Epidural Hydromorphone: A Double-blind Comparison with Intramuscular Hydromorphone for Postcesarean Section Analgesia

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Epidural narcotics, including morphine,1-5 hydromorphone,6,7 meperidine,8 methadone,9 and fentanyl10 are effective analgesics after cesarean delivery. Epidural hydromorphone may be preferable to other narcotics, since it has a longer duration of action than epidural methadone,9,11 meperidine,8 and fentanyl10, and may have a lower incidence of side effects than morphine.6,11,12

Since Bromage et al.11 first demonstrated the efficacy of epidural hydromorphone for postoperative analgesia following thoracic and upper and lower abdominal surgery, two other groups have described the use of epidural hydromorphone for postcesarean section analgesia. Albright,6 in a study to assess the use of a respiratory apnea monitor following epidural narcotics, described effective postcesarean analgesia, with a mean duration of 6.2 h, using 1–1.25 mg epidural hydromorphone. Chestnut et al.7 found 1 mg of epidural hydromorphone provided excellent analgesia with a mean duration of 13 h, at the cost of an increased incidence of pruritus, nausea, and vomiting when compared to epidural bupivacaine.

Comparison of im or iv administration with epidural administration of morphine or meperidine for postcesarean delivery analgesia has demonstrated improved duration and quality of analgesia following epidural administration.5,5,8† The incidence of side effects with epidural and iv administration has been comparable, with the exception of pruritus and urinary retention, which have a higher incidence following epidural narcotics.

While it would seem reasonable to assume that epidural administration is superior to im or iv administration for hydromorphone and other narcotics, this may not be true. For example, it appears that epidural methadone may not be superior to iv methadone for postoperative analgesia. Gourley et al.,13 using iv methadone doses titrated to be just above the minimal effective concentration, achieved a mean duration of action of approximately 22 h following upper abdominal surgery. This long duration of action has been attributed to the long terminal elimination half-life of methadone. With epidural methadone, adequate pain relief has been obtained with lower doses than used by Gourley et al.,13 but the duration of action was only 4.9–8.7 h.9,11

A prospective, randomized, double-blind, single-dose study was designed to test the hypothesis that epidural hydromorphone is superior to im hydromorphone for postcesarean delivery analgesia. The duration and quality of analgesia and the incidence of side effects are reported.

METHODS

The protocol was approved by our Institutional Review Board, and written informed consent was obtained from each patient upon entry into the study. The study design was a first dose only, non-crossover, placebo-controlled study, with randomized, double-blind assignment to the patient groups.

Postoperative analgesia was studied in 30 ASA physical status I or II patients who had undergone elective cesarean section under lumbar epidural anesthesia. Patients with major complications of pregnancy, major organ system disease, or a history of drug or alcohol abuse were ex-
cluded from the study. Double-blinded patient assignment to one of two treatment groups was performed when the patients were enrolled in the study, using a computer generated random number table. All subjects were the first or second scheduled cesarean section of the day, so there would be minimal interference with normal post-partum routine.

During the routine preoperative anesthetic evaluation, each patient was familiarized with a horizontal 10-cm visual analogue pain intensity scale. Oral premedication of 30 ml of sodium citrate was given 10–15 min prior to beginning the epidural anesthetic. An epidural catheter was inserted at L₂₋₃ or L₃₋₄, after identifying the epidural space with the loss of resistance technique. Following a test dose with 3 ml of 0.5% bupivacaine with epinephrine 1/200,000, fractional doses of plain 0.5% bupivacaine were given to achieve an upper level of sensory blockade at T₅₋₆. To avoid the use of potentially toxic doses of bupivacaine to achieve the desired level of sensory blockade, an occasional patient also received 3% 2-chloroprocaine in addition to bupivacaine. Patients requiring supplemental narcotic analgesia or general anesthesia intraperatively were dropped from the study.

