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Epidural Sufentanil for Postoperative Analgesia after Cesarean Section

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The greater lipid solubility of sufentanil when compared to morphine¹ is likely to result in a more rapid onset of analgesia when used as an epidural agent. In addition, sufentanil has a higher affinity for opiate receptor sites,² which may provide a prolonged duration of analgesia. High lipid solubility of sufentanil may result in rapid clearance of sufentanil from cerebrospinal fluid and allow for less cephalad spread. Cephalad spread of spinal opioids has been associated with the occurrence of side effects, such as pruritus, nausea, and respiratory depression;³ sufentanil may result in fewer and less severe side effects than morphine when administered epidurally to provide analgesia. This prospective study was undertaken to evaluate the efficacy, dose response, and side effects of sufentanil when administered as a postoperative epidural analgesic for cesarean section and to compare these results with epidural administration of morphine sulfate (5.0 mg), commonly used at our institution.

MATERIALS AND METHODS

With approval from the University of California, San Francisco Committee on Human Research and informed consent from each patient, 40 healthy women undergoing cesarean section with epidural anesthesia were studied. Major complications during pregnancy, major organ diseases, or a history of drug abuse excluded a patient from study. However, patients with lesser medical problems or complications of pregnancy, such as gestational diabetes, mild preeclampsia, cephalopelvic disproportion, or premature rupture of membranes were included.

Patients were given no preoperative medication except an antacid. Epidural anesthesia was provided with 2% lidocaine and epinephrine (1:200,000) administered through a catheter inserted at the L2-3 or L3-4 interspace. Diazepam, not exceeding 7.5 mg iv, and/or fentanyl, not exceeding 100 µg iv, were used during the cesarean procedure to supplement anesthesia. The epidural catheters were left in place following surgery.

When patients first requested pain relief during recovery, they were randomly assigned to one of four groups that received either sufentanil (30, 45, or 60 µg) or morphine sulfate (5.0 mg) through the indwelling epidural catheters. Each group consisted of 10 patients. Each dose of epidural opioid (morphine or sufentanil) was prepared in advance by a pharmacist (CJ) in a 10-ml volume of sterile preservative-free normal saline and packaged in single-administration glass ampules with coded labels. The codes were assigned by and known only to the pharmacist. Neither the investigator nor the patient knew which opioid the patient had received.

The intensity of pain was assessed by each patient using a visual linear analog scale⁴ immediately before epidural administration of opioid, and, thereafter, at 15, 30, 45, and 60 min, followed by every half hour for the next 2 h, then every hour for 9 h. Blood pressure, pulse, and respiratory rates in each patient were mea-

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sured the same time as pain intensity assessments. For patients asleep at any observation point, pain intensity was recorded as 0 = no pain. Asleep patients were not awakened to elicit information, and blood pressure and pulse rate were not measured during sleep. However, respiratory rates were monitored and asleep patients were observed for signs of airway obstruction or shallow breathing. Respiratory depression was defined as a respiratory rate of less than ten.

The presence and intensity of side effects, including nausea, vomiting, or pruritus, were also evaluated at the same time as pain intensity assessments. The patients were asked whether they were experiencing these or other side effects, the severity of which was assessed according to the scales shown in table 1. During the study period, if treatment for side effects was required, prochlorperazine (12.5 mg iv) was given for nausea, and diphenhydramine (25 mg iv) for pruritus. If this was inadequate, naloxone (0.04 mg iv) was administered. After the study period, naloxone was administered for side effects.

When patients experienced effective pain relief lasting longer than 2 h, but less than 10 h, a second dose of the same opioid was administered through the indwelling epidural catheter. Neither the investigator nor the patient knew which opioid the patient received for the second dose. The epidural catheter was then removed. Patients who had received sufentanil were given the same dose of 30, 45, or 60 µg for the second administration, but patients who had received morphine were given a smaller second dose of 2.0 mg. The doses of epidural opioids used for the second administration were prepared identically to those used for the first dose, in 10-ml volume of sterile preservative-free normal saline, packaged in glass ampules with coded labels indicating second dose. Following the second dose, assessments of pain intensity, vital signs, and side effects were conducted at the same intervals employed after the first dose of epidural opioid. All epidural catheters were removed within 10 h after the first epidural administration of opioid. Patients received a maximum of 2 doses of epidural opioids, and then routine postoperative analgesics were prescribed by each patient's personal physician. Duration of analgesia was defined as time from the epidural administration of epidural opioid to the first request for additional analgesic medication.

All parenteral and oral analgesics administered after termination of epidural opioids were tabulated for each patient over the first 72 postoperative hours, and were equated to an analgesic equivalent of im morphine as follows: 10 mg of im morphine sulfate = 100 mg of im meperidine hydrochloride = 120 mg of oral codeine phosphate = 15 mg of oral oxycodone hydrochloride.

TABLE 1. Scales Used by Independent Investigator to Assess Side Effects

Side Effects		
Nausea	Vomiting	Pruritus
0 = none 1 = mild 2 = moderate/ severe	0 = none 1 = single 2 = multiple episodes	0 = none 1 = mild 2 = moderate/severe localized 3 = mild generalized 4 = moderate/severe generalized

For purposes of comparison, each patient's assessment of pain was compared to her initial evaluation of pain using data from the visual linear analog scale. Maternal pain relief was the percentage change from her initial assessment of pain immediately before a dose of epidural opioid was administered, according to methods previously described.⁵

Age, height, and weight are expressed as mean ± SD and were compared using ANOVA, followed by Student-Newman-Keuls testing where indicated. Onset and duration of analgesia and postoperative narcotic requirements are expressed as median values with semi-quartile ranges, and were compared using the Kruskal-Wallis test. When indicated, pairwise comparisons were made using the Mann-Whitney rank-sum test, including a Bonferroni adjustment. The incidence of side effects and the administration of intraoperative diazepam and fentanyl