# The addition of hydromorphone to epidural fentanyl does not affect analgesia in early labour

## *[L'addition d'hydromorphone à l'injection épidurale de fentanyl n'affecte pas l'analgésie au début du travail]*

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**Purpose:** Epidural fentanyl after a lidocaine and epinephrine test dose, provides adequate analgesia and allows for ambulation during early labour. The current study was designed to determine the influence of hydromorphone added to an epidural fentanyl bolus (e.g., whether there is an increase in duration of analgesia).

**Methods:** Forty-four labouring primigravid women, at less than 5 cm cervical dilation, who requested epidural analgesia were enrolled in this randomized, double-blind study. After a 3 mL test dose of lidocaine with epinephrine, patients received fentanyl 100 μg (in 10 mL volume). They randomly received the fentanyl with either saline or hydromorphone (300 μg).

After administration of the initial analgesic, pain scores and side effects were recorded for each patient at ten, 20, and 30 min, and every 30 min thereafter, by an observer blinded to the technique used.

**Results:** The patients were taller in the hydromorphone group ($P < 0.04$). There were no other demographic differences between the two groups. The mean duration prior to re-dose was not significantly different in the group that received hydromorphone (135 ± 52 min) compared to the control group (145 ± 46 min). Side effects were similar between the two groups. No patient in either group experienced any detectable motor block.

**Conclusion:** In early labouring patients, the addition of hydromorphone (300 μg) to epidural fentanyl (100 μg after a lidocaine and epinephrine test dose) neither prolongs the duration of analgesia nor affects the ability to ambulate, and cannot be recommended according to the current study.

***Objectif :*** *L'administration épidurale de fentanyl suivant une dose test de lidocaïne et d'épinéphrine fournit une analgésie adéquate et permet de marcher au début du travail obstétrical. La présente étude cherchait à déterminer l'influence d'un ajout d'hydromorphone au bolus de fentanyl épidural. Entre autres, l'analgésie est-elle prolongée?*

***Méthode :*** *Quarante-quatre primigestes en travail chez qui la dilatation du col était de moins de 5 cm et qui avaient demandé une analgésie épidurale ont été recrutées pour l'étude randomisée et à double insu. Après avoir reçu une dose test de 3 mL de lidocaïne avec de l'épinéphrine, les patientes ont eu 100 μg de fentanyl (dans un volume 10 mL). Elles ont reçu de façon aléatoire le fentanyl et, soit une solution salée, soit de l'hydromorphone (300 μg). Après l'administration de l'analgésique initial, les scores de douleur et les effets secondaires ont été enregistrés pour chaque patiente à dix, 20 et 30 min et à toutes les 30 min par la suite par un observateur objectif.*

***Résultats :*** *La seule caractéristique personnelle différente entre les patientes des deux groupes était que les patientes ayant reçu l'hydromorphone étaient plus grandes ($P < 0,04$). Que ce soit avec l'hydromorphone (135 ± 52 min) ou la substance témoin (145 ± 46 min), le temps moyen précédant une seconde dose était comparable. Les effets secondaires ont été similaires dans les deux groupes. Aucune patiente n'a expérimenté de blocage moteur détectable.*

***Conclusion :*** *Au début du travail, l'ajout d'hydromorphone (300 μg) à l'administration péridurale de fentanyl (100 μg après une dose test de lidocaïne et d'épinéphrine) ne prolonge pas l'analgésie et n'affecte pas la capacité de marcher. Il ne peut être recommandé selon la présente étude.*

WE previously showed that epidural fentanyl or sufentanil, after a lidocaine-epinephrine test dose, provides approximately two hours of analgesia, while allowing patients to ambulate.[1–6] Fentanyl is the most commonly chosen opioid at our institution for early labour ambulatory epidurals based on its low

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cost and the fact there was a lack of significant analgesic difference compared to sufentanil.[3]

In a pilot study, hydromorphone 300 μg following a lidocaine-epinephrine test dose demonstrated an analgesic onset time of greater than 20 min, which was determined to be too long to be clinically useful. We postulated that combining a "quick-onset" short-acting opioid (i.e., fentanyl) with a longer-onset, longer-acting opioid (i.e., hydromorphone) would achieve the benefits of both medications: a quick-onset, long duration "ambulatory" epidural. We thus undertook this study to determine the influence of hydromorphone on the duration of analgesia when administered along with fentanyl after a lidocaine and epinephrine test dose, in primigravid patients during the early first stage of labour.

