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Does Epidural Administration of Butorphanol Offer Any Clinical Advantage over the Intravenous Route?

A Double-blind, Placebo-controlled Trial

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The differential effects of intravenous *versus* epidural administration of short-acting, lipid-soluble opioids is controversial. This study was undertaken to compare these two routes of administration using the mixed agonist–antagonist opioid, butorphanol. Forty-five women undergoing elective cesarean delivery at term under epidural lidocaine anesthesia were randomized to receive a single bolus of either epidural or intravenous butorphanol 2 mg or saline control for postoperative analgesia. At precisely 60 min after the last dose of epidural local anesthetic, all patients received a simultaneous epidural and intravenous injection in a randomized, double-blinded fashion. The intravenous group received butorphanol intravenous and saline epidurally; the epidural group received saline intravenous and butorphanol epidurally; and a control group received saline *via* both routes. When additional analgesia was requested, all patients received patient-controlled analgesia (PCA) with intravenous morphine (2-mg demand dose, 7-min lockout interval). Analgesia was quantitated using a visual analogue scale and subsequent PCA morphine requirements. The interval from study drug injection until first request for PCA use was equivalent for the intravenous and epidural groups (89 ± 9 and 83 ± 8 min, respectively) and significantly longer than in control group (39 ± 4 min, $P < 0.001$, intravenous and epidural *vs.* control). Analgesia was equivalent in the intravenous and epidural groups at all observation points, and pain scores were significantly lower than control for the first 120 min after study drug injection. Both intravenous and epidural groups had similar patterns of morphine usage. Both butorphanol groups used significantly less morphine during the first 2 h of the study period than did the control group; thereafter, morphine usage was similar in all three groups. After initiation of PCA therapy, pruritus was noted in 60% (9 of 15) of control patients, 13% (2 of 15) in the epidural group, and none in the intravenous group ($P < 0.005$, intravenous and epidural *vs.* control). Nausea occurred in 53% (8 of 15) in the control group and 13% (2 of 15) in both intravenous and epidural groups ($P < 0.05$, intravenous, epidural *vs.* control). Somnolence occurred in 66% (10 of 15) in the intravenous group, 13% (2 of 15) in the epidural group, and 7% (1 of 15) in the control group ($P < 0.005$, intravenous *vs.* control and epidural). In summary, 2 mg of either intravenous or epidural butorphanol produced similar analgesic profiles, and both were equally effective in decreasing pruritus and nausea during subsequent PCA morphine usage. We conclude that under the conditions of this study, epidural administration of butorphanol offers few, if any, clinical advantages over the intravenous route. (Key words: Analgesics: butorphanol. Anesthetic techniques: epidural; intravenous. Pain, postoperative: cesarean delivery.)

BUTORPHANOL is a synthetic μ-opioid receptor antagonist, κ-opioid receptor agonist. A number of investigations have examined the analgesic profile of epidural butorphanol.[1–4,¶] These studies generally agree that butorphanol is a safe and effective, albeit short-acting (2–5 h) analgesic when administered epidurally. The majority of these studies also report that sedation is a common finding after epidural administration of butorphanol. Parenteral administration of butorphanol also produces profound sedative effects.[5] Moreover, the usual dose of epidural butorphanol (2–4 mg) is similar to the usual dose for parenteral use. It is interesting that none of the studies of epidural butorphanol has included a control group of patients receiving comparable doses of parenteral butorphanol.

In addition, opioids with combined agonist–antagonist properties have recently been shown to be useful adjuncts (both intravenously and epidurally) to lessen or eliminate undesirable side effects (pruritus, nausea, or respiratory depression) from the administration of pure μ-agonist opioids.[6–9] This double-blind, placebo-controlled trial was designed to directly compare the intravenous and epidural administration of a single bolus dose (2 mg) of butorphanol. We sought to determine if either route of administration conferred any clinical advantage in terms of analgesic profile or frequency of side effects during subsequent use of patient-controlled analgesia (PCA) with intravenous morphine following elective cesarean delivery.

Materials and Methods

Forty-five ASA physical status 1, nonlaboring patients requesting epidural anesthesia for elective cesarean de-

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

livery at term were enrolled in the study after written, informed consent to an institutionally approved protocol was obtained. All patients received preanesthetic medication consisting only of 30 ml 0.3 M sodium citrate by mouth. After receiving 1,500 ml lactated Ringer's solution intravenously, patients had an epidural catheter inserted 2 cm into the epidural space *via* the L2–L3 or L3–L4 interspace with the loss-of-resistance to air technique. All patients received lidocaine 2% with 1:200,000 epinephrine (Xylocaine, Astra Pharmaceuticals, Westborough, MA) in 5-ml incremental doses *via* the epidural catheter to obtain a bilateral level of sensory anesthesia to the T4 dermatome.

