Epidural morphine vs hydromorphone in post-Caesarean section patients

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Purpose: *The purpose of this randomized controlled double blind study was to compare the efficacy of pain relief and the side effects of epidural hydromorphone and morphine in post-Caesarean patients.*

Methods: *In all patients, epidural anaesthesia was induced using carbonated lidocaine 2% with 1:200,000 epinephrine and 50μg fentanyl, given in incremental doses. Patients in Group 1 (n = 24) received 0.6 mg hydromorphone and patients in Group 2 (n = 22) received 3 mg morphine after delivery of the infant. Pain, pruritus and nausea were measured using a visual analog scale (at times: baseline, on admission to the recovery room, 3, 6, 12, 18 and 24 hr postoperatively), by the number of requests for additional medications and by an overall satisfaction score.*

Results: *There was no difference between the groups in pain relief or in the incidence and severity of side effects. Pruritus was more pronounced within the first six hours in Group 1 and at 18 hr in Group 2.*

Conclusion: *Hydromorphone provides no clinical benefit over epidural morphine for post operative analgesia following Caesarean section.*

Objectif: *L'objectif de cette étude aléatoire et en double aveugle était de comparer l'efficacité du soulagement et les effets secondaires produits par l'administration épidurale d'hydromorphone avec celle de la morphine après la césarienne.*

Méthodes: *L'anesthésie épidurale a été induite chez toutes les patientes avec de la lidocaïne carbonatée à 2% adrénalinée à 1:200 000 et fentanyl 50 μg, administrés en doses fractionnées. Après l'accouchement, les patientes du groupe 1 (n = 24) ont reçu 0,6 mg d'hydromorphone et les patientes du groupe 2 (n = 22), 3 mg de morphine. La douleur, le prurit et la nausée ont été évalués sur une échelle visuelle analogique (aux instants suivants: ligne de base, à l'admission à la salle de réveil, 3, 6, 12, 18 et 24 h après l'opération), d'après le nombre de doses d'analgésiques complémentaires et un score de satisfaction générale.*

Résultats: *Il n'y a pas eu de différence entre les groupes au regard du soulagement de la douleur et de l'incidence et la gravité des effets secondaires. Le prurit était plus marqué pendant les six heures initiales dans le groupe 1 et à la dix-huitième heure dans le groupe 2.*

Conclusion: *Cliniquement, l'hydromorphone n'est pas supérieure à la morphine épidurale pour l'analgésie post-opératoire de la césarienne.*

Key words
ANAESTHESIA: obstetrical, caesarean section, epidural;
ANALGESIA: postoperative, side effects;
ANALGESICS: morphine, hydromorphone, RCT.

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Epidural morphine is commonly used for pain relief after Caesarean section.[1] It provides excellent analgesia but commonly causes troubling side effects. Pruritus is the most common side effect and its presence often detracts from the excellent analgesia obtained. Other side effects such as breakthrough pain, nausea and vomiting also occur. Opioids such as fentanyl and sufentanil have been used instead of epidural morphine in an effort to reduce side effects. However, the analgesia is not as prolonged as with epidural morphine.[2,3] Opioid agonist-antagonists such as buprenorphine and butorphanol have been used, but these drugs have a shorter duration of action than epidural morphine.[4]

Epidural hydromorphone has been shown to be as effective as morphine for analgesia in non-obstetrical patients with a similar duration of action. Hydromorphone may have a lower incidence of side effects, par-

ticularly pruritus.[5] This study compares the analgesic effectiveness and incidence of nausea and pruritus of epidural morphine and hydromorphone when used for pain relief after Caesarean section.

