pain score of ≤10 mm (on a 100-mm pain scale) reported within 20 min of injection. The median effective doses were calculated using the formula of Dixon and Massey and verified using isotonic regression.

Results A decrease was observed in the median local analgesic doses (effective dose [ED50]) estimated according to the formulas of Dixon and Massey, with a between-group difference of −0.45 mg. The precision of the estimate was wide-ranging (95% confidence interval −1.23 to 0.33), so no definitive conclusion can be drawn.

Conclusion Further research is needed to determine whether or not intrathecal hydromorphone 100 μg changes the dose of intrathecal bupivacaine required to induce labour analgesia within 20 min.

Trial registration The trial was conducted in 2007 prior to widespread acceptance of the standard for clinical trial registration.

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Résumé

Objectif Il a été décrit que l'hydromorphone administrée par voie neuraxiale favorisait l'installation rapide de

l'analgésie pour le travail obstétrical, un soulagement efficace de la douleur segmentaire, et une durée d'action prolongée comparativement aux opioïdes lipophiles couramment utilisés. Cette étude a été réalisée afin de tester l'hypothèse selon laquelle l'hydromorphone administrée par voie intrathécale réduirait la dose requise de bupivacaïne intrathécale pour induire une analgésie rapide chez les femmes au premier stade du travail obstétrical.

Méthode *Dans cette étude d'attribution séquentielle randomisée contrôlée à double insu, 88 parturientes en travail obstétrical ont reçu une analgésie rachi-péridurale combinée lorsque leur dilatation cervicale était située entre 2 et 6 cm. Les participantes ont reçu de la bupivacaïne intrathécale seule ou de la bupivacaïne avec 100 μg d'hydromorphone; la dose de bupivacaïne a été déterminée selon une méthode d'attribution séquentielle verticale (up-down). On a défini la dose efficace comme un score de douleur sur l'échelle visuelle analogique ≤ 10 mm (sur une échelle de douleur de 100 mm) rapporté dans les 20 min suivant l'injection. Les doses efficaces moyennes ont été calculées à l'aide de la formule de Dixon et Massey et vérifiées par régression isotonique.*

Résultats *Une réduction a été observée dans les doses moyennes d'analgésique local (dose efficace [DE50]) estimées selon la formule de Dixon et Massey, et une différence de −0,45 mg a été observée entre les groupes. La précision de cet estimé était faible (intervalle de confiance 95 % −1,23 à 0,33); par conséquent, aucune conclusion définitive n'a pu être tirée.*

Conclusion *Des recherches supplémentaires sont nécessaires afin de déterminer si l'administration de 100 μg d'hydromorphone intrathécale modifie la dose de bupivacaïne intrathécale nécessaire à induire l'analgésie du travail obstétrical en 20 minutes.*

Enregistrement de l'étude *Cette étude a été réalisée en 2007, soit avant que l'enregistrement des études cliniques ne soit devenu la norme acceptée.*

Lipophilic opioids, such as fentanyl and sufentanil, play an important role in contemporary neuraxial labour analgesia. Nevertheless, high lipid solubility increases systemic absorption and reduces bioavailability in the dorsal horn of the spinal cord.[1] The hydrophilic opioid, hydromorphone, has been proposed as an alternative that may offer enhanced bioavailability and result in a more favourable ratio of analgesia to side effects when compared with lipophilic fentanyl or sufentanil. In previous clinical studies, spinal or epidural hydromorphone in combination with bupivacaine has been reported to have relatively quick onset (5-20 min)[2,A] and to deliver primarily segmental analgesia with high analgesic potency.[3] These trials employed a relatively high dose of bupivacaine (2.5 mg in the spinal space[A] or 8-10 mL of a 0.25% solution in the epidural space)[2]; therefore, it is not clear if the rapid onset was a function of the hydromorphone or the co-administered bupivacaine.

We designed this randomized double-blind sequential allocation study to test the hypothesis that intrathecal hydromorphone reduces the dose requirement for intrathecal bupivacaine to achieve rapid analgesia for women in the first stage of labour. Our primary outcome was the median effective dose (ED50) of intrathecal bupivacaine. Specifically, a statistically significant decrease in the ED50 of intrathecal bupivacaine—also known as the minimum local anesthetic dose—in the presence of co-administered hydromorphone 100 μg would indicate a dose-sparing effect when compared with bupivacaine alone. Secondary outcomes included potential side effects of intrathecal hydromorphone, including nausea, itching, sedation, bradypnea, or nonreassuring fetal heart rate patterns.