Patients were positioned on the operating table with 15° left uterine displacement and received oxygen 5 $l \cdot min^{-1}$ *via* face mask. Monitoring included blood pressure cuff, ECG, and finger pulse oximetry. Additional doses of epidural lidocaine were administered if needed. No opioids, either systemic or epidural, were administered in the operating room. Diazepam in doses no greater than 3 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 postanesthesia care unit (PACU), patients were randomly assigned (using sequentially numbered, sealed, opaque envelopes) to one of three groups. At precisely 60 min after the last dose of epidural lidocaine, subjects received a simultaneous intravenous and epidural injection. The intravenous group (n = 15) received butorphanol (Stadol, Bristol Laboratories, Evansville, IN) 2 mg intravenously and saline epidurally. The epidural group (n = 15) received butorphanol 2 mg epidurally and saline intravenously. A control group (n = 15) received only saline *via* both routes. All study solutions were prepared by an anesthesiologist not involved with subsequent data collection. The epidural catheter was removed after the study injection. All injections were prepared in a final volume of 10-ml of preservative-free normal saline. Neither the patient nor the investigator was aware of the content of the syringes. All subsequent data acquisition was made by one of the investigators, who was unaware of the patient's group assignment.

The injection of the study drug was considered time zero. Pain intensity was subsequently quantitated on a 10-cm linear visual analogue scale (VAS), marked such that 0 = no pain and 10 = worst pain imaginable. The VAS score was recorded at time zero and again at 30, 60, 90, 120, 240, and 360 min thereafter. When additional analgesics were requested, all patients were connected *via* intravenous tubing to a PCA device (LifeCare PCA Plus, Abbott Laboratories, Chicago, IL). A loading dose of 6–12 mg of morphine sulfate was administered intravenously according to the analgesic needs of the patient; the patient could then demand 2 mg morphine sulfate with a lockout interval of 7 min and a maximum dose of 30 mg over any 4-h period.

Pruritus and nausea were assessed at the above time intervals using a four-point ordinal scale such that 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Somnolence was assessed using a scale on which 0 = none (patient wide awake), 1 = mild (awake but drowsy), 2 = moderate (sleepy but arousable), and 3 = severe (unarousable).

On the morning after operation, a printout was obtained from all PCA pumps using a dedicated device designed to interface with the memory mode of the pump. This printout displayed the time of all medications administered *via* the pump. Morphine usage was assessed at 2, 4, 6, 8, and 12 h after administration of the study drug.

All data are expressed as means ± standard error of the mean except VAS scores, which are depicted as median and interquartile range (25—75% confidence intervals). Nominal data were compared using chi-squared analysis for a 2 × 3 contingency table. Continuous interval data were analyzed using analysis of variance and Sheffé's test for multiple comparisons. Ordinal data (VAS scores) were analyzed using the Kruskall-Wallis test. A value of $P < 0.05$ was considered to indicate statistical significance.

Results

Maternal demographic characteristics did not differ among groups although there was a numerically greater number of nulliparous women in the intravenous group (table 1). All patients were awake, alert, and comfortable (pain score of 0) upon arrival in the PACU and at time of study drug administration (time zero). Patients in the control group generally began to experience discomfort within 30 min after time zero and most began PCA usage shortly thereafter (figs. 1 and 2). Patients in the intravenous and epidural groups had similar VAS scores at all observation points. These scores were significantly lower than control group scores for the first 120 min after study

TABLE 1. Maternal Demographic Characteristics

Characteristic	Control (n = 15)	Intravenous (n = 15)	Epidural (n = 15)
Age	32 ± 1.2	31 ± 1.6	33 ± 1.2
Height (cm)	171 ± 2	172 ± 3	170 ± 1.5
Weight (kg)	77 ± 2.3	75 ± 4	80 ± 5
Parity			
Nulliparous	4	8	3
Multiparous	11	7	12
Birth weight (kg)	3.6 ± .3	3.4 ± .2	3.7 ± .2
Duration of surgery (min)	58 ± 3	47 ± 4	53 ± 4
Total doselocal anesthetic (ml)	30 ± 2	27 ± 2	28 ± 2

No significant differences among groups.

