Epidural nalbuphine for analgesia following caesarean delivery: dose-response and effect of local anaesthetic choice

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The analgesic profile of epidural nalbuphine for postoperative pain relief and the impact of local anaesthetic choice upon this profile was investigated in 58 patients undergoing elective Caesarean delivery under epidural anaesthesia. Patients were randomized to receive either lidocaine 2% with 1:200,000 epinephrine or 2-chloroprocaine 3% for perioperative anaesthesia, followed by either 10, 20, or 30 mg of epidural nalbuphine administered at the first complaint of postoperative discomfort. Postoperative analgesia was quantitated on a visual analogue (VAS) scale, and by the time from the epidural opioid injection until the first request for supplemental pain medication. The duration of analgesia after lidocaine anaesthesia followed by 10, 20 or 30 mg nalbuphine was 77 (53–127) min, 205 (110–269) min, and 185 (116–241), respectively (median, 95% confidence interval, $P < 0.01$, 20 and 30 mg vs 10 mg). Following 2-chloroprocaine anaesthesia, VAS remained consistently elevated: the median duration of analgesia was only 30–40 min and did not differ among the three doses of nalbuphine. Side-effects consisted only of somnolence, and were noted only following lidocaine anaesthesia. Somnolence was observed in 0, 20% and 50% of those receiving 10 mg, 20 mg and 30 mg of nalbuphine respectively (NS). No evidence of respiratory depression was noted in any patient. It is concluded

that 20 or 30 mg of epidural nalbuphine provides analgesia for only two to four hours following Caesarean delivery with lidocaine anaesthesia, but anaesthesia with 2-chloroprocaine resulted in minimal or no analgesia from this opioid. Nalbuphine appears to be a disappointing agent for epidural use after Caesarean delivery.

Nous avons évalué l'efficacité analgésique de la nalbuphine épidurale, de même que l'impact de l'anesthésique local utilisé chez 58 candidates à une césarienne électorale sous anesthésie épidurale. Après randomisation, on injectait dans l'espace épidural des patientes soit de la lidocaïne 2% avec adrénaline 1:200,000, soit de la 2-chloroprocaine 3% en tant qu'anesthésique puis 10, 20 ou 30 mg de nalbuphine à titre d'analgésique dès qu'elles se plaignaient de douleur. On mesurait l'intensité des douleurs avec une échelle visuelle analogue (VAS) et l'intervalle entre l'injection de la nalbuphine et la réapparition de douleur nécessitant à nouveau un analgésique. Dans le groupe lidocaïne, la durée de l'analgésie avec 10, 20 ou 30 mg de nalbuphine était de (médiane, intervalle de confiance à 95%) 77 (53–127), 205 (110–269) et 185 (116–241) min, ($P < 0,01$, 20 et 30 mg vs 10 mg). Chez les patientes du groupe 2-chloroprocaine, le VAS demeurait élevé malgré la nalbuphine et la durée médiane de l'analgésie était au plus de 30 à 40 min avec les trois doses de nalbuphine. Le seul effet secondaire noté consistait en de la somnolence survenue seulement chez le groupe lidocaïne à raison de 0, 20 et 50% des patientes ayant reçu 10, 20 et 30 mg de nalbuphine (NS). Aucune patiente n'a démontré de dépression respiratoire. Vingt ou trente mg de nalbuphine épidurale n'offrent qu'une ou deux heures d'analgésie après une césarienne avec de la lidocaïne comme anesthésique. Si on a utilisé de la 2-chloroprocaine, la nalbuphine épidurale n'offre pratiquement pas d'analgésie valable. Bref, l'usage de nalbuphine par voie épidurale en tant qu'analgésique post-césarienne est décevant.

Key words

ANAESTHETIC TECHNIQUE: epidural;
ANAESTHETIC AGENTS: chloroprocaine, lidocaine;
ANALGESIA: postoperative, nalbuphine.