Methods

The study was approved by the Institutional Review Board of the University of Michigan Medical School (HUM#00010064, approved January 11, 2007) and was funded by the Department of Anesthesiology. All patients were recruited at the time of admission for labour and delivery and gave written informed consent. We included American Society of Anesthesiologists physical status I and II women with singleton term pregnancies (> 36 weeks' gestation), vertex fetal presentation, and in active labour who anticipated neuraxial analgesia and vaginal delivery. Exclusion criteria included difficulty understanding English, contraindications to neuraxial analgesia, allergy to bupivacaine or hydromorphone, severe preeclampsia, known fetal abnormality, and a body mass index > 40. A research assistant screened potential subjects at the time of admission and recruited those meeting eligibility criteria. We enrolled and randomized patients at the time of neuraxial block placement after excluding those patients with a visual analogue pain score < 50 mm (on a 100-mm pain scale),

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[A] *Tiouririne M, Holiday J, Durieux M, Wheeler A*. Duration of intrathecal hydromorphone for labor analgesia. Anesthesiology 2006; 105: A915.

cervical dilation > 7 cm, or opioid medication administered within the previous two hours. All study-related procedures took place on the University of Michigan Labour and Delivery Unit.

Participants were randomized to receive either intrathecal bupivacaine (bupivacaine hydrochloride; Hospira, Inc., Lake Forest, IL, USA) alone or intrathecal bupivacaine in combination with hydromorphone 100 μg (hydromorphone hydrochloride; Hospira, Inc., Lake Forest, IL, USA). The hydromorphone dose was based on an observational trial in which the combination of intrathecal bupivacaine 1.3 mg and hydromorphone 100 μg provided effective labour analgesia within seven minutes with minimal side effects.[A] The first patient studied in each group received bupivacaine 2.5 mg, and thereafter, the dose of bupivacaine in each individual syringe was determined by the response of the previous patient in that group according to up-down sequential allocation. The testing interval was bupivacaine 0.25 mg for all groups.[4]

An investigator with no other study responsibilities (M.G.) implemented a simple randomization scheme in Excel by generating the sequence 1-100 and assigning the numbers 1-50 to control and 51-100 to hydromorphone. The order of the numbers was then randomized using Excel's RAND function to produce the treatment allocation sequence, which was maintained on a secure network drive. This investigator recorded patient outcomes, as reported by the investigator responsible for data interpretation (L.P.), tracked and reported adverse events to the Institutional Review Board, and used the allocation sequence and prior subject outcomes to assign the group (hydromorphone or control) and dose of bupivacaine for each upcoming patient. Two anesthesiologists not involved in recruitment, data collection, or direct patient care (J.M. and R.H.) prepared syringes of the blinded study solution within 30 hr of administration using preservative-free normal saline, 0.25% wt/vol plain bupivacaine and preservative-free hydromorphone to achieve the desired doses of bupivacaine and hydromorphone at room temperature (20°C) in a standardized volume of 2.5 mL. Study patients, physicians and nurses, and research assistants responsible for recruitment, enrolment, and study implementation were unaware of treatment assignments at any time during the study. Study coordination is illustrated in the Appendix as Electronic Supplementary Material.

Study medications were administered using a combined spinal-epidural technique. After intravenous prehydration with lactated Ringer's solution 500-1000 mL, patients were placed in the flexed sitting position. After raising a midline wheal with 1.0% wt/vol lidocaine, the epidural space was identified using an 18-G Tuohy needle with loss of resistance to saline (1-5 mL) at L2-3 or L3-4. A 25-G 119-mm Whitacre spinal needle was placed through the Tuohy needle at a depth sufficient to puncture the dura mater and obtain cerebrospinal fluid. The study drug solution was then injected in a 2.5 mL volume. After the Whitacre needle was withdrawn, a three-hole polyamide catheter (Portex[TM], Smiths Medical, London, UK) was advanced 4-5 cm into the epidural space in a cephalad direction for subsequent epidural labour analgesia. The epidural catheter was secured using a sterile transparent occlusive dressing at the skin. Catheter placement was confirmed using aspiration. A test dose of lidocaine with epinephrine was deferred until study data had been collected. After catheter placement, the parturient was placed in the supine position with left uterine displacement and 30° elevation of the head of the bed. Time zero was defined as the end of the intrathecal injection.