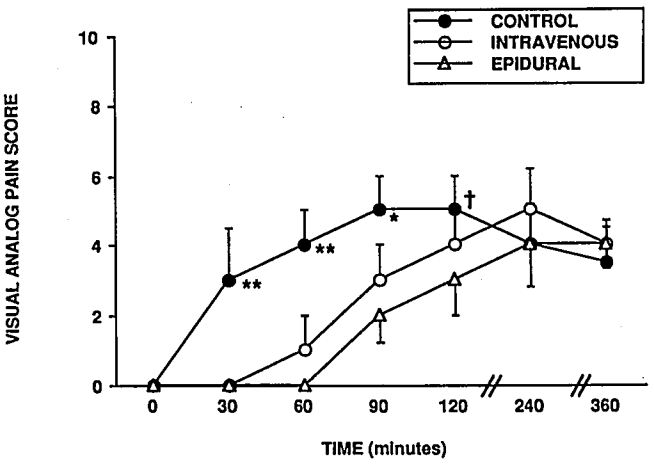

FIG. 1. VAS scores (median and interquartile range) after study drug administration. $**P < 0.001$, $*P < 0.01$ (control *vs.* epidural and intravenous). $\dagger P < 0.05$ (control *vs.* intravenous).

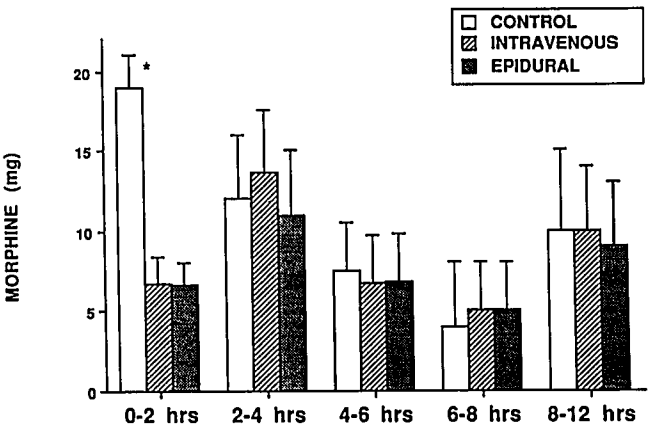

FIG. 3. Morphine usage (mean and SEM) during indicated time intervals after administration of study drug. $*P < 0.001$, (control *vs.* intravenous and epidural).

drug administration (fig. 1). The interval from time zero to the first use of PCA was similar in the intravenous and epidural groups, and in both groups this interval was significantly longer than in the control group (fig. 2). The morphine usage was similar in the intravenous and epidural groups at all observation points and was significantly less than control for the first 2 h after time zero (fig 3). After the 2-h observation point, morphine usage was similar in all groups.

SIDE EFFECTS

Pruritus was noted in 60% (9 of 15) of patients in the control group (3 mild, 3 moderate, and 3 severe), 13% (2 of 15) in the epidural group (both mild), and none in the intravenous group ($P = 0.001$, intravenous and epidural *vs.* control). Pruritus, when observed, occurred only after initiation of PCA therapy. Three patients in the control group discontinued PCA use between the 8- and 12-h observation points because of intractable pruritus. Somnolence occurred in 66% (10 of 15) in the intravenous group, 13% (2 of 15) in the epidural group, and 7% (1 of 15) in the control group ($P = 0.004$, intravenous *vs.* epidural and control). No patient was unarousable or dysphoric, was disturbed by excessive sedation, or demonstrated respiratory rate of less than 12 breaths · min^{-1} at any time. Nausea occurred in 53% (8 of 15) in the control group (2 mild, 2 moderate, and 4 severe), and in 13% (2 of 15) in both intravenous and epidural groups (1 mild and 1 moderate, $P = 0.04$, control *vs.* intravenous and epidural).

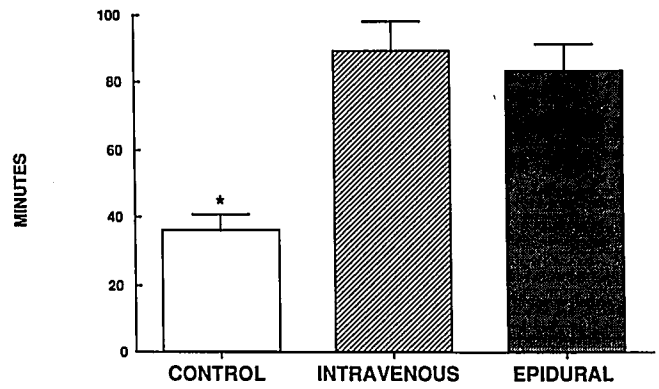

FIG. 2. Time from administration of study drug to first use of PCA (mean and SEM). $*P < 0.001$ (control *vs.* epidural and intravenous).

