A Randomized Comparison of Programmed Intermittent Epidural Bolus with Continuous Epidural Infusion for Labor Analgesia

Cynthia A. Wong, MD, John T. Ratliff, MD, John T. Sullivan, MD, Barbara M. Scavone, MD, Paloma Toledo, MD, and Robert J. McCarthy, PharmD

Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Ilinois

Bolus injection through an epidural catheter may result in better distribution of anesthetic solution in the epidural space compared with continuous infusion of the same anesthetic solution. In this randomized, double-blind study we compared total bupivacaine consumption, need for supplemental epidural analgesia, quality of analgesia, and patient satisfaction in women who received programmed intermittent epidural boluses (PIEB) compared with continuous epidural infusion (CEI) for maintenance of labor analgesia. The primary outcome variable was bupivacaine consumption per hour of analgesia. Combined spinal epidural analgesia was initiated in multiparas scheduled for induction of labor with cervical dilation between 2 and 5 cm. Subjects were randomized to PIEB (6-mL bolus every 30 min beginning 45 min after the intrathecal injection) or CEI (12-mL/h infusion beginning 15 min the after the intrathecal injection). The epidural analgesia solution was bupivacaine 0.625 mg/mL and fentanyl 2 μg/mL. Breakthrough pain in both groups was treated initially with patient-controlled epidural analgesia (PCEA) followed by manual bolus rescue analgesia using bupivacaine 0.125%. The median total bupivacaine dose per hour of analgesia was less in the PIEB ($n = 63$) (10.5 mg/h; 95% confidence interval, 9.5–11.8 mg/h) compared with the CEI group ($n = 63$) (12.3 mg/h; 95% confidence interval, 10.5–14.0 mg/h) ($P < 0.01$), fewer manual rescue boluses were required (rate difference 22%, 95% confidence interval of difference 5% to 38%), and satisfaction scores were higher. Labor pain, PCEA requests, and delivered PCEA doses did not differ. PIEB combined with PCEA provided similar analgesia, but with a smaller bupivacaine dose and better patient satisfaction compared with CEI with PCEA for maintenance of epidural labor analgesia.

(Anesth Analg 2006;102:904–9)

The maintenance analgesia technique for epidural labor analgesia has evolved from intermittent manual bolus injections to continuous infusions with or without patient controlled epidural analgesia (PCEA). Although continuous epidural infusion (CEI) analgesia is associated with more consistent analgesia, improved patient satisfaction, and reduced workload for the anesthesiologist, total anesthetic doses are larger and motor block may be more profound (1–3).

Automated systems that are designed to administer a small bolus dose of anesthetic at programmable intervals may combine the advantages of both manual bolus and CEI systems. Similar to CEI, small intermittent boluses may avoid wide fluctuations in sensory levels common with manually administered boluses but, in contrast to CEI, reduce the total anesthetic dose.

We hypothesized that programmed intermittent epidural bolus (PIEB) administration would result in less total bupivacaine use, less need for PCEA and manual bolus administration, and improved patient satisfaction compared with CEI for the maintenance of labor analgesia. The primary outcome variable was total bupivacaine dose per hour of epidural analgesia.

Methods

The study was approved by the Northwestern University IRB. Healthy, parous (at least one previous vaginal delivery), term women with singleton, vertex pregnancies, scheduled for induction of labor were eligible to participate in the study. Subjects who met

Accepted for publication October 26, 2005.

The epidural pumps and disposable pump tubing used in this study were loaned and donated by B. Braun Medical Inc., Bethlehem, PA.

Address correspondence to Cynthia A. Wong, MD, Department of Anesthesiology, 251 E. Huron Street, F5-704, Chicago, IL 60611. Address e-mail to c-wong2@northwestern.edu.

DOI: 10.1213/01.ane.0000197778.57615.1a

0003-2999/06

the above criteria were recruited shortly after admission to the labor and delivery unit and gave written informed consent to participate. Subjects were recruited between June 2003 and April 2005. Exclusion criteria included the presence of systemic disease (e.g., diabetes mellitus, hypertension, preeclampsia) and chronic analgesic use.

At the time of request for labor analgesia the cervix was examined. If cervical dilation was between 2 and 5 cm and no systemic opioid analgesics had been administered, the parturient was randomized to receive maintenance of analgesia by either PIEB or by CEI. A sequentially numbered opaque envelope containing the group assignment (computer generated random number sequence) was opened by the unblinded anesthesia researcher at the time of randomization. The subject and other study personnel were blinded as to group assignment.