The efficacy of the study drug was assessed by the patient using a 100-mm vertical visual analogue pain scale (VAPS) with the anchors "no pain" and "worst pain ever." The VAPS was recorded at five-minute intervals for 20 min following intrathecal injection.

An *effective* dose, defined as a VAPS ≤ 10 mm within 20 min of injection[4-7] directed a decrement of bupivacaine 0.25 mg for the next patient randomized to that group. The duration of effective spinal analgesia (defined as the time interval from the intrathecal injection to the time when the parturient experienced her first painful contraction) was recorded. At that time, the patient received a standard epidural test dose of 1.5% lidocaine 3 mL with epinephrine 1:200,000 followed by a bolus and infusion of 0.05% bupivacaine with fentanyl 3 μg·mL^{-1}. Subsequent epidural catheter management was at the discretion of the clinical care team. An *ineffective* dose was defined as a VAPS > 10 mm at 20 min after injection, with pain located within the T8-L5 dermatomes. An ineffective result directed an increase of bupivacaine 0.25 mg for the next patient randomized to that group. The trial was *rejected* if the spinal space could not be identified, if the patient progressed to the second stage of labour in < 60 min, if the source of pain underlying a VAPS > 10 mm originated outside the T8-L5 dermatome, or in cases of protocol violations. When the trial was rejected, the same dose of bupivacaine was repeated for the next participant randomized to the same group. In cases where the trial was ineffective or rejected, the epidural catheter was dosed as described above after 20 min.

The following data were recorded for all women at the time of combined spinal-epidural insertion: age, weight, height, ethnicity, gestational weeks, parity, cervical dilation, membrane status (spontaneously ruptured, artificially ruptured, or intact), the use of pharmacologic agents to induce or to augment labour (including oxytocin, vaginal misoprostol, vaginal dinoprostone, and vaginal laminaria), baseline maternal and fetal vital signs (blood pressure, heart

rate, respiratory rate, and cardiotocography), maternal pain, nausea (measured using a 100-mm visual analogue scale [VAS] with the anchors "no nausea" and "the most severe nausea you can imagine"), pruritus (measured using a 100-mm VAS with the anchors "no pruritus" and "the most severe pruritus you can imagine"), and maternal sedation (assessed by any decrease in response to verbal stimulation).

After intrathecal injection, maternal monitoring included blood pressure, heart rate, and pulse oximetry measurements every five minutes during the first 20 min and again at 30 min. Hypotension was defined as a systolic blood pressure < 100 mmHg or a 20% fall below the baseline recording. Hypotension was treated with ephedrine 5 mg with additional doses as required and intravenous fluid boluses. The VAPS was measured every five minutes during the first 20 min for all patients and then at 60 and 120 min for women with effective analgesia. Sensation to pinprick using a Neuropen® (Owen Mumford Ltd, Woodstock, UK) was measured at 20 min and again at 60 and 120 min. Additional measurements at 20, 60, and 120 min included the presence of motor block,[8] and the presence and severity of nausea, pruritus, and sedation, assessed as described above.[9] The fetal heart rate was continuously monitored by cardiotocography, and adverse events documented by the clinical care team were recorded. The date, time, and mode of delivery, and any indication for Cesarean delivery were also recorded.

Statistical analysis

All analyses were conducted using included patients only. The distributions of continuous data were visually inspected. Continuous data were summarized as mean (SD) or median (interquartile range [IQR]) if the data were skewed, and categorical data were presented as counts with frequencies. Side effects, including nausea, pruritus, and sedation, were presented as the proportion of women who experienced any measured effect at any of the three time points (20, 60, and 120 min).

For each group, an estimate of ED50 and the standard error of the estimate were determined from the up-down sequences using the formula of Dixon and Massey.[10] The two-sample Student's t test with unequal variances was used to compare these estimates and to generate the 95% confidence interval (CI) for the difference in means.