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A wide variety of opioids has been investigated for epidural use since the discovery of spinal opiate receptors.

The concept of opiate receptor subtypes (μ , κ and σ) and the advent of drugs with receptor-specific agonist and antagonist properties have further expanded the role of epidural opioids for intraoperative, postoperative, and obstetrical uses. Nalbuphine, a synthetic μ -receptor antagonist, κ -receptor agonist opioid, is structurally related to the pure opioid agonist oxymorphone and the pure opioid antagonist naloxone. This drug has gained popularity as a parenteral analgesic in various clinical settings. Few reports exist concerning the epidural use of this opioid, since a preservative-free preparation of nalbuphine did not become commercially available until recently. Moreover, in animal studies, intrathecal nalbuphine failed to provide satisfactory analgesia.^{1,2} A preliminary study in humans (undergoing abdominal surgery under general anaesthesia) has reported only fair to moderate analgesia following the use of epidural nalbuphine.³ Moreover, lumbar epidural nalbuphine was found to be an ineffective analgesic in post-thoracotomy patients.⁴

The current dose-response study attempted to define the analgesic profile of epidural nalbuphine after Caesarean delivery and examined if the choice of local anaesthetic affected this profile. Several reports have suggested that the local anaesthetic 2-chloroprocaine (2-CP) or its metabolites may antagonise the efficacy of subsequently administered epidural opioids.⁵⁻⁹ Although a recent investigation suggested the possibility of a μ -receptor specific interaction, the aetiology of this phenomenon is unclear.⁹ It is also possible that this alleged antagonism may be a reflection of the rapid regression of sensory analgesia following 2-CP.

Methods

Sixty ASA physical status I, nonlabouring parturients requesting epidural anaesthesia for elective Caesarean delivery were randomly assigned to one of six groups after written, informed consent to an institutionally approved protocol was obtained. The groups were designated L-10, L-20 and L-30 (lidocaine and 10, 20, 30 mg nalbuphine, respectively) and CP-10, CP-20 and CP-30 (2-CP and 10, 20, 30 mg nalbuphine, respectively). Preanaesthetic medication consisted of 30 ml, 0.3 M sodium citrate by mouth. After receiving 1500 ml of lactated Ringer's solution *iv*, patients were placed in the right lateral decubitus position and an epidural catheter was inserted 2 cm into the epidural space via the L₂₋₃ or L₃₋₄ interspace with the loss-of-resistance to air technique. Patients in groups L-10, L-20 and L-30 received lidocaine 2% with 1:200,000 epinephrine (Xylocaine, Astra Pharmaceuticals, Westborough, MA) and those in groups CP-10, CP-20 and CP-30 received 2-CP 3% (Nesacaine-MPF, Astra Pharmaceuticals, Westborough, MA) in 5 ml

incremental doses via the epidural catheter to obtain a bilateral level of sensory anaesthesia to the fourth thoracic dermatome measured in the midclavicular line. All patients received oxygen 5 L $\cdot$ min⁻¹ via face mask and were positioned on the operating table with left uterine displacement. Monitoring included blood pressure cuff, ECG and finger pulse oximetry. Additional doses of local anaesthetic, if needed, were administered in accordance with standard clinical practice. No opioids, either systemic or epidural, were administered in the operating room. Diazepam in doses not greater than 4 mg *iv* was administered after delivery of the infant if anxiolysis was requested by the patient. Epidural catheters were left in place after operation. In the recovery room, epidural anaesthesia was allowed to recede until patients first complained of discomfort, at which time they were given 10, 20, or 30 mg nalbuphine (Nubain, Abbott Laboratories, Chicago, IL) via the epidural catheter, according to their group assignment. The nalbuphine was diluted in preservative-free saline solution to a final volume of 10 ml and administered in a double-blind fashion.