Baseline pain was assessed with the Visual Analog Scale (VAS) (100 mm unmarked line with end-points labeled "no pain" and "worst pain imaginable"). Combined spinal-epidural analgesia was initiated at the L3-4 or L2-3 interspace with the subject in the sitting position using a needle-through-needle technique. The epidural space was identified using loss-of-resistance to air (1 to 2 mL). After ascertaining free flow of cerebrospinal fluid from the spinal needle, plain bupivacaine 1.25 mg and fentanyl 15 μg were injected intrathecally. A single orifice epidural catheter (Arrow FlexTip Plus™; Arrow International, Inc., Reading, PA) was sited 4 to 5 cm in the epidural space and a 3 mL epidural test dose of lidocaine 1.5% with epinephrine 1:200,000 was administered. The catheter was secured and the parturient was placed in the lateral position.

Subjects continued in the study if their VAS < 10 mm 10 min after the intrathecal injection. An unblinded researcher set up two epidural pumps (CMS 4000; Curlin Medical, LLC, Huntington Beach, CA) for each subject. One pump administered either the PIEB or CEI while the second pump administered PCEA. The epidural infusion tubing from the pumps was connected via a 3-way stopcock to the hub of the epidural catheter. The epidural solution for both pumps consisted of bupivacaine 0.625 mg/mL and fentanyl 2 μg/mL.

Depending on group assignment, the first pump was programmed as follows: the PIEB pump delivered a 6-mL bolus at a rate of 400 mL/h every 30 min beginning 45 min after administration of the intrathecal dose; the CEI pump delivered a continuous infusion at 12 mL/h beginning 15 min after the intrathecal dose. The PCEA pump was programmed to deliver 5 mL patient-activated boluses with a lockout interval of 10 min and a per hour maximum of 15 mL. The subject was instructed on the use of the PCEA pump and was told to push the button whenever she felt uncomfortable. If the parturient felt she had inadequate analgesia after having activated the PCEA bolus twice in a 20-min period an anesthesiologist administered manual boluses of bupivacaine 1.25 mg/mL (5 to 15 mL) until the VAS was <10 mm.

VAS for pain was obtained every 60 min beginning 15 min after the intrathecal injection until delivery. A modified Bromage score (0 = no impairment; 1 = unable to raise extended leg but able to move knees and feet; 2 = unable to raise extended leg as well as flex knees, able to move foot; 3 = not able to flex ankle, feet or knees [complete block]) was determined every 60 min during the first stage of labor. The epidural infusions were discontinued shortly after completion of the perineal repair. Before discharge from the Labor and Delivery Unit the subject was asked to rate her overall satisfaction (0–100 mm VAS) with labor analgesia.

Data collected for each subject included demographic characteristics, labor data, and method of delivery. The records of the epidural infusions including PCEA requests, delivered PCEA boluses, and total infused volumes were obtained from the infusion pumps. The number and total volume of manual rescue boluses were recorded. Local anesthetic administered specifically for forceps delivery analgesia was not included in the total drug calculation.

The primary outcome variable was bupivacaine consumption per hour of infusion. This was calculated by adding the bupivacaine administered by both epidural pumps and by manual bolus and dividing the total by the duration of the epidural analgesia (beginning 15 min after the intrathecal injection until the time of delivery). A sample of 128 subjects (64 per group) was estimated by assuming the difference in the sample mean divided by the standard deviation of the entire sample of the primary outcome variable was 0.5. This sample size would be required to avoid a type II error at $\alpha = 0.05$ and power = 0.80. Thirty additional subjects were included in the randomization to allow for anticipated exclusion of subjects from data analysis. Subjects who delivered within 90 min of intrathecal injection were excluded from the analysis because this was the expected duration of intrathecal analgesia and epidural analgesia would have had a limited role in their analgesic consumption (4). Subjects in the PIEB group were excluded if the duration of the programmed epidural bolus exceeded 2 min. This problem was identified during preliminary experience with the pump because the resistance limit to flow was exceeded in some patients. This resulted in the "bolus" dose being given in small increments over minutes, thus approaching the characteristics of a continuous infusion rather than a bolus.