Each patient received both an epidural and an im injection of study medication at the end of surgery during fascial closure. The IM group received a 1 ml im injection of 2 mg of hydromorphone in saline, and a 10 ml epidural injection of preservative-free sterile normal saline. The epidural group received a 1 ml im injection of sterile normal saline, and 10 ml epidural injection of 1 mg of preservative-free hydromorphone in saline. Both the anesthesiologist and the nursing staff that subsequently cared for the patient were blinded to which treatment group the patient entered. Each patient was informed that additional postoperative, im pain medications (1–2 mg im hydromorphone or its equivalent) could be obtained on demand from their nurse, every 2–3 h. Equivalent doses of other narcotics were based on: 1.5 mg hydromorphone = 10 mg morphine = 100 mg meperidine = 120 mg codeine.

Arterial blood pressure, heart rate, respiratory rate, and level of consciousness were assessed every 15 min while the patient remained in the recovery room. Patients were transferred to the general postpartum ward when the sensory level had fallen below T₁₀, and they could move freely from the recovery room cart to their bed. On the postpartum ward, respiratory rate and level of consciousness were assessed every 30 min for the first 8 h, and then hourly for the next 4 h. Respiratory rate was determined by a nurse observer counting respirations over at least a 30-s interval. Level of consciousness was evaluated using a simple scale: 1 = awake and alert; 2 = sedated or asleep, but easily arousable; 3 = heavily sedated or asleep, difficult to arouse; and 4 = unresponsive.

The intensity of pain experienced by each patient was assessed hourly for 12 h postoperatively using a horizontal, 10-cm linear analogue pain intensity scale. For each evaluation, a new, unmarked, 10-cm line was presented to the patient, on which she could represent the degree of pain she was experiencing by placing a mark somewhere between “no pain” and “the worst pain I can imagine.” Such a determination was also made immediately before administration of the first supplemental pain medication. Patients who were remedicated before 12 h were considered treatment failures for the remainder of the observation period, and were assigned the pain intensity score they indicated at the time of administration of first supplemental pain medication. No attempt was made to assess the adequacy of pain relief once the patients had received their first dose of supplemental pain medications, since the study was designed only to look at the effects of the first dose of pain medications. The time of administration of the first additional pain medication, total narcotic dose in the first 24 h, and the time of first ambulation were also recorded for each patient. Duration of analgesia was defined as the time from administration of study medications until the time of first request for additional pain medication.

The incidence of nausea, vomiting, and pruritus was estimated by directly questioning all patients for the presence of these side effects. The incidence of urinary retention was not assessed, since it is the obstetricians’ practice to keep these patients catheterized in the early postoperative period. On the first postoperative day, each patient was asked if she was satisfied with her postoperative analgesia.

Due to the wide variance in the data for the duration of analgesia, the total narcotic dose administered in the first 24 h, and the time of first ambulation, these data were analyzed with Wilcoxon’s rank sum test. Hourly pain intensity data were analyzed with a two-factor ANOVA, with repeat measures on one factor, with post hoc testing using paired and non-paired t tests, as appropriate, with Bonferroni’s correction for multiple comparisons. The incidence of side effects was analyzed with Fisher’s exact test. The criterion for rejection of the null hypothesis in all instances was \( p < 0.05 \).

**RESULTS**

Epidural hydromorphone had a much longer duration of action compared to im hydromorphone (table 1). Patients who received epidural hydromorphone had a median duration of action of approximately 19.3 h, compared to patients who received im hydromorphone, who had a median duration of action of 5 h. All but one patient in the im group had received supplemental analgesics by 7 h after the initial injection (fig. 1). Five of the 15 patients
in the epidural group received additional analgesics between 7 and 15 h, seven patients received additional analgesics between 15 and 24 h, and three patients in the epidural group did not require additional analgesics in the first 24 h. One patient in the im group did not require additional analgesics until 24 h after her initial injection.

When patients received supplemental analgesics prior to 12 h, they were assigned the pain intensity score they had at the time of the first supplement for the remainder of the 12-h evaluation period. The mean pain scores (±S.D.) for the 12 hourly determinations are shown in figure 2. In the im group, there was a difference (P < 0.05) from baseline (1 h) beginning at 4 h. There was no difference from baseline in the epidural group throughout the 12-h evaluation period.