Discussion

The principal finding of this study is that butorphanol 2 mg, administered either intravenously or epidurally following cesarean delivery, produced a similar analgesic profile as quantitated by VAS scores, time to first PCA usage, and time-based PCA morphine requirements. Both routes of administration produced significantly better analgesia than did placebo, and both were equally efficacious in attenuating pruritus and nausea caused by subsequent PCA morphine usage. The sole difference appeared to be more sedation following the intravenous route. However, no patient complained of excessive somnolence or dysphoria or had an extended PACU stay. All patients were awake and alert upon discharge from the PACU.

Despite the popularity of epidural opioid use, surprisingly few studies directly compare epidural and parenteral administration of these agents. Many short-acting, lipophilic opioids (*e.g.*, fentanyl,[10] sufentanil,[11] meperidine,[12] butorphanol,[1-4] and nalbuphine)[13,14] have been studied in epidural doses similar to or even greater than the typical doses of these agents for parenteral use. Thus, it is not at all clear that the epidural administration of these opioids

results in substantially superior analgesia or fewer side effects than does simple parenteral use. This is in accord with evidence that the lipid solubility and the potency of intrathecal and epidural opioids are inversely related.[15] Two recent papers compared intravenous to epidural fentanyl infusions after either anterior cruciate ligament repair[16] or cesarean delivery,[17] and both found no clinical difference in either analgesia or side effect profile between the two routes of administration. In rats, epidural and intravenous sufentanil produced an equivalent analgesic profile and similar plasma, cortical, and cerebellar concentrations of this opioid.[18] In humans, a pilot study using either intravenous or epidural sufentanil 30 μg produced a statistically similar duration of analgesia and side effect profile following both routes, with the exception of more sedation following intravenous administration.[19] The same study ultimately concluded a similar and rapid onset but significantly longer duration of analgesia following epidural than intravenous administration; these results, however, were based on different doses of intravenous (10 μg) and epidural (50 μg) sufentanil. A recent investigation of epidural nalbuphine found a plasma pharmacokinetic profile quite similar to that reported for intravenous nalbuphine.[13]

We chose to perform a direct comparison of the same dose of butorphanol for several reasons. None of the previously published studies of epidural butorphanol has included an intravenous control group, yet virtually all report marked sedation as a frequent side effect of this agent. The most common dose of epidural butorphanol seems to be 2 mg, which is also a common dose for parenteral use. Doses greater than 2 mg have generally been associated with unacceptable degrees of sedation and/or dysphoria. Moreover, most of these reports observed a duration of analgesia of 2–3 h following epidural butorphanol, similar to that found for intravenous butorphanol in other studies.[20]

The neuraxial use of mixed agonist–antagonist opioids is currently under much investigation. Butorphanol has provided only moderate analgesia, and nalbuphine virtually no analgesia, when administered epidurally in humans.[1–4,13,14] κ-Agonist opioids have generally resulted in profound (albeit often stimulus-dependent) spinal analgesia in animal models.[21–23] Of note is that histologic analysis of these animal models characteristically show an abundance of κ receptors in the spinal cord, whereas similar analysis in humans demonstrates that most κ receptors are located in the brain and not the spinal cord.[24,25] Thus, epidural administration of κ-agonist opioids in humans may ultimately produce analgesia largely by supraspinal (*i.e.*, systemic) rather than spinal mechanisms. This finding may contribute to the equality of analgesia obtained from epidural or intravenous butorphanol in this study. In addition, this may in part explain our previous observation of a lack of inhibition of butorphanol analgesia by epidural 2-chloroprocaine.[3]

This is a growing body of evidence that the most useful role of agonist–antagonist opioids in anesthesia practice may be in the prevention and treatment of undesirable μ agonist side effects.[7–9] Our findings support the observations of others[6–9] in that pruritus and nausea during PCA morphine use were significantly reduced after butorphanol administration compared to the control group.

In summary, 2 mg of either intravenous or epidural butorphanol produced a similar analgesic profile following elective cesarean delivery with epidural anesthesia. Both routes were equally effective in blunting morphine-induced nausea and pruritus during subsequent PCA use. Although sedation was noticed after epidural administration, it was more marked after the intravenous route. The choice of intravenous or epidural administration of butorphanol may ultimately depend on the clinician's assessment of whether or not some degree of sedation is desirable for a particular patient. Certainly more work is warranted to assess further whether epidural administration of other short-acting, lipophilic opioids offers any advantage over parenteral use.

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