By study design the infusion volume delivered by the epidural pump in the CEI group for an individual subject was larger than that delivered by the PIEB

Table 1. Subject Characteristics

	PIEB ($n = 63$)	CEI ($n = 63$)	P value
Gestational age (wk)	39 (37–41)	39 (37–41)	0.91
Parity	1 (1–4)	1 (1–3)	0.15
Height (cm)	165 ± 6	167 ± 7	0.15
Weight (kg)	76 ± 10	81 ± 13	0.06
Cervical dilation at initiation of labor analgesia (cm)	3 (2–5)	3 (2–5)	0.47
Baseline visual analog scale (0-100) for pain (mm)	59 ± 18	57 ± 16	0.59
Labor analgesia initiation to delivery interval (min)	188 (92–498)	184 (96–614)	0.73
Mode of delivery (cesarean/forceps/NSVD) (n)	1/3/59	0/4/59	0.56

PIEB = programmed intermittent epidural bolus; CEI = continuous epidural infusion; NSVD = normal spontaneous vaginal delivery. Data are presented as mean ± SD or median (range) unless stated otherwise.

pump during the interval between PIEP boluses. As this difference could account for the difference in total bupivacaine dose per hour between groups, we performed a second analysis of bupivacaine dose per hour after adjusting for the difference in bupivacaine delivered by the infusion pump (the median difference between groups in bupivacaine dose/h administered by the infusion pump was subtracted from the bupivacaine/h dose in subjects in the CEI group).

Secondary outcome variables included labor pain as measured by calculating the area under the VAS × time curve using the trapezium rule, time to first PCEA request, number of PCEA requests, actual delivered PCEA boluses and total PCEA dose, and total manual bolus bupivacaine dose. These values were adjusted for the difference in epidural infusion duration by dividing by the duration of epidural analgesia. Other outcomes included the number of subjects who received one or more manual rescue boluses, the number of subjects with a Bromage score >0, and subject assessment of overall labor analgesia satisfaction.

In addition, it was anticipated that the contribution of the epidural component of combined spinal-epidural analgesia would become more important as a function of the duration of labor. Therefore a planned *post hoc* analysis was performed to examine the effect of duration of labor on total bupivacaine consumption per hour by dividing both the PIEB and CEI groups into subgroups at the overall median duration of analgesia.

Interval and ordinal data were compared between groups using the two-tailed Student's *t*-test or the Mann-Whitney *U*-test after testing for normal distribution. Categorical data were compared using a χ^2 statistic or the Fisher's exact test. The Bonferroni method was used to correct for multiple comparisons. The time to first PCEA request was compared by the Kaplan Meier method and the log-rank test. Subjects who did not request additional analgesia were censored at the time of delivery. $P < 0.05$ was required to reject the null hypothesis. Sample size calculations and data analysis were performed by the authors using PASS and NCSS 2004 (NCSS, Kaysville, UT).

Results

One-hundred-and-fifty-eight subjects were randomized to either the PIEB group or the CEI group. Data from 126 subjects, 63 per group, were included in the analysis. Excluded from the analysis were 20 subjects (PIEB = 11; CEI = 9) who delivered within 90 min of intrathecal analgesia and 10 subjects in the PIEB group who did not receive programmed boluses because pump occlusion limits were exceeded during programmed boluses. An additional 2 subjects had VAS > 10 mm 10 min after the intrathecal injection. The study groups did not differ with respect to subject age, weight, height, baseline VAS for pain, method of delivery, or the intrathecal injection to delivery interval (Table 1).

The median total bupivacaine delivered per hour of infusion was less in the PIEB group (10.5 mg/h; 95% confidence interval [CI], 9.5–11.8 mg/h) compared with the CEI group (12.3 mg/h; 95% CI, 10.5–14.0 mg/h) ($P < 0.01$) (Fig. 1). The median difference in the basal dose of bupivacaine per hour administered by PIEB pump compared with the CEI pump was −0.339 mg/h (95% CI −0.630 to −0.119 mg/h) ($P < 0.01$). After correction for this difference, the median total bupivacaine delivered per hour of infusion was still less in the PIEB group (10.5 mg/h; 95% CI, 9.5–11.8 mg/h) compared with the CEI group (11.9 mg/h; 95% CI, 10.2–13.6 mg/h) ($P = 0.04$). Similarly, the median fentanyl dose per hour of infusion was less in the PIEB group compared with the CEI group (Table 2). The number of subjects who received manual rescue boluses, the number of manual rescue boluses per subject, and the amount of bupivacaine administered as manual rescue boluses were less in the PIEB group. Despite reduced bupivacaine consumption, labor pain as assessed by hourly VAS (data not shown), the area under the VAS × time curve, as well as the time to first PCEA request, number of requests, and delivered PCEA boluses of bupivacaine were similar (Table 2).