In the first 24 h, the epidural group required significantly less supplemental narcotics than the im group (1 mg vs. 9 mg, table 1). The results are expressed as "hydromorphone equivalents," using the equivalencies listed in the methods section.

The time to first ambulation was recorded as an assessment of patient mobility. There were no differences between the groups for the time to first ambulation (table 1). There was no difference between the groups in the incidence of nausea, nausea and vomiting, or nausea and vomiting, or nausea and vomiting requiring treatment (table 2).

Pruritus was frequent in both groups, and varied in severity from mild, localized itching of the face or chest, to generalized, severe itching. Significantly more patients in the epidural group needed treatment for pruritus (7/15 vs. 1/15, P < 0.05). Two patients in the epidural group were treated with im diphenhydramine (Benedryl®), and one of these patients also needed 200 µg of iv naloxone to relieve her pruritus. The remaining six patients were treated with 25-50 mg im hydroxyzine (Vistaril®) with good results.

Only three of the 30 study patients appeared overly sedated. These patients were in the im group, and all episodes of over-sedation occurred within 1 h after receiving a supplemental im injection. The episodes were manifested by difficult arousal from sleep, and no patient had a respiratory rate less than 16 breaths per minute. Two patients had received 2 mg of hydromorphone, and one had received 100 mg of meperidine. These doses were comparable to what other patients in the study received, and these patients had received these same doses previously or received them subsequently, without similar episodes of over-sedation.

There were no episodes of depressed respiration in either group as measured by respiratory rate. All recorded respiratory rates were greater than or equal to 16 breaths per minute, except for three patients in the im group who had respiratory rates of 12 breaths per minute within 30 min of an im injection of 2 mg of hydromorphone. Only one of these three patients appeared excessively sedated. She had received 50 mg of hydroxyzine in addition to the hydromorphone, which may have contributed to the sedative and respiratory depressant effects of the hydromorphone.

When questioned on the first postoperative day, all patients in both groups were satisfied with their postoperative pain relief. No patient thought that the side effects were severe enough to prompt them to request another form of pain medication in the future.

**DISCUSSION**

In this prospective comparison of epidural and im hydromorphone for postcesarean section pain relief, epi-
Fig. 2. Hourly linear analogue pain intensity (mean ± S.D.). Patients who received supplemental analgesics prior to 12 h were assigned the pain intensity score they had at the time of the first supplement, for the remainder of the 12-h evaluation period. The im group (hatched bars) was different (P < 0.05) from baseline beginning at 4 h. There was no difference from baseline in the epidural group (open bars) throughout the 12-h evaluation period.

Dural administration resulted in a much longer duration of analgesia, as measured by the time until the first request for supplemental analgesics, a lowered requirement for narcotics in the first 24 h, and a superior quality of analgesia, as measured by linear analogue pain intensity scales. The superior quality and duration of analgesia for epidural administration when compared with im administration is consistent with results for other narcotics when epidural has been compared to im.

Although the median duration of analgesia for epidural hydromorphone (19.3 h) reported in this study is considerably longer than previously reported for epidural hydromorphone, we must be cautious in comparing results from different study designs and patient populations. Following general surgical procedures, Bromage et al. reported a mean duration of 11.9 ± 5.8 (x ± S.D.) h for 19 patients, and Parker et al. reported a mean duration greater than 15 h in six patients. Following cesarean section, Albright reported a mean duration of only 6.2 h in 12 patients, and Chestnut et al. reported a mean duration of 13.0 ± 12.4 (x ± S.D.) h in 52 patients. The large standard deviations reported in these studies, and the disparity between studies for the duration of action reported, illustrates a wide variability in patient response.

This study was not designed to compare epidural hydromorphone with other epidural narcotics. Yet, the duration of action of epidural hydromorphone found in our series of patients is comparable to the duration reported for epidural morphine following cesarean section, and is far longer than that reported for epidural fentanyl, meperidine, or methadone.