## Methods

Before this study was initiated, Institutional Review Board approval was obtained. Forty-four primigravid ASA physical status I or II obstetric patients, at greater than 36 weeks of gestation, who had requested labour analgesia, gave written informed consent. Patients were excluded if cervical dilation was greater than 5 cm, if they had received *iv* opioid agonists or agonist/antagonists, had pre-eclampsia, or had a contraindication to fentanyl or hydromorphone. A normal fetal heart rate pattern (absence of decelerations) was required for inclusion in the study. Patients were randomized to group C (control) or group HYD (hydromorphone) using a random series of 44 numbers generated with Microsoft Excel's Randbetween function.

Before the procedure began, the patients' vital signs (blood pressure, heart rate, and respiratory rate) were documented, and the patients were asked to relate any symptoms of pruritus, nausea, or vomiting. Each patient also completed a baseline assessment using a 100-mm visual analogue scale (VAS) for pain, with 0 representing no pain and 100 being the worst possible pain. Each patient received a minimum of 500 mL of Ringer's lactate solution intravenously. All procedures were performed with patients in the sitting position. A lumbar epidural catheter was inserted approximately 5 cm into the epidural space by using a Tuohy-Schiff needle (B-Braun Medical, Bethlehem, PA, USA). The patients then received a test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine. If the test dose was negative for intravascular injection (heart rate within 15 beats·min$^{-1}$ of baseline values in two minutes of monitoring) and intrathecal injection (no spinal block after three minutes of monitoring), the patient was given one of two epidural injections in a double-blinded fashion as follows: group C: fentanyl 100 μg with normal saline to a total volume of 10 mL; group HYD: fentanyl 100 μg and hydromorphone 300 μg with normal saline to a total volume of 10 mL.

Patients were placed in the recumbent position with left uterine displacement. VAS scores and the severity of side effects were recorded ten, 20, and 30 min after the administration of the study infusion and every 30 min thereafter. Observations were performed by an individual blinded to the analgesic technique. At the time of each assessment, vital signs, modified Bromage motor scale scores,[7] pruritus, nausea, vomiting and sedation were evaluated. Motor block was defined as none, partial (just able to move the knees), almost complete (able to move the feet only), or complete (unable to move the lower extremities). Pruritus was rated as none, minimal (present with minimal symptoms), moderate (bothersome but not requiring therapy), or severe (requiring therapy). Sedation was categorized as none (awake), mild (drowsy), moderate (sleepy) or severe (unarousable). The fetal heart rate pattern was evaluated at each interval and any changes were documented. After the first 30 min, patients were allowed to ambulate with assistance provided there was no detectable motor block and the fetal heart rate pattern was reassuring. Oxygen saturation was monitored while patients were at bedrest. The time at which each patient requested additional analgesia was recorded, vital signs were documented, pain and side effect assessments were performed, and the study period was concluded. The epidural anesthetics were subsequently managed by the anesthesia team, as appropriate, for the remainder of labour. The length of labour, incidence of Cesarean delivery, incidence of postdural puncture headache (PDPH), and neonatal Apgar scores were recorded.

A plan for treating inadequate analgesia was standardized. If a patient did not experience adequate analgesia 20 min after the initial study dose, 15 mL of 0.125% bupivacaine would be administered via the epidural catheter. If this did not provide relief after an additional 20 min, 10 mL of 2% lidocaine would be administered. If this did not result in an adequate level of analgesia, then the epidural catheter would be replaced.

Before this study was instituted, a power analysis was performed assuming: a duration of fentanyl analgesia of 124 ± 42 min,[1,3] a hydromorphone analgesia duration of 165 ± 45 min; 90% power, and an alpha of 0.05. This yielded a required sample size of 21 patients per group.

Demographic data were analyzed by using analysis of variance. Pain scores were analyzed by using the Mann- Whitney U test. Presence or absence of side effects was analyzed by contingency testing. A Kaplan-

TABLE

| *Group* | *Age (yr)* | *Height (cm)* | *Weight (kg)* | *Gestational age (weeks)* | *Cesarean section (n)* | *Forceps/ vacuum(n)* | *Cervical dilation at initial dose* | *Cervical dilation at re-dose* |
|---|---|---|---|---|---|---|---|---|
| Hydromorphone/ fentanyl | 27 ± 6 | 167 ± 7 | 84 ± 16 | 40 ± 1 | 9/21 | 0/21 | 2.9 ± 1.2 | 5.1 ± 2.4 |
| Fentanyl | 26 ± 7 | 162 ± 8 | 86 ± 18 | 40 ± 2 | 6/21 | 1/21 | 3.1 ± 1.1 | 4.6 ± 2.0 |

Data are expressed as mean ± SD. The patients in the hydromorphone group were significantly taller ($P < 0.04$) than the patients in the control group. There were no other statistically significant differences between the groups.