Methods

The study was conducted in two centres (Women's College Hospital and The Toronto Hospital (General Division)) and approval was obtained form the Research Ethics Boards of both institutions. After obtaining informed consent healthy patients (ASA 1 or 2) presenting for elective Caesarean section with normal singleton fetuses were enrolled. Patients who were allergic to opioids, or had been treated for pruritus of pregnancy were excluded. All patients received epidural anaesthesia in the same manner: After an intravenous fluid bolus of 1000 to 1500 ml Ringers lactate, an epidural catheter was placed at the L_3–L_4 or L_2–L_3 interspace. A test dose of 3 ml carbonated lidocaine 2% with 5 $\mu \cdot ml^{-1}$ epinephrine was given. Epidural anaesthesia was then given using 5 ml aliquots of the same solution until a level of T_4 was achieved. In addition, all patients received 50 μg epidural fentanyl (1 ml). After clamping of the umbilical cord, patients were randomized into two groups: Group 1 received 0.6 mg epidural hydromorphone in 6 ml normal saline, and Group 2 received 3.0 mg epidural morphine in the same volume.

Randomization was performed centrally in the pharmacy at Women's College Hospital and both the anaesthetist giving the solution and the patient were unaware of the drug used. All data were collected by research personnel who were blinded to treatment group. Randomization was performed in blocks of four to ensure an equal distribution of patients in each group at each site. Patients who requested additional pain medication were treated using acetaminophen and codeine (Tylenol® #3, two tablets) *po* every four hours as requested or 50 mg *im* meperidine if this was insufficient. Pruritus was treated with 25 mg diphenhydramine *im* or 0.1 mg naloxone *iv* bolus followed by an *iv* infusion of 0.1 to 0.2 mg per hour for severe itching. Nausea was treated with 25 mg of *im* dimenhydrinate.

The following demographic data were collected: maternal age, height, weight, dose of local anaesthetic and the number of patients who had primary Caesarean sections. The number of patients who required intraoperative vasopressors, antiemetics and analgesics was recorded. The primary outcomes of the study were the incidence and severity of pruritus. These were measured three ways: (1) using a visual analog scale (VAS), immediately preoperatively (baseline), on entrance to the recovery room (time 0), and at 3, 6, 12, 18, and 24 hr after time 0, (2) by counting the number of treatments required during each of the time periods listed above, and (3) by asking at the end of 24 hr whether or not the patient considered this symptom as "bothersome." Pain and nausea were analyzed in the same manner. The VAS scores were recorded by the patient on a blank line measuring 100 mm long.

Power analysis was done using VAS scores and whether or not the patient received treatment for pruritus. Previous clinical data at Women's College Hospital showed that approximately 75% of women who received epidural morphine requested medication for the treatment of pruritus. We assumed a probability of a type I error at 0.05, a type II error at 0.2, and a clinically important difference (delta) at 37.5%. The sample size was determined to be 25 in each group. Using this sample size, this study would detect a 0.75 standard deviation difference in visual analog scores for pruritus. A priori power analysis was not performed for pain or nausea.

Data were analyzed using repeated measures analysis of variance for VAS scores, Fisher's Exact test and chi square were used for dichotomous data such as the satisfaction scores and the requests for medication. A P value of 0.05 was considered statistically significant.

Results

Fifty patients were enrolled in the study but four were removed from the analysis because of break in protocol ($n = 2$) and because of inadequate epidural anaesthesia requiring conversion to general anaesthesia ($n = 2$). Data on 46 patients were analyzed, 24 in Group 1 and 22 in Group 2. The Table shows the demographic data. There was no differences in the overall pruritus, nausea or pain visual analog scores (Figures 1–3). Eight patients in Group 1 and 11 in Group 2 received diphenhydramine (NS). No patient required naloxone for relief of pruritus. Five patients in Group 1 and six in Group 2 considered itching an important problem (NS).

The median number of Tylenol® #3 doses, required for additional pain relief, was 5.1 in Group 1 compared with 4.7 in Group 2 (Range 0–12) (NS) in 24 hr. None of the patients required meperidine *im*. All patients in each group were satisfied with their pain relief.

There was an average of 0.67 (range 0–3) doses of dimenhyrinate given in Group 1 compared with 0.73 (range 0–3) in Group 2 (NS). Twelve patients in Group 1 and 13 in Group 2 considered nausea an important problem (NS).