Improvement in early mobility has been reported for patients receiving epidural narcotics compared to those receiving parenteral narcotics for postoperative pain. A commonly used index of early mobility is the time to first ambulation. No difference for time to first ambulation was found between the epidural and im groups in this study. This may reflect the obstetricians' policy of aggressively encouraging early ambulation. It may also reflect a reluctance on the part of the nursing staff to attempt ambulation in these patients prior to 10–12 h, to ensure that there is no residual sensory or motor blockade remaining following their epidural anesthetic. There have been several reports of epidural narcotic potentiation of bupivacaine epidural blockades, leading to the proposal that ambulation was delayed in the epidural group because of residual epidural blockade. However, all patients had sensory levels below T, and were able to move freely from the recovery room cart to their bed within 3–4 h. Assuming a normal pattern of regression of the epidural block, it is unlikely that a significant degree of motor or sensory blockade remained after 6 or 7 h.

There was no difference in the incidence of nausea and vomiting between the im group and the epidural group. The incidence of nausea and vomiting in the epidural group was similar to data previously reported by Chestnut et al. for epidural hydromorphone and for epidural morphine by several investigators. Although this seems to conflict with the early reports by Bromage et al. that there are fewer side effects with epidural hydromorphone than with epidural morphine, a direct comparison of morphine and hydromorphone needs to be done in this patient population to resolve this issue.

Almost 50% of the patients in the epidural group requested treatment for pruritus, making it the most bothersome side effect encountered. As with the incidence of nausea and vomiting, the incidence of pruritus in the epidural group was higher than in the im group. The incidence of pruritus requiring treatment was higher in the epidural group. The incidence of respiratory rate < 10 bpm was similar in both groups.

### Table 2. Incidence of Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Intramuscular</th>
<th>Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6/15</td>
<td>7/15</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>4/15</td>
<td>5/15</td>
</tr>
<tr>
<td>Nausea and vomiting, requiring treatment</td>
<td>2/15</td>
<td>5/15</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7/15</td>
<td>12/15</td>
</tr>
<tr>
<td>Pruritus, requiring treatment</td>
<td>1/15</td>
<td>7/15*</td>
</tr>
<tr>
<td>Respiratory rate &lt; 10 bpm</td>
<td>0/15</td>
<td>0/15*</td>
</tr>
</tbody>
</table>

* Epidural group different from the im group, P < 0.05.
dural group was similar to data previously reported by Chestnut et al.\textsuperscript{7} for epidural hydromorphone and by several investigators for epidural morphine.\textsuperscript{11-13} However, the presence of pruritus did not diminish patient satisfaction with the analgesic technique and, in all cases, except one, it was easily treated with small doses of diphenhydramine or hydroxyzine. The one case that did not respond to diphenhydramine did respond promptly to a small dose of naloxone without reversal of analgesia.

Perhaps the agents we chose to treat pruritus may have inadvertently influenced our results on the analgesic effectiveness of the epidural hydromorphone. We deliberately avoided the use of naloxone, since it can antagonize the analgesia of epidural narcotics.\textsuperscript{22,23} Although, clinically, it appears that much larger doses of naloxone are required to reverse analgesia following epidural narcotics than are required to reverse pruritus, the smaller doses used to treat pruritus may cause subtle changes in analgesic effectiveness. Because hydroxyzine potentiates im narcotics,\textsuperscript{15} perhaps it potentiated epidural narcotics in a similar manner. The smallest dose effective in the treatment of pruritus was used to minimize this effect, if it is present. Hydroxyzine was chosen to treat pruritus because our prior experiences indicated that small doses were effective in reversing pruritus, while producing minimal sedation. With its combined anticholinergic, antiserotonin, and antihistaminic actions, it may be superior to a pure antihistamine (eg., diphenhydramine),\textsuperscript{24} although none of these systems has been linked directly to narcotic-induced pruritus.

No case of serious, life-threatening, respiratory depression was detected in either group. Estimates of the incidence of respiratory depression following epidural morphine have been placed at 0.1–0.4%.\textsuperscript{4,25,26} With a study involving only 15 patients, no conclusions can be made about the incidence of a side effect that may occur only once in 1000 patients. No studies have been performed on postcesarean section patients to ascertain the incidence of serious respiratory depression or to measure the decrease in respiratory drive following parenteral or epidural administration of hydromorphone. Until such studies are performed, we assume that the potential for serious respiratory depression is present whenever epidural narcotics are administered. The fact that only patients in the im group became over-sedated or had mildly depressed respiratory rates, illustrates that the potential for serious respiratory depression is present whenever potent narcotics are given, regardless of the route of administration. All patients receiving potent narcotics, whether parenteral or epidural, should be watched closely for respiratory depression.