Meier plot of the patients remaining comfortable over time was generated. Data are expressed as mean ± SD. Significance was determined at the $P < 0.05$ level.

## Results

Forty-four patients were enrolled in the study. All patients, except one, achieved adequate initial analgesia with the epidural fentanyl; this patient did not get comfortable following the administration of epidural local anesthetic, but analgesia was achieved following replacement of the epidural catheter. One patient's data were excluded due to a protocol violation: a bupivacaine infusion was initiated immediately after the epidural medication was administered. These patients' data were excluded from analysis. The patients in the HYD group were significantly taller than those in group C ($P < 0.04$). There were no other differences in demographic variables, cervical dilation at the time of enrollment, rupture of membranes, or oxytocin use between the two study groups (Table). Baseline VAS pain scores and the incidence of nausea and pruritus were similar in the two groups. The median VAS scores in both groups were decreased 81% and 69% by the 10-min evaluation in the C and HYD groups, respectively ($P$ = not significant). At 20 min, VAS scores were reduced by 88% (C) and 83% (HYD; $P$ = not significant). There was no significant difference in pain scores between the groups at any of the time points (Figure 1). The duration until re-dose was not significantly different between the C (145 ± 46 min) and the HYD groups (135 ± 52 min; Figure 2).

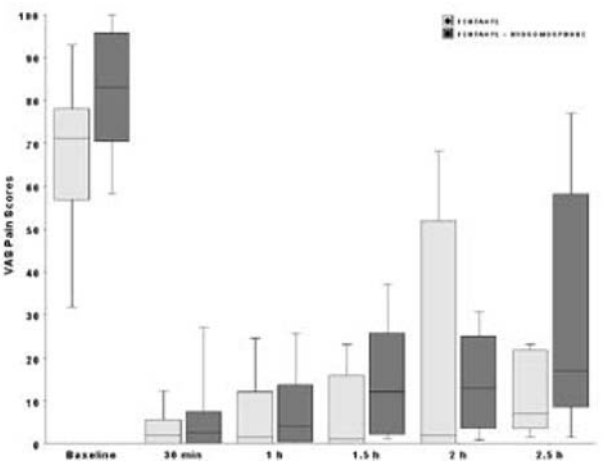


FIGURE 1 The visual analogue scale (VAS) pain scores for the two groups at time intervals up to 2.5 hours. The box represents the 25th–75th percentiles and the median is represented by the solid line. The extended bars represent the 10th–90th percentiles. Pain scores were not obtained following administration of additional analgesic medication. There were no significant differences between the groups at any time period.

Before administration of the study analgesic, 12 patients had experienced nausea (six in C, six in HYD) and five patients had vomited (three in C, two in HYD). During the entire study period, nine patients experienced nausea (two in C, seven in HYD) and two patients vomited (two in C, zero in HYD). Four patients experienced mild sedation at least once during the study period (two in group C, two in group HYD). No patient experienced moderate or severe sedation. At no time, did any patient experience severe pruritus. No patient required specific treatment for nausea, vomiting, or pruritus. There were three patients who reported at one time interval the presence of moderate pruritus (one in C, two in HYD).

Two patients delivered without the need for a re-dose (both in C group; $P$ = not significant). The incidence of Cesarean delivery was not significantly different between the groups (six in C; nine in HYD); none of the patients required a Cesarean delivery before the need for a re-dose. One patient had an accidental dural puncture; no patient, in either group, developed symptoms of a PDPH.

During the study period, motor block, as reflected by the Bromage score, was absent (score of 0) in all patients. Seventeen patients (39%) ambulated at least

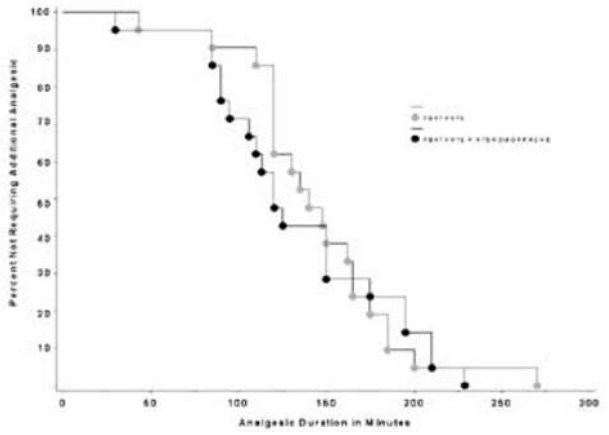


FIGURE 2 Kaplan-Meier plot of the percent of patients in each group who continued to remain comfortable.

once during their labour (ten in C, seven in HYD). Apgar scores at birth were comparable between groups.