Discussion

This investigation shows that there was no difference in the analgesic effectiveness or of side effects (pruritus, nausea) of epidural hydromorphone compared with morphine when used for pain relief after Caesarean section. Pain visual analog scores, pruritus visual analog

TABLE Demographic data

	Group 1 (Hydromorphone)	*Group 2 (Morphine)*
Number per group	24	22
Number at TTH*	7	7
Number at WCH*	17	15
Maternal age (yrs)	34 (3.6)†	33 (4.3)†
Maternal height (cm)	162 (6.9)†	161 (5.5)†
Maternal weight (kg)	75 (4.6)†	69 (3.0)†
Number of repeat Caesarean sections	17	14
Dose of lidocaine (ml)	21 (5.7)†	20 (3.9)†
Previous history of nausea with anaesthesia (N)	5	3
Number of patients who received intraoperative intravenous fentanyl	4	2
Number of patients who received intraoperative intravenous droperidol	2	0
Number of patients who received intraoperative intravenous dimenhyrinate	0	3
Number of patients who received intraoperative intravenous metoclopromide	8	6
Number of patients who received intraoperative intravenous ephedrine	9	11

*TTH = The Toronto Hospital, WCH = Women's College Hospital.
†Expressed as mean and standard deviation.

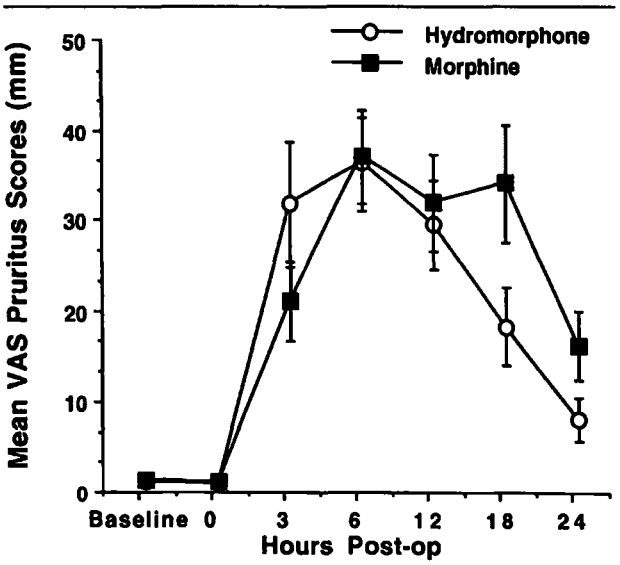

FIGURE 1 Visual analog scores for pruritus. Values expressed as mean ± SEM.

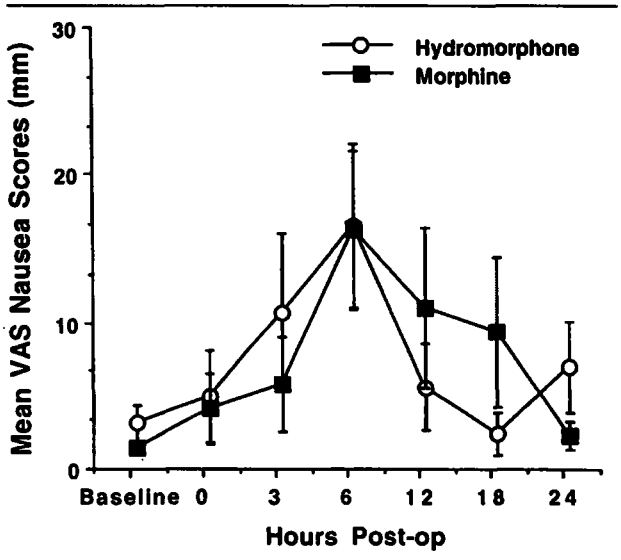

FIGURE 2 Visual analog scores for nausea. Values expressed as mean ± SEM.

scores, use of supplementary analgesics or diphenhydramine were similar in both groups.