The technique of isotonic regression was used to confirm the ED50 for each group. Pace and Stylianou[11] introduced this analytic method to minimize reliance on unverifiable assumptions save for the assumption that drug effect increases as dose increases in a monotonic fashion. First, an adjusted response probability was calculated using the pooled adjusted violations algorithm. Second, a non-parametric isotonic regression estimator of ED50 was

calculated, and the 95% CI was obtained using a parametric bootstrap routine.[11] Third, the bootstrap sampling distributions for the control and hydromorphone group were used jointly to estimate the 95% CI for the between-group difference in ED50.

To illustrate the change in pain score over time in each group, serial two-sided Student's t tests were used to calculate the 95% CI for the between-group difference in mean pain score measured for each group at each time.

The duration of effective analgesia was compared using the between-group difference in median durations, with the Bonett-Price 95% CI calculated by applying the *bpdifmed* command in Stata.

Isotonic regression estimation was performed in the boot package 1.3-9 running under R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) using previously reported functions.[11] All other analyses were completed with Microsoft Excel 5.0 for Windows and Stata 12.0 (Stata Corps, College Town, TX, USA). All reported P values are two-sided and declared significant if $P \leq 0.05$.

Sample size estimations are based on a previous up-down sequential allocation study of intrathecal bupivacaine with varying doses of fentanyl in which the median (SD) local anesthetic dose of plain bupivacaine was estimated to be 1.99 (0.486) mg.[4] Using the two-sided Student's t test with an estimated standard deviation of 0.486 mg and assuming equal variance between groups, 15 patients per group were required to estimate a 25% difference ≥ 0.5 mg at alpha $= 0.05$ (two-sided), with power of 0.8. Estimations of the ED50 and 95% CIs using the formula of Dixon and Massey are based on the sequence of successful or failed doses, whichever series includes fewer observations;[12] therefore, recruitment continued until a minimum number of 15 effective and ineffective outcomes were recorded for each group.

Results

Eighty-eight women met inclusion criteria and were randomized from January 30, 2007 through November 28, 2007 (Fig. 1). Twenty-one women were excluded after randomization. No differences in demographic or obstetric characteristics were noted between groups (Table 1). No participants experienced pruritus at baseline.

A decrease in the median dose of local analgesic (ED50) was observed, as estimated according to the formulas of Dixon and Massey (hydromorphone ED50, 2.16 mg; standard error [SE] 0.11 vs control ED50, 2.61 mg; SE 0.37) (Figs. 2a, 2b), with an observed between-group difference of −0.45 mg (95% CI −1.23 to 0.33). Nevertheless, the range of observed bupivacaine doses
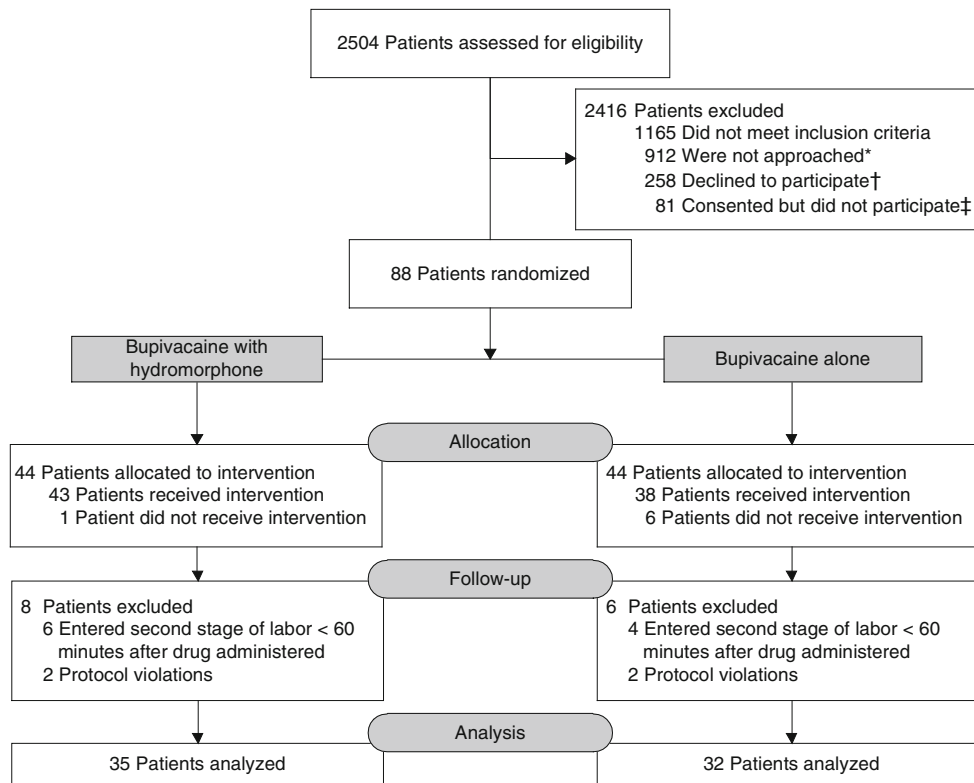
Fig. 1 Patient assessment, randomization, allocation, follow-up, and analysis for the trial. *The chief reasons for not approaching potential study participants were: (1) no research assistants were available on the weekend shifts; (2) the patient was sleeping; or (3) the patient had a rapid delivery before she could be approached. †The chief reasons that patients gave for declining to participate in the study were: (1) the patient was unwilling or uninterested in being in a study; or (2) she was not planning to have epidural analgesia. ‡The chief reasons why patients who consented to be in the study did not participate were: (1) at the time of the patient's request for epidural analgesia, she no longer met study inclusion criteria (e.g., an opioid had been given < two hours before epidural; cervical dilation was > 7 cm; visual analogue pain scale was < 50 mm); or (2) the patient received epidural analgesia when research assistants were not available (e.g., the research assistant was with another study patient, not working, on weekends and night shifts)