The intensity of pain was assessed by the patient with the use of a 10-cm linear visual analogue scale (VAS) in which 0 = no pain and 10 = worst pain imaginable. The VAS and sensory level to pinprick were recorded prior to epidural opioid administration, and again at 30 and 60 min thereafter. The time until the first request for additional opioid was noted, at which time patients received *im* analgesics as ordered by their obstetrician. Duration of analgesia was defined as the time from epidural opioid injection to the time of first request for additional pain medication. Patients who both reported no decrease in VAS and requested additional opioid within 30 min of epidural opioid injection were assigned a duration of analgesia of 0 min. No patient had opioid medication withheld at any time for the purpose of the study. Twenty-four hour opioid requirements were noted and converted to morphine "equivalents" according to the formula: 10 mg morphine = 1.5 mg hydromorphone = 100 mg meperidine.¹⁰ All postoperative pain assessments were made by an observer blinded to the patient's group assignment. Pruritus was assessed using a three-point ordinal scale where 0 = no pruritus, 1 = mild, no treatment required, and 2 = moderate, treatment requested. Somnolence was assessed using a four-point ordinal scale where 0 = awake, 1 = drowsy but arousable, 2 = sleeping, and 3 = unarousable. The incidence of nausea, vomiting, or respiratory rate less than 12 breaths $\cdot$ min⁻¹ was noted.

Statistical analysis included both parametric and non-parametric methods, as appropriate. Continuous interval data were analysed with one-way or two-way analysis of variance followed by Sheffe's test for comparisons among

TABLE Maternal demographic characteristics

	L-10 n = 10	L-20 n = 10	L-30 n = 10	CP-10 n = 9	CP-20 n = 9	CP-30 n = 10
Age (yr)	34 ± 6	31 ± 4	35 ± 5	31.5 ± 5	31.2 ± 5	34 ± 6
Height (cm)	170 ± 6	170 ± 6	168 ± 3	166 ± 3	166 ± 4	168 ± 4
Weight (kg)	81 ± 9.4	82 ± 16	84 ± 14	76 ± 11	84 ± 14	89 ± 20
Parity						
– Nulliparous	2	4	3	1	0	2
– Multiparous	8	6	7	8	9	7
Birth weight (kg)	3.9 ± .7	3.6 ± .5	3.3 ± .8	3.5 ± .4	3.6 ± .7	3.9 ± .6
Duration of surgery (min)	55 ± 20	50 ± 7	57 ± 9	59 ± 21	59 ± 16	56 ± 11

Mean ± SD. No significant differences among groups.

multiple groups. Ordinal or skewed data were subjected to Kruskal-Wallis analysis of variance and/or Mann-Whitney rank-sum test. Categorical data were compared with Fisher's exact test. A value of $P < 0.05$ was considered to indicate statistical significance.

Results

Sixty patients were enrolled in the study. One patient (group CP-10) had her epidural catheter removed before administration of the study drug and another (CP-20) had a dural puncture during epidural catheter placement with subsequent conversion to continuous spinal anaesthesia. Thus 58 patients were included for data analysis. Maternal demographic characteristics did not differ among groups (Table), nor did the distribution of VAS scores at the time of epidural opioid administration (Figure 1). Those patients who received 2-CP had consistently elevated VAS scores, while those who received lidocaine had significant decreases in VAS scores at 30 and 60 minutes (Figure 1). (For purposes of graphical clarity, the VAS scores for the three lidocaine groups and the three 2-CP groups are combined at each observation point, as within-group analysis revealed no significant differences over the three dosages of nalbuphine at each interval). The interval from the last dose of epidural local anaesthetic to the administration of the epidural opioid was 67 ± 19 min in the 2-CP group, and 120 ± 38 min (mean ± SD) in the lidocaine group ($P < 0.001$). At the time of epidural opioid administration, the sensory levels (median and range) in the groups did not differ (2-CP: $T_{6.5}$ (T_3 to T_{12}); lidocaine T_6 (T_4 to T_{12}) $P = \text{NS}$). At the 30-min observation interval, all patients who had received lidocaine anaesthesia still had detectable sensory levels (median T_8 , range T_4 to T_{12}); among those who had received 2-CP anaesthesia, 19 (68%) still had detectable sensory levels (median T_{10} , range T_8 to $L1$, $P = 0.003$, 2-CP vs lidocaine) while nine (32%) had complete sensory resolution. At 60 min, 15 (50%) of the lidocaine patients still had a detectable sensory level (median T_9 ,