One subject in each group had a Bromage score ≥1 during labor. Subject satisfaction with analgesia management was greater in the PIEB group compared with the CEI group (Fig. 2). The median VAS for

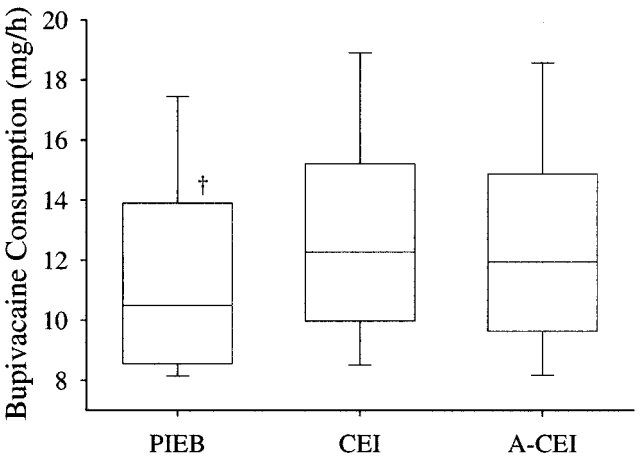

Figure 1. Box plot of total bupivacaine consumption per hour from the start of the epidural infusion until delivery. PIEB = programmed intermittent epidural bolus; CEI = continuous epidural infusion; A-CEI = adjusted continuous epidural infusion. †PIEB different from CEI ($P = 0.007$) and A-CEI ($P = 0.04$).

satisfaction was 92 mm (95% CI, 89–95 mm) for the PIEB group and 85 mm (95% CI, 77–90 mm) for the CEI group ($P < 0.01$).

For subjects whose labor analgesia to delivery interval was less than the median (186 min) the median total bupivacaine consumption per hour was not different between the PIEB group and the CEI group (Fig. 3). Likewise the number of subjects requiring manual rescue boluses was not different between groups (PIEB 34%, CEI 41%; $P = 0.80$). In contrast, in subjects whose duration of labor analgesia was more than 186 min the total bupivacaine consumption per hour was less in the PIEB group compared with the CEI group even when corrected for the difference in pump infusion doses (Fig. 3). Similarly, the number of subjects requiring manual rescue boluses was larger in the PIEB group (36%) compared with the CEI group (68%) whose analgesia duration was more than the median ($P = 0.02$).

Discussion

The important finding of this study was that PIEB combined with PCEA resulted in less bupivacaine consumption compared with CEI plus PCEA while providing equivalent labor analgesia. The difference in bupivacaine delivery was larger in subjects who had longer labor durations. In addition, we found that patient satisfaction was higher with PIEB compared with CEI analgesia.

Advantages to PIEB administration were also observed by Chua and Sia (5). In their study, time to first manual epidural rescue bolus was longer and pain scores were lower in subjects assigned to PIEB compared with those receiving CEI.

Automated methods of bolus injection may combine the advantages of manual epidural boluses and CEI while limiting the disadvantages of the two techniques. Our findings support the findings of previous studies that have shown that intermittent manual bolus injection has a dose-sparing effect on total local anesthetic consumption compared with CEI of the same solution (1–3). Manual epidural boluses, however, require more interventions by the anesthesiologist. The number of manual bolus injections in the current study was less with PIEB compared with CEI. Another potential disadvantage of manual intermittent boluses is that the epidural system is opened more often with an increased risk for contamination and drug error compared with a closed CEI. Manual boluses may also be associated with wider variation in pain relief depending on the interval between boluses. Pain, as assessed by area under the VAS × time curve, was similar in both groups of subjects in the current study. This is likely a result of the inclusion of PCEA, in addition to the administration of manual boluses, for breakthrough pain, allowing subjects to titrate to a similar degree of analgesia.