Table 1 Patient demographics and baseline characteristics

| Characteristic	Hydromorphone (n = 35)	Control (n = 32)
Age (yr)	28.6 (5.1)	28.6 (5.3)
Race/ethnicity		
White	27 (77.2%)	24 (75.0%)
Black	5 (14.3%)	4 (12.5%)
Other	3 (8.6%)	4 (12.5%)
Body mass index (kg·m^{-2})	30.1 (4.6)	31.2 (4.8)
Parity		
Nulliparous	9 (25.7%)	16 (50.0%)
Primiparous	17 (48.5%)	8 (25.0%)
Multiparous	9 (25.7%)	8 (25.0%)
Gestational age (weeks)	39.2 (1.2)	39.3 (1.3)
Cervical dilation (cm)	4.1 (1.2)	4.4 (1.2)
Baseline visual analogue pain score	80.9 (15.3)	77.1 (14.0)
Any baseline nausea	1 (2.9%)	5 (15.6%)
Any baseline sedation	1 (2.9%)	0

Data are mean (standard deviation), frequencies (%). No participant experienced pruritus at baseline

(control group: 1.75-3.50 mg, eight dose levels; hydromorphone group: 1.50-2.75 mg, six dose levels) resulted in an imprecise estimate of the treatment effect, and no definitive conclusion can be drawn. As a sensitivity analysis, similar results were shown by using the isotonic regression estimator and bias corrected bootstrapping to calculate the 95% CIs of each ED50 and the difference in ED50s (data not shown).

Based on visual inspection, the onset of analgesia appeared to be more gradual in the hydromorphone group (Fig. 3). Repeated measures analysis of variance confirmed a significant treatment-by-time interaction over the first 20 min after spinal injection (P = 0.03). Table 2 lists the mean VAPS for each group, the observed difference between groups, and the 95% confidence interval for the between-group difference.

The median duration of effective analgesia was not significantly different between groups (hydromorphone: 88 min, IQR [58,146] vs control: 55 min, IQR [45,73]) based on the difference of 33 min in median duration of effective analgesia (95% CI −9.0 to 75.0; P = 0.12).

