

Chloroprocaine Antagonism of Epidural Opioid Analgesia: A Receptor-specific Phenomenon?

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Sixty healthy patients scheduled for elective cesarean delivery under epidural anesthesia were randomized to receive either lidocaine or 2-chloroprocaine as the primary local anesthetic agent. When patients first complained of postoperative pain in the recovery room, they were given either fentanyl 50 µg or butorphanol 2 mg, epidurally, in a randomized, blinded fashion. Postoperative analgesia, quantitated on a visual analogue scale, as well as time elapsed until first request for supplemental opioid, did not differ for patients receiving butorphanol after either 2-chloroprocaine or lidocaine anesthesia. In contrast, epidural fentanyl produced a shorter and lesser degree of sensory analgesia after 2-chloroprocaine use, whereas epidural fentanyl after lidocaine anesthesia provided pain relief similar to that seen in the butorphanol groups. Side effects were limited to somnolence with butorphanol and pruritus with fentanyl. No evidence of respiratory depression was seen in any patient. We conclude that 2 mg of butorphanol epidurally provides approximately 2 to 3 h of effective analgesia after cesarean delivery with either lidocaine or 2-chloroprocaine anesthesia. Epidural fentanyl seems to be antagonized when 2-chloroprocaine, but not lidocaine, is used as the primary local anesthetic agent. We suggest a possible mu-receptor-specific etiology for this effect. (Key words: Anesthetic Techniques: epidural. Anesthetic Agents: chloroprocaine, lidocaine. Analgesia: postoperative; butorphanol, fentanyl.)

2-CHLOROPROCAINE (2-CP) is a useful local anesthetic agent for epidural use during cesarean delivery because of rapid onset, profound anesthetic action, and relative absence of maternal or neonatal side effects. However, several investigators have observed a tendency of 2-CP to antagonize the analgesic efficacy of subsequently administered epidural fentanyl.^{1,2,§} The mechanism for this antagonism is unclear. Studies on pH adjustment of 2-CP³ as well as on possible direct mu-receptor antagonism by a 2-CP metabolite⁴ have not been able to explain this interaction.

To date, only pure mu-receptor agonist opioids (fentanyl and morphine) have demonstrated decreased anal-

gesic efficacy after 2-CP use. The current study, using epidural butorphanol, was conducted to determine if this local anesthetic-opioid interaction extends to an opioid with kappa-receptor agonist activity as well.

Methods

Sixty ASA physical status 1, nonlaboring parturients requesting epidural anesthesia for elective cesarean delivery were randomly assigned (with the use of sequentially numbered, sealed, opaque envelopes) to one of four groups after written, informed consent to an institutionally approved protocol was obtained. The groups were designated CF (2-CP and fentanyl), CB (2-CP and butorphanol), LF (lidocaine and fentanyl), and LB (lidocaine and butorphanol). Preanesthetic medication consisted of 30 ml 0.3 M sodium citrate by mouth. After receiving 1500 ml lactated Ringer's solution intravenously, patients were placed in the right lateral position and an epidural catheter was inserted 2 cm into the epidural space *via* the L2-L3 or L3-L4 interspace with the loss-of-resistance to air technique. Patients in groups LF and LB received lidocaine 2% with 1:200,000 epinephrine (Xylocaine, Astra Pharmaceuticals, Westborough, MA), and those in groups CF and CB 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 anesthesia to the fourth thoracic dermatome.

Patients were positioned on the operating table with 15° left uterine displacement, and received oxygen 5 l·min⁻¹ *via* face mask. Monitoring included blood pressure cuff, ECG, and finger pulse oximeter. Additional doses of local anesthetic, 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 no greater than 4 mg intravenously 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 anesthesia was allowed to recede until patients first complained of discomfort, at which time patients in groups LF and CF received 50 µg fentanyl (Elkins-Sinn, Cherry Hill, NJ) and those in groups LB and CB received 2 mg butorphanol (Stadol, Bristol Laboratories, Syracuse, NY) *via* the epidural catheter. All drugs were diluted in 10 ml preservative-free saline solution and were administered in a double-blind fashion.

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§ Malinow AM, Mokrisli BLK, Wakefield ML, McGuinn WJ, Martz DG, Sesverreux JN, Matjasko MJ: Choice of local anesthetic affects post-cesarean epidural fentanyl analgesia. *Reg Anesth* 13:141-145, 1988.

TABLE 1. Maternal Demographic Characteristics

Characteristic	Group LF (n = 15)	Group LB (n = 15)	Group CF (n = 14)	Group CB (n = 15)
Age	28.7 ± 1.2	32.6 ± 1.1	31.2 ± 9	32.3 ± 1.2
Height (cm)	168 ± 6	168 ± 4	168 ± 5	166 ± 1
Weight (kg)	89 ± 9.5	77.7 ± 1.7	89.1 ± 3.8	74 ± 4.1
Parity				
Nulliparous	4	6	5	3
Multiparous	11	9	9	12
Birth weight (g)	3772 ± 45	3636 ± 88	3363 ± 44	3363 ± 88
Duration of surgery (min)	61 ± 4.1	61 ± 5.7	52 ± 3.1	48.7 ± 3.1

No significant differences among groups.