The infrequent incidence of motor blockade in both groups in the present study is likely explained by the use of a lower concentration bupivacaine solution. Because motor blockade is considered undesirable during labor analgesia, the potential dose-sparing effect of an intermittent bolus technique may be more clinically relevant when higher concentration local anesthetic solutions are used. In addition to bupivacaine, we found a dose-sparing effect for fentanyl. Systemic absorption of epidural fentanyl may result in fetal depression (6). Therefore, an analgesic technique that minimizes the total fentanyl dose might have implications for neonatal outcome.

Subject satisfaction with labor analgesia was high in both groups; however, we found a greater satisfaction rating in subjects who received PIEB. The median difference in satisfaction score between the groups in this study was 7. This difference was found to represent a clinically significant difference in satisfaction when measured by a 100-mm VAS (7).

Several mechanisms have been proposed to explain the advantages of bolus compared with continuous infusion administration of epidural solutions. When injected as a bolus through a multiorifice epidural catheter, the solution exits the distal end of the epidural catheter through all the orifices (8). In contrast, when a continuous infusion of the same volume is injected through the catheter, the solution primarily exits through the proximal orifice. This suggests that an epidural bolus through a multiorifice epidural catheter could result in wider sensory blockade compared with a continuous infusion of the same volume and might result in improved analgesia (8). Indeed, Chua and Sia used a multiorifice catheter in their

Table 2. Labor Analgesia and Pain Management

	PIEB (n = 63)	CEI (n = 63)	P value
Labor pain*	6.7 (0–42.3)	10.3 (0–57.6)	0.25
Epidural bupivacaine dose (mg/h)†	7.1 (5.1–7.7)	7.4 (5.7–7.4)	<0.01
Epidural fentanyl dose (μg/h)	22.0 (14.0–30.8)	23.1 (19.4–25.8)	<0.01
Time to first PCEA request (min)‡	127 (25–322)	116 (29–306)	0.42
PCEA requests (number/h)	1.1 (0–5.4)	1.3 (0–6.7)	0.60
PCEA bupivacaine dose (mg/h)	2.5 (0–6.7)	2.6 (0–8.4)	0.87
Manual bolus (number of subjects)	20	34	0.01
Manual bolus (number per subject)	0 (0–2)	1 (0–3)	<0.01
Manual bupivacaine dose (mg/h)	0 (0–10.6)	1.6 (0–17.4)	0.02
Total bupivacaine dose (mg)	32.6 (10.7–83.3)	37.5 (15.6–111.0)	0.06

PIEB = programmed intermittent epidural bolus; CEI = continuous epidural infusion; PCEA = patient-controlled epidural analgesia. Data are presented as median (range) unless stated.

*Area under the VAS × time curve from start of epidural infusion (15 min after intrathecal injection) to delivery. VAS = visual analogue scale.

†Amount of bupivacaine administered by PIEB or CEI infusion pump.

‡Time from start of epidural infusion.

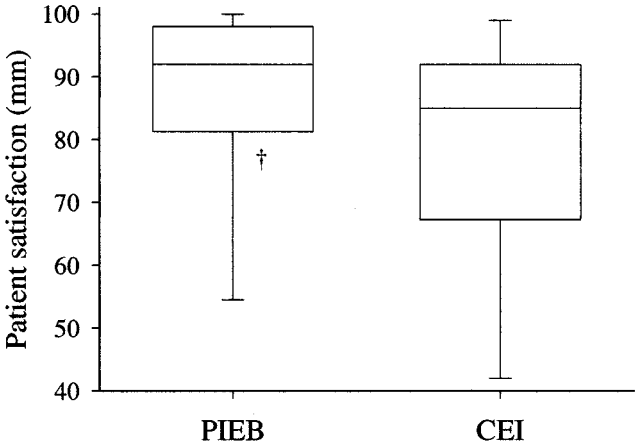

Figure 2. Box plot of subject satisfaction with labor analgesia: 100 mm line where 0 = not satisfied at all and 100 = very satisfied. PIEB = programmed intermittent epidural bolus; CEI = continuous epidural infusion. †PIEB different from CEI (P = 0.003).