Fig. 2 (a) Bupivacaine control; (b) Bupivacaine with hydromorphone. The up-down sequences of the administered dose of bupivacaine and the results obtained in the presence (Fig. 2a) and absence (Fig. 2b) of co-administered hydromorphone. Horizontal lines represent the effective dose (ED)50 calculated using the formula of Dixon and Massey. Error bars represent the 95% confidence interval for each ED50 estimate
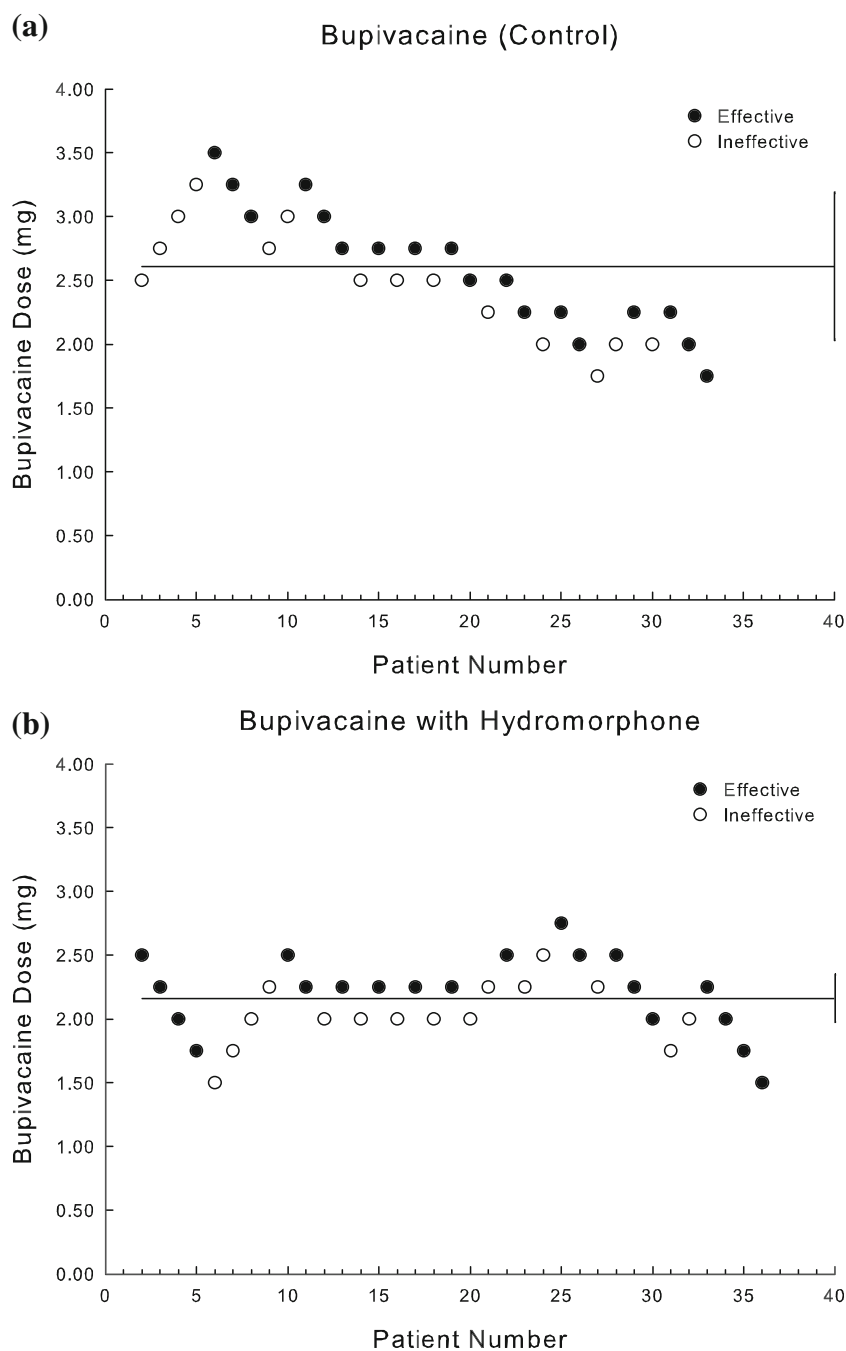
Block height at 20 min, pruritus, nausea, sedation, hypotension, and mode of delivery are presented in Table 3.

Two patients randomized to the hydromorphone group experienced clinically significant non-reassuring fetal heart rate tracings within 30 min of receiving the study drug. One woman experienced rapid dilation to 10 cm and delivered vaginally with vacuum assistance. A second woman experienced fetal heart rate decelerations in the context of maternal hypotension within 15 min of receiving the study drug; however, this resolved after ephedrine was administered. There were no complications or adverse sequelae in either the mothers or their babies following these events, and all were discharged home within three days of delivery.