range T_5 to T_{12}); all of the 2-CP patients had complete sensory resolution. The median duration of nalbuphine analgesia was short (30–40 min) and did not differ among the groups receiving 2-CP (Figure 2). After lidocaine anaesthesia, 10 mg of epidural nalbuphine provided a median of 77 min of analgesia, while 20 and 30 mg both provided between two to four hrs of analgesia ($P < 0.01$, L-20 and L-30 vs L-10, Figure 2). Total 24-hr opioid requirements did not differ among any of the groups.

The only side-effect noted was somnolence, observed in two (20%) patients in group L-20 and five (50%) patients in group L-30; no patient in group L-10 or any of the 2-CP groups was somnolent. No patient was unarousable or complained of excessive somnolence. This trend toward increasing somnolence with nalbuphine following lidocaine anaesthesia was not statistically significant. No patient in any group experienced pruritus, nausea or a respiratory rate less than 12 breaths per min during the period of analgesia.

Discussion

This study suggests that epidural nalbuphine (20 or 30 mg) provides only two to four hours of effective analgesia following Caesarean delivery, and then only in the presence of some degree of residual lidocaine anaesthesia. When 2-CP was used as the primary local anaesthetic agent, postoperative epidural nalbuphine (regardless of dose) failed to provide any analgesic effects in the absence of residual local anaesthetic block.

There are few reports of neuraxial administration of nalbuphine. A preliminary study in rats demonstrated that intrathecal nalbuphine had no effect on tail-flick or hot plate response latencies.¹ Further work assessing visceral stimulation (writhing response to intraperitoneal saline injection in term pregnant rats) showed that intrathecal nalbuphine failed to provide effective spinal analgesia.² Epidural administration of nalbuphine in humans has given mixed results. Weksler and Ovadia administered $0.15 \text{ mg} \cdot \text{kg}^{-1}$ nalbuphine epidurally to 30 patients

FIGURE 1 Visual analogue pain scores (median, 95% confidence interval) before and after epidural nalbuphine injection * $P < 0.001$ L vs CP at 30 min, $P < 0.01$ L (30 min) vs L (initial), ** $P < 0.01$ L vs CP at 60 min, $P < 0.01$ L (60 min) vs L (initial).

FIGURE 2 Duration of analgesia after epidural nalbuphine administration (median, 95% confidence interval). * $P < 0.01$, L-20 and L-30 vs L-10. ** $P < 0.001$ vs all lidocaine groups.

following upper abdominal surgery, which produced a mean duration of analgesia of 6.5 hr.³ Somnolence was the only bothersome side-effect, occurring in 55% of the patients; however, no patient developed respiratory depression as measured by sequential arterial PaCO₂ measurements for 24 hr. McMorland *et al.** reported only fair and inconsistent analgesia following epidural nalbuphine (dose range 5–20 mg) after Caesarean delivery in 40 patients. Side-effects were minimal and the respiratory response to a CO₂ challenge at three and six hours after epidural opioid was unaffected. In a recent study, lumbar

*McMorland GH *et al.* Epidural nalbuphine for post caesarean section analgesia (Abstract). Presented at the Society of Obstetric Anesthesia and Perinatology Annual Meeting. Seattle, WA 1989.

epidural nalbuphine (0.075–0.3 mg·kg⁻¹) has been found by Baxter *et al.* to be an ineffective analgesic for post-thoracotomy patients.⁴ These authors found no evidence of a dose–response effect in the nalbuphine dose-range studied. Moreover, the pharmacokinetic profile of epidural nalbuphine was similar to that seen with *iv* injection.