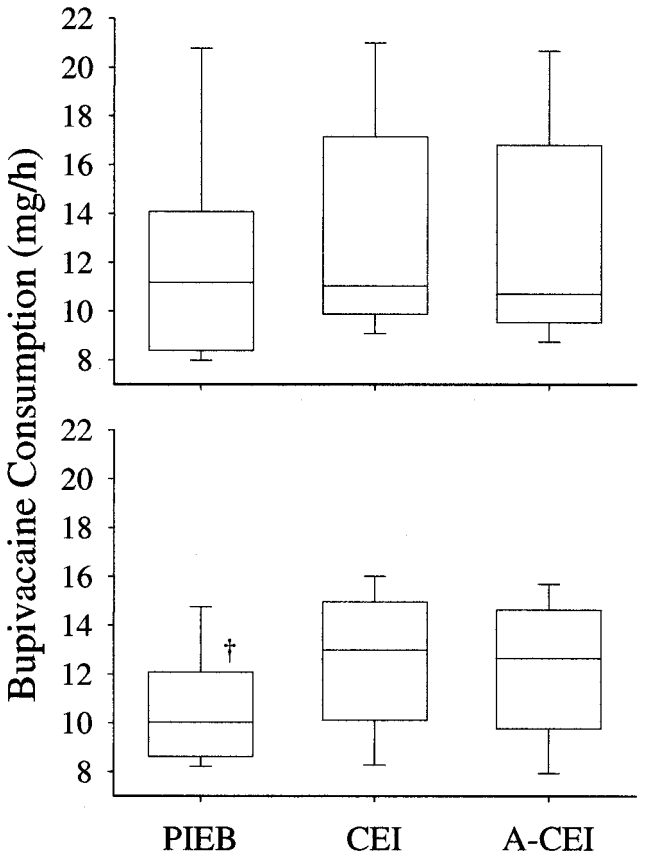

Figure 3. Upper: Box plot of bupivacaine consumption per hour for subjects whose labor analgesia to delivery interval was less than the median (186 min). Lower: Box plot of bupivacaine consumption per hour for subjects whose labor analgesia to delivery interval was more than the median (186 min). †PIEB different from CEI (P = 0.01) and A-CEI (P = 0.03). PIEB = programmed intermittent epidural bolus; CEI = continuous epidural infusion; A-CEI = adjusted epidural infusion.

study; however, a single orifice catheter was used in the present study with similar results. Another possible explanation for the finding of reduced bupivacaine consumption with bolus techniques may be that the distribution of solutions in the epidural space is nonuniform and spread is more uniform when large volumes (and correspondingly high injectate pressures) are delivered (9). In support of this theory, Ueda et al. (10) found that programmed epidural bolus administration of ropivacaine resulted in more blocked spinal segments compared with a continuous infusion in patients who received postoperative thoracic epidural analgesia.

There are several limitations to the generalization of our study conclusions. By study design, subjects randomized to the CEI received, on average, more drug (bupivacaine and fentanyl) via the infusion pump than subjects randomized to PIEB. However, despite this inherent bias and even after correction for the additional bupivacaine/fentanyl, subjects in the PIEB group had similar analgesia, required fewer manual boluses, and were more satisfied with their analgesia. Furthermore, the technique for administration of drug in the control (CEI) group was primarily a continuous

infusion; PCEA was used as a rescue modality. PCEA without a background infusion is also an intermittent bolus technique. It remains to be determined whether the PIEB is superior to PCEA when it is used as the primary mode of analgesic administration.

Another limitation is that we studied multiparas who had relatively short labors. It is likely, however, that the results of the present study would apply to other laboring women. In the current study the salutary effect of PIEB was greater in women with longer labors and therefore may be of greater value in nulliparous women or others with long labors. Indeed, similar results have been observed in nulliparous women (5). In addition, our patient population did not have a high rate of operative delivery. Women who deliver by cesarean after labor have greater labor analgesic requirements than women who deliver vaginally and may therefore benefit from different modes of maintenance analgesia (11).

In summary, we found that PIEB combined with PCEA was superior to CEI combined with PCEA for labor analgesia. The greatest impediment to the implementation of PIEB analgesia is the lack of readily available epidural pumps designed to deliver timed boluses or time boluses with PCEA. The two-pump system we used is not clinically practical. Further studies are warranted to determine whether this technique has benefit in other clinical applications of epidural pain management. In addition, studies are needed to determine the optimal combination of bolus volume, time interval, and drug concentration for use with this technique and whether this technique offers benefits compared with PCEA without a background infusion.

The authors wish to acknowledge the obstetric anesthesia nurses Roshani Patel, RN and Carmen Robles, RN, in addition to the Labor and Delivery Unit nursing staff, for their help in completing this study.

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