Discussion

Epidural hydromorphone has been reported to provide rapid and effective neuraxial analgesia with minimal side effects.[3] An analgesic onset of less than ten minutes was
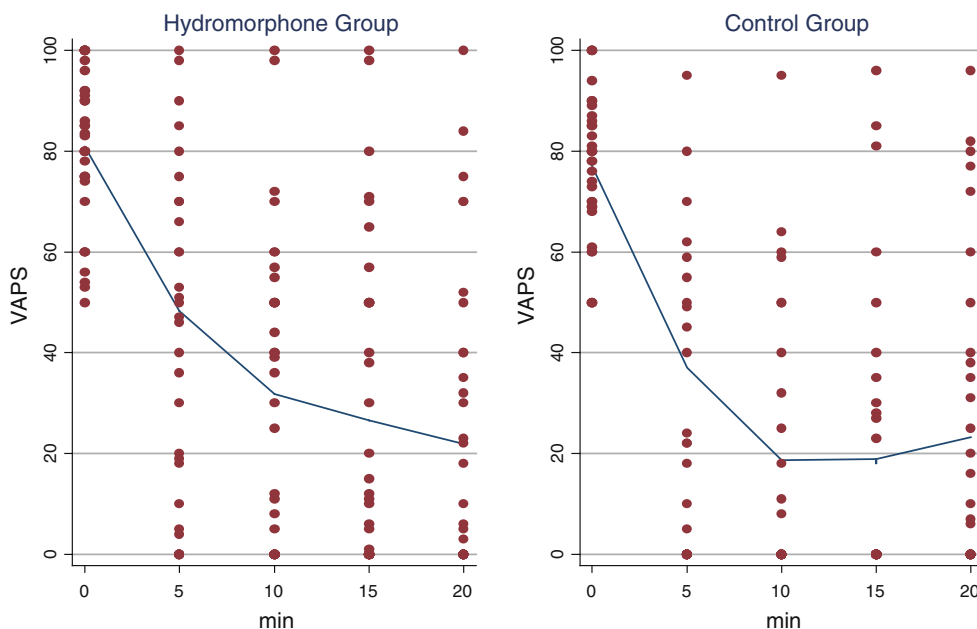
Fig. 3 Visual analogue pain score (VAPS) following intrathecal dosing. The serial VAPS measurements are shown for all included participants over the first 20 min regardless whether the dose was considered effective or ineffective. The two lines are projected with the locally weighted scatterplot smoothing (LOWESS) function using maximum likelihood estimation. VAPS = visual analogue pain score (on a scale of 0-100 mm)

Table 2 The visual analogue pain scores measured by group and between-group differences at each time point during the first 20 min after intrathecal drug administration

Variable	Hydromorphone n = 35 Mean (SD)	Control n = 32 Mean (SD)	Between group difference (95% CI)
Pre-procedural VAPS	80.9 (15.3)	77.1 (14.0)	3.8 (−3.4 to 11.0)
VAPS at 5 min	37.7 (33.6)	23.5 (29.1)	14.2 (−1.6 to 30.0)
VAPS at 10 min	31.2 (30.1)	16 (25.9)	15.2 (1.4 to 29.0)
VAPS at 15 min	26.5 (31.5)	17.9 (28.8)	8.7 (−6.2 to 23.6)
VAPS at 20 min	21.9 (29.1)	23.3 (30.5)	−1.4 (−15.9 to 13.1)

CI = confidence interval; VAPS = visual analogue pain score

Table 3 Mode of delivery, sensory level, and side effects

Characteristic	Hydromorphone (n = 35)	Control (n = 32)
Mode of delivery		
Spontaneous vaginal delivery	31 (88.6%)	29 (90.6%)
Vacuum-assisted vaginal delivery	3 (8.6%)	1 (3.1%)
Cesarean delivery	1 (2.9%)	2 (6.3%)
Sensory level to Neuropen® at 20 min	T9 [T8,T11]	T10 [T8,T11]
Hypotension within 20 min	6 (17.1%)	14 (43.8%)
Pruritus within 2 hr	11 (31.4%)	4 (12.5%)
Nausea within 2 hr	9 (25.7%)	4 (12.5%)
Sedation within 2 hr	10 (28.6%)	9 (28.1%)

Data are count (%) or median [interquartile range]