The similar chemical structures and physical properties of morphine and hydromorphone largely explain the many pharmacological similarities between the two drugs. Following lumbar epidural administration in human subjects morphine and hydromorphone have the same kinetics of rostral migration in cerebrospinal fluid (CSF) and blood pharmacokinetic profiles. The CSF concentrations of both drugs measured at the cervical spine peak one hour after lumbar epidural administration.[6] Both drugs share nearly identical octanol-pH 7.4 buffer distribution coefficients (hydromorphone: 1.23, morphine: 1.27) which accounts for their similar spinal cord uptake and elimination from the CSF.[7] Despite these shared characteristics, clinical studies in non obstetrical patients suggest that epidural hydromorphone has both a faster onset and shorter duration of action than epidural morphine.[5,8,9] Although we were unable to compare the onset of the two opioids (the analgesic effects of the epidurally administered fentanyl and lidocaine overlapped the administration of the study drugs), our results indicate that both drugs provided a similar duration of analgesia following Caesarean section. The similar analgesic profiles of both drugs that we observed is compatible with the pharmacokinetic data available on hydromorphone and morphine.

The basis of pruritus caused by epidural opioid administration has not been fully elucidated. However, three lines of indirect evidence suggest that this side effect of epidural opioids is mediated by mu receptors located centrally.[5] First, pruritus occurs most commonly when selective mu opioid receptor agonists are used for analgesia. Second, pruritus is more closely associated with CSF rather than blood concentrations. Finally, opi-

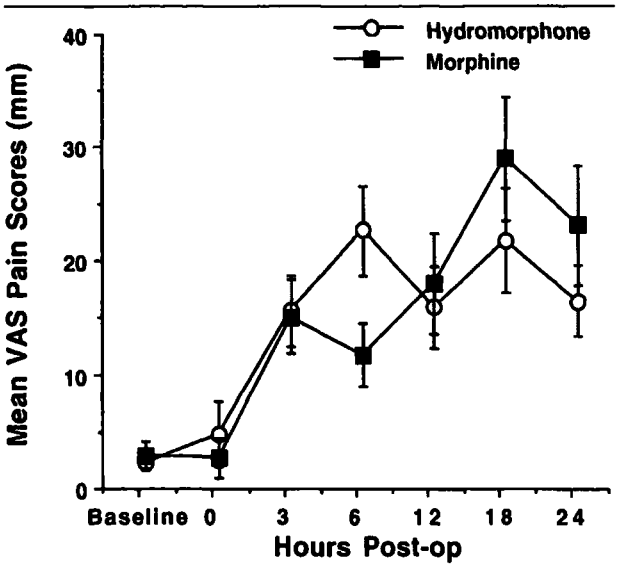

FIGURE 3 Visual analog scores for pain. Values expressed as mean ± SEM.

oid antagonists specifically inhibit pruritus caused by epidural or subarachnoid opioids.

Our results do not support previous anecdotal evidence[5,9,10] and the results from one randomized blinded study by Chaplan *et al.* which indicate that the incidence of pruritus can be lessened if epidural hydromorphone is substituted for epidural morphine.[5] Although we observed no overall difference in the VAS itching scores, the time to peak itch scores occurred sooner in the hydromorphone group. Apparent discrepancies between the results of our study and that of Chaplan *et al.* may be attributed to differences in the populations studied or study design. Chaplan *et al.* studied non-obstetrical patients undergoing major thoracic, abdominal and pelvic surgical procedures in which epidural analgesia was provided by continuous infusion postoperatively.

This randomized double blind study was designed to detect a clinically significant difference in pruritus caused by the use of hydromorphone versus morphine. However, two limitations to this study bear mentioning. First, we used a visual analog scale to assess pruritus. Although this tool has been promoted in the assessment of pruritus, no "gold standard" exists. Nevertheless the visual analog scale is a sensitive method of measuring itch latency, itch duration and maximal itch intensity following experimental histamine-induced itch.[11] A second problem was that treatment for pruritus was left to the discretion of each patient and her nurse in the absence of stringent criteria. Although this might increase the variability in this outcome, it would not bias the results since all patients and attending nurses who administered diphenhydramine were blinded to study drug allocation. In addition, the request for medication is a clinically important outcome.

This study shows that the incidence and severity of pruritus in women following Caesarean section is not reduced by substituting epidural hydromorphone for epidural morphine. In addition, the level of analgesia and the severity of nausea are similar when both drugs are used. We conclude that hydromorphone provides no clinical benefit over epidural morphine for postoperative analgesia following Caesarean section.

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