## Discussion

Epidural analgesia allowing ambulation during labour is increasingly popular, in part because of the perceived importance of preservation of motor power. We have successfully utilized epidural opioids following a lidocaine-epinephrine test dose to provide satisfactory analgesia without a significant motor block.[1–6]

The current study compared 100 μg of fentanyl after a lidocaine and epinephrine test dose in primigravid patients with and without concomitant hydromorphone (300 μg). The goal of the hydromorphone was to prolong the duration of analgesia. We did not find any prolongation of analgesia by the addition of hydromorphone. While the average height was 5 cm taller in the HYD group, it is unlikely that this affected the findings of this study. We chose the dose of hydromorphone for this study by extrapolation from postCesarean delivery data in which patients used an average of 300–400 μg of epidural hydromorphone per four-hour period when utilizing patient-controlled epidural analgesia.[8,9] Use of a higher dose (e.g., > 500 μg) may have improved the analgesia. However, use of large epidural hydromorphone doses (900 μg) has been associated with significant side effects including nausea, vomiting, pruritus, and urinary retention, without causing an improvement in analgesia when compared to a lower dose (300 μg)[8]. An additional study in postCesarean patients demonstrated similar side effects and efficacy with hydromorphone 600 μg *vs* morphine 3 mg. One-third of patients in the HYD 600 μg group received *iv* diphenhydramine to treat pruritus.[10] With this current study we were reluctant to increase the hydromorphone dose above 300 μg risking the increase in side effects.

In treating patients with ambulatory epidural injections, we prefer the epidural opioid technique, rather than the combined spinal epidural (CSE) technique, because the former avoids an added step, the expense of a CSE needle, and the necessity of an intentional dural puncture.[1–6] The accidental dural puncture rate using the epidural technique has been reported to be 0.69–4.2%.[11,12] We had one accidental dural puncture in our study of 44 patients (with epidural catheters placed by residents in a teaching institution).

When epidural fentanyl (50 μg) is combined with clonidine (120 μg) the mean duration of analgesia was 80 min.[13] In a study comparing CSE with epidural fentanyl (100 μg in 10 mL volume) the mean duration of analgesia with epidural fentanyl was 83 min.[14] In a study utilizing 40 μg epidural fentanyl with 20 mL 0.08% bupivacaine, the analgesic duration was shown to be 91 ± 24 min.[15] These times are significantly less than the analgesia in our previous studies of epidural opioids,[1–4] as well as in the current study (135–145 min). However, Breen *et al.*'s study population included both primigravidous and multigravidous patients.[14] Any study only evaluating primigravidous patients in early labour (and excluding multigravidous patients) probably results in patient groups with longer labour and is the probable reason for the longer and more consistent duration of analgesia in our studies. The analgesic duration in both groups in the current study is consistent with that of epidural fentanyl or sufentanil when utilized for labour pain management.[1–4] Whether the hydromorphone resulted in no effect due to a change in the intensity of pain as labour progressed (such that opioid alone is inadequate), or that the analgesic duration of hydromorphone in labour is not significantly different than that of fentanyl, remains unclear. A study of postCesarean delivery pain found no difference between epidural morphine 3 mg and hydromorphone 600 μg.[10] While postCesarean delivery pain and labour pain cannot be equated, these results leave a question unanswered. Namely, whether 300 μg hydromorphone is adequate to demonstrate the prolonged duration we had hypothesized. Further studies should include a dose-response analysis.

Use of a lidocaine and epinephrine test dose has been implicated in a decreased ability for parturients to ambulate.[16] However, all patients in Cohen's study

received an initial 12 mL epidural bolus of bupivacaine (0.0625% or 0.125%) in addition to the lidocaine-epinephrine test dose. Epidural 0.1% bupivacaine with sufentanil, as part of a patient-controlled epidural analgesia technique, results in detectable motor block in approximately 20% of patients.[17] Our use of epidural opioid after a test dose, without the use of adjuvant local anesthetic, does not result in significant motor block.[1–6] We believe that when sufficient opioid is utilized initially, an initial bolus of local anesthesia is avoided, and ambulation can be achieved without eliminating the test dose. Although the usefulness of the test dose has been challenged recently,[16] we believe that it does improve the ability to detect intravascular and intrathecal catheter placement.

We have demonstrated satisfactory results with epidural fentanyl after a lidocaine and epinephrine test dose for the management of labouring patients. Adding hydromorphone 300 μg does not prolong the analgesic duration. When performing an ambulatory epidural in early labour, after a lidocaine and epinephrine test dose, we found no advantage in adding hydromorphone 300 μg to fentanyl.

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