Nausea, pruritus, and sedation are presented as the proportion of women who experienced any measured effect at any of the three time points (20, 60, or 120 min)

reported in an observational review of 1,830 labouring parturients treated with epidural hydromorphone 100 µg, but the hydromorphone was dosed in conjunction with 0.25% bupivacaine 8-10 mL with epinephrine 1:200,000.[2] Likewise, a randomized controlled trial compared epidural fentanyl 100 µg with and without co-administered hydromorphone 300 µg when administered following a pharmacologic test dose with 1.5% lidocaine 3 mL with epinephrine 1:200,000;[13] the median VAPS in both groups fell at least 69% within ten minutes. Studies of intrathecal hydromorphone for labour analgesia report a similar rapid onset.[A]

Physiologic explanations for the relatively rapid onset observed in these studies and in clinical practice usually rest on the intermediate lipophilicity of hydromorphone. Hydromorphone has an octanol/buffer coefficient of 1.11-1.35, which is comparable with morphine (0.70-1.39) and much less than fentanyl (688-724) or sufentanil (1700-2842).[14,15] It is debatable whether a small increase in lipophilicity relative to morphine is present and clinically

significant.[16,17] An alternate explanation is that co-administration with local anesthetic, epinephrine, or a lipophilic opioid may have helped to facilitate rapid analgesic onset.[2,A,13]

Although the current study was designed to test whether intrathecal hydromorphone 100 μg changes the dose of intrathecal bupivacaine required to induce effective labour analgesia within 20 min, the study results are inconclusive. While the observed difference in intrathecal doses of bupivacaine was 0.45 mg, the 95% CI ranges from a 1.23 mg decrease in dose to a 0.33 mg increase in dose; this range includes clinically important differences.

Hydromorphone is not licensed for intrathecal or epidural use and is rated as Pregnancy Category C by the United States Food and Drug Administration.[18] There is a lack of adequate and well-controlled studies in pregnant women, and the effect of hydromorphone, if any, on the later growth, development, and functional maturation of the child is unknown. According to the package insert, hydromorphone should be used during pregnancy, labour, and delivery, or in nursing mothers only if the potential benefit justifies the potential risk to the fetus or newborn. Nevertheless, intrathecal hydromorphone has been used safely for women in labour,[A] and epidural hydromorphone has been used for women in labour and following Cesarean delivery.[2,19-24] There have been no reports of delayed respiratory depression in obstetric patients with epidural or intrathecal hydromorphone.[3] Intrathecal hydromorphone 100 μg induces an equianalgesic response to approximately 250-500 μg of intrathecal morphine,[25,26] with a lower incidence of side effects, including nausea, vomiting, pruritus, urinary retention, and sedation.[26] An increasing number of papers describe safe administration of long-term intrathecal hydromorphone for chronic pain,[26,27] and hydromorphone is now listed with morphine as a first-line agent for intrathecal administration in chronic pain patients.[28]

The current study is limited by a number of factors. The small sample size resulted in an imprecise estimate of the treatment effect; hence, no definitive conclusion can be drawn. Analgesic outcome was determined at 20 min; however, a longer study period may have revealed a significant local anesthetic dose-sparing effect. Hydromorphone 100 μg was not compared with other doses to determine a dose-response effect or with other opioids to determine potency ratios or relative frequency of side effects. This study targeted the ED50 to minimize the contribution of local anesthetic to any resulting analgesia; therefore, the study results may not apply at the ED95. Fourteen patients were excluded from analysis after receiving the randomized treatment, including ten who delivered within 60 min of the spinal dose. This was a practical consideration that allowed the recruitment team to assure prospective participants that they would not be required to participate in active study assessments during

the second stage of labour. It is not possible to perform a retrospective intent-to-treat analysis because case exclusions resulted in alterations in the dose sequence. The study was not designed to identify differences in rates of hypotension, pruritus, nausea, sedation, or operative delivery; but events were tabulated so they may be combined with future study results. Likewise, this study was not designed to test the hypothesis that intrathecal hydromorphone could prolong the duration of effective intrathecal labour analgesia. Future research is needed to explore the utility of hydromorphone as an adjuvant for maintenance of neuraxial analgesia.

In conclusion, further research is needed to determine whether or not intrathecal hydromorphone 100 μg changes the dose of intrathecal bupivacaine required to induce labour analgesia within 20 min.

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