Our study used doses of nalbuphine comparable to, or greater than, those used for parenteral analgesic therapy. Thus our results, and those of others,^{3,4} may reflect systemic, rather than spinally mediated, effects. We cannot conclude this with certainty, since we did not measure blood levels of nalbuphine, nor did we include a control group of patients receiving only parenteral nalbuphine. Nevertheless, the duration of analgesia following epidural nalbuphine was short in our study. One of the purported advantages of epidural opioid administration is the ability to provide pain relief using small doses of drug. We thus conclude that nalbuphine is a rather disappointing agent for epidural use and seems to offer no advantage over currently used short-acting epidural opioids such as fentanyl.

The question of epidural opioid analgesia in relation to choice of local anaesthetic is controversial. The notion that 2-CP can affect subsequent epidural opioid analgesia was first published by Malinow,⁵ and others,^{6–9} wherein 50 µg epidural fentanyl failed to provide any analgesia after 2-CP, whereas this same dose of fentanyl provided satisfactory, albeit short duration, analgesia after lidocaine as the epidural local anaesthetic.⁵ However, other opioids, such as morphine¹¹ or hydromorphone¹² have produced satisfactory, prolonged pain relief after 2-CP use. It has been suggested that the rapid sensory regression of 2-CP anaesthesia, combined with the slow onset of an agent such as epidural morphine, may produce a “window” wherein pain is perceived.¹¹ This “window” can be closed if small doses of *iv* opioids are administered during the immediate postoperative period.¹¹ Failure to appreciate this “window” effect may have contributed to early claims of poor analgesia from epidural morphine after 2-CP use.

It is not clear if the observed interaction between 2-CP and epidural fentanyl represents true “antagonism,” or is simply a reflection of the rapid regression of sensory anaesthesia following 2-CP. A recent study by our own group attempted to examine this drug interaction further.⁹ We suggested that 2-CP may be a pure mu-receptor antagonist, inasmuch as epidural butorphanol (a kappa-receptor agonist) showed a similar analgesic profile after either lidocaine or 2-CP anaesthesia. However, that study did not assess the possible contribution of supraspinal (i.e., systemic) effects of the epidural butorphanol. In view of the current study using nalbuphine (also a

kappa-receptor agonist), this receptor specific theory may be incorrect. Another possible explanation that these results differ from our study with butorphanol may be related to the apparent ineffectiveness of nalbuphine when injected epidurally. Ultimately, the concept of 2-CP "antagonism" of epidural opioid analgesia may be regarded as a phenomenon more apparent than real, although future studies are warranted to clarify this possible interaction.

Finally, a concern regarding any drug injected into the central nervous system is the potential for neurotoxicity. In a sheep model, high doses of intrathecal butorphanol ($0.375 \text{ mg} \cdot \text{kg}^{-1}$) and sufentanil ($7.5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) were associated with spinal cord histopathological changes, while nalbuphine ($0.75 \text{ mg} \cdot \text{kg}^{-1}$) was not.¹³ All drugs were given every six hours for 72 hr. The clinical relevance of this study is unclear, as the doses used were far in excess of those commonly used in humans. Although the lack of neurotoxicity with nalbuphine is reassuring, prudence would dictate further studies in other animal models before clinical use of epidural nalbuphine can be advocated.

In summary, this double-blind, dose response trial of epidural nalbuphine examined the quality and duration of postoperative analgesia following Caesarean delivery. Doses as high as 30 mg failed to provide analgesia for longer than two to four hr, and then only following a lidocaine anaesthetic. When 2-CP was used as the local anaesthetic, epidural nalbuphine failed to provide any analgesia in the absence of residual local anaesthetic effect. At this time we cannot recommend nalbuphine for epidural use.

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