In conclusion, following cesarean section, epidural hydromorphone provides superior analgesia with longer duration than im hydromorphone. Pruritus is more frequent following epidural hydromorphone, but the incidence of other side effects is comparable to im hydromorphone. The readily available commercial preparation is preservative-free; thus, a specially formulated preparation for epidural use is not required.

REFERENCES

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Bronchial Obstruction and Hypoxia during One-lung Ventilation

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One-lung ventilation using a double lumen endobronchial tube is often indicated during thoracotomy for lung resection to facilitate an operative exposure.1 Burton et al.2 recommend that the bronchial cuff of double lumen tubes remain deflated until the institution of one-lung ventilation to prevent bronchial rupture from excess cuff pressure. We report a case of bronchial obstruction secondary to migration of necrotic tumor from the non-dependent lung to the dependent lung during thoracotomy, prior to the institution of one-lung ventilation using a double lumen tube with a deflated bronchial cuff.

CASE REPORT

A 65-yr-old, 200 cm, 100 kg man with a history of hypertension, chronic obstructive pulmonary disease, hypothyroidism, and arthritis was scheduled for right middle and lower lobectomy for resection of squamous cell carcinoma. Preoperative metastatic workup was negative. Bronchoscopy revealed external compression of the right middle lobe bronchus and complete obstruction of the right lower lobe bronchus by tumor. Medications included IV aminophylline, beclomethasone and albuterol inhalers, levohyroxine 0.1 mg daily, and ranitidine 150 mg bid.

The patient was brought to the operating room where a 16-guage peripheral iv and a 20-guage left radial artery catheter were inserted. Additional monitoring included EKG, esophageal stethoscope, pulse oximeter, temperature probe, and urinary catheter. Anesthesia was induced with thiopental 6 mg/kg, fentanyl 250 μg iv and inhalation of isoflurane 1–2%, and O₂. Following succinylcholine 200 mg iv, a 35 French left-sided PVC endobronchial tube was inserted without difficulty. After the correct position of the double lumen tube was confirmed by auscultation,3 the bronchial cuff was deflated, and the patient was positioned in the left lateral decubitus position. Correct position of the double lumen tube was again confirmed, the bronchial cuff deflated, and anesthesia maintained with 1–2% isoflurane and O₂.

Following thoracotomy, the surgeon requested that two-lung ventilation be maintained while pleural adhesions were lysed. During manipulation of the non-dependent lung, peak inspiratory pressure (PIP) increased from 35 cm H₂O to 45 cm H₂O. There were no concomitant changes in heart rate, arterial blood pressure, breath sounds, or pulse oximeter readings. Shortly thereafter, one-lung ventilation was attempted by inflating the bronchial cuff and clamping the tracheal lumen; however, we were unable to ventilate the dependent lung, and very high PIP was noted. The tracheal lumen was immediately unclamped, but severe resistance to ventilation was still present. The tube was then withdrawn 4 cm without improvement. The pulse oximeter showed a rapid decrease in arterial saturation from 100–70% with an Fio₂ of 1.0. The bronchial lumen was suctioned with catheters and via a pediatric flexible fiberoptic bronchoscope; plugs of necrotic tissue were removed with difficulty. This proved inadequate with continued high PIPs and arterial desaturation to 50%. We then elected to turn the patient to the supine position and perform bronchoscopy. The double lumen tube was removed, and ventilation via mask was undertaken with an Fio₂ of 1.0 and an improvement in arterial saturation to 60%. Rigid bronchoscopy followed by fiberoptic bronchoscopy through a 9.0 endotracheal tube was performed. The bronchial tree was cleared of necrotic tissue with improvement of arterial saturation to 100%. After discussion with the surgeon, the decision was made to proceed with the operation because of the perceived danger of recurrent tumor migration if the diseased lung was not resected. A 37 French