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. VAS was recorded just prior to epidural opioid administration, and again at 10, 20, 30, 60, and 90 min thereafter. The time until first request for additional opioid was noted, at which point patients received intramuscular 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. However, 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 Dilaudid "equivalents" according to the formula: 1.5 mg Dilaudid = 10 mg morphine = 100 mg meperidine.⁵ All postoperative pain assessments were made by an observer blinded to the patient's group assignment. The incidence of nausea, vomiting, pruritus, somnolence, or respiratory rate less than 10 breaths per min was noted.

Data are expressed as mean ± SEM, except for VAS scores, which are depicted as median and 95% confidence intervals. However, no assumption was made regarding the distribution of the data, and all statistical tests were for nonparametric data. Comparisons of categorical data were performed with chi-squared analysis, with continuity correction for two-by-two contingency tables. Continuous data among multiple groups were compared with the

Kruskal-Wallis analysis of variance (ANOVA) method, and between two groups with the Mann-Whitney rank sum test. A value of $P < 0.05$ was considered to indicate statistical significance.

Results

Maternal demographic characteristics did not differ among groups (table 1). One patient in group CF had inadequate surgical anesthesia and required general anesthesia; this patient was eliminated from data analysis. The distribution of VAS scores at the time of epidural narcotic injection did not differ among the four groups (table 2). Graphic display of VAS scores over time demonstrates that VAS scores in group CF were higher than those in group LF at 20 min after opioid injection, and were higher than all other groups at each subsequent observation point (fig. 1). Distribution of VAS scores did not differ at any point among groups CB, LB, and LF. Duration of analgesia did not differ among groups LF, LB, and CB, and yet was significantly shorter in group CF as compared to all other groups (fig. 2). Total 24-h opioid requirements did not differ among any of the groups (table 2).

Side effects were limited mainly to somnolence, observed in 11 (36%) of patients receiving butorphanol and 2 (6%) of those receiving fentanyl ($P < 0.02$). No patient was unarousable, had an extended recovery room stay, or complained of excessive sedation or dysphoria. Seven (23%) of the patients receiving fentanyl reported pruritus

TABLE 2. Initial VAS Scores and Local Anesthetic Usage

	LF	LB	CF	CB
VAS at time of epidural opioid injection	4 (3.1–4.9)	4 (3.2–4.9)	4 (3.5–4.6)	5 (3.9–6.2)
Dose local anesthetic (ml)	31 ± 2.4	32 ± 1.4	44 ± 2.4	43 ± 2.5
Time from last dose of local anesthetic to epidural opioid injection (min)	103 ± 6.7	100 ± 6.4	56 ± 3.2	62 ± 6.5
24-h opioid usage (Dilaudid equivalents)	8.9 ± 1.2	11.3 ± .8	9.2 ± .8	11.2 ± 1.4

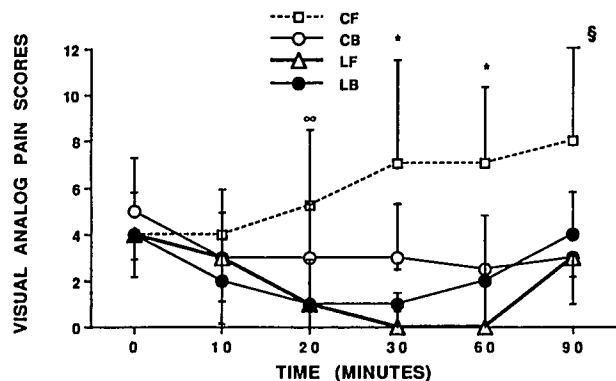


FIG. 1. Visual analog pain scores (median, 95% CI) after epidural opioid administration. [∞]CF versus LF, $P < 0.005$. *CF versus all other groups, $P < 0.001$. [§]CF versus all other groups, $P < 0.01$.

(no treatment required); no pruritus was seen in any patient receiving butorphanol ($P < 0.01$). None in either group reported nausea. No patient demonstrated a respiratory rate lower than 10 breaths per min during the period of analgesia.

Discussion

The principal finding of this study is that there was no difference in analgesia provided by epidural injection of butorphanol 2 mg after either lidocaine or 2-CP anesthesia for cesarean delivery. In addition, we confirm previous results demonstrating that epidural fentanyl provides minimal or no postoperative analgesia if 2-CP is used as the primary local anesthetic.^{1-3,¶}

The observation that 2-CP may adversely affect subsequent epidural opioid analgesia was first suggested by Kotelko *et al.*,^{**} who showed that the duration of analgesia provided by 5 mg epidural morphine was markedly shortened after 2-CP compared to that after either lidocaine or bupivacaine (2 h vs. approximately 20 h, respectively). Hughes and colleagues⁶ have suggested that this antagonism is actually a reflection of the rapid regression of 2-CP and the slow onset of epidural morphine, which together produce a "window" effect during which pain is appreciated. Small doses of intravenous opioids, administered during this window, have allowed for subsequent satisfactory postoperative analgesia (up to 18 h) with epidural morphine after 2-CP anesthesia.⁶ Thus, the effect of 2-CP on epidural morphine analgesia still remains controversial.

¶ Malinow AM, Mokrisi BLK, Wakefield ML, McGuinn WJ, Martz DG, Sesverreux JN, Matjasko MJ: Choice of local anesthetic affects post-cesarean epidural fentanyl analgesia. *Reg Anesth* 13:141-145, 1988.

** Kotelko DM, Thigpen JW, Shnider SM, Footz SE, Rosen MA, Hughes SC: Postoperative epidural morphine analgesia after various local anesthetics (abstract). *ANESTHESIOLOGY* 59:A413, 1983.

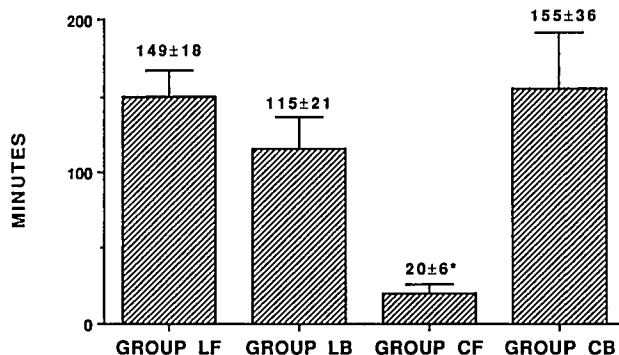


FIG. 2. Duration of analgesia after epidural opioid injection. Bar heights represent mean times; error bars show SEM. * $P < 0.001$.

Malinow *et al.* have shown that epidural fentanyl produces no postoperative analgesia independent of local anesthetic sensory block when 2-CP is used as the primary anesthetic agent.[¶] Further work by the same authors showed that this antagonism could not be reversed by pH adjustment of the 2-CP.³ The possibility that 2-CP or its metabolite 4-amino-2-chlorobenzoic acid (ACBA) may act as direct mu-receptor antagonists was studied by Naughton *et al.* in a dog model of ventilatory depression after cisternal administration of morphine.⁴ Although results with their model did not implicate 2-CP as a direct mu-receptor antagonist, it is not clear if ventilatory effects in dogs can be extrapolated to analgesic effects in humans after lumbar epidural use of these agents.

Butorphanol has been studied as an epidural analgesic after cesarean delivery with either lidocaine or bupivacaine used as local anesthetic agents. A 2-mg dose of butorphanol has been reported by Abboud *et al.* to provide approximately 5 h of analgesia with few side effects.⁷ However, in a result in agreement with the current study, Ackerman *et al.* found only 2 h of analgesia with 2 mg epidural butorphanol.^{††} The most common side effect of epidural butorphanol is somnolence, usually seen when doses greater than 2 mg are used. Mild depression of CO₂-response curves has been demonstrated with epidural administration of 2 mg butorphanol, and greater depression when 4 mg is used.⁷ However, neither dose produced any clinical evidence of respiratory depression (defined as a respiratory rate of less than 10 breaths per min).

In the current study, we waited until all patients complained of discomfort in the recovery room before administration of the epidural opioid. It is noteworthy that the distribution of VAS scores at this stage did not differ among the four groups (table 2). Thus, any analgesia (de-

†† Ackerman WE, Juneja MM, Colclough GW, Guiler JM, Guiler DS: A comparison of epidural fentanyl, buprenorphine and butorphanol for the management of post-cesarean section pain. *Anesth Rev* 16:37-40, 1989

fined as a decrease in VAS) that ensued could be attributed to the epidural opioid, since any "overlap" effect of different local anesthetics, which may recede at different rates, was minimized. Interpretation of previous work may be hampered by this overlap effect.^{‡‡} Abboud *et al.* have also shown that longer acting opioids (*i.e.*, morphine) are similarly effective (mean duration of analgesia was 21 h after lidocaine epidural anesthesia) when administered at the onset of, rather than prior to, postoperative pain after cesarean delivery.⁷ Clearly, lidocaine and 2-CP resolve at different rates, and this difference may to some degree affect the course of VAS scores over time. However, any decrease in VAS can be due only to the epidural opioid. Thus, the significance of the aforementioned window effect may need further evaluation.

The primary drawback of 2-CP epidural anesthesia has been the inability to provide effective epidural opioid analgesia postoperatively. Although butorphanol 2 mg in this setting is not a long-acting (*i.e.*, morphinelike) analgesic, it does seem to provide 2–3 h of analgesia, which may ease the transition into the postoperative period and prevent the abrupt onset of severe pain coincident with the rapid regression of 2-CP. Although our data suggest a possible mu-receptor-specific phenomenon, the exact

mechanism of the 2-CP–epidural opioid interaction still remains unknown. Further work with different doses of butorphanol or other kappa-agonist narcotics, such as nalbuphine, after 2-CP anesthesia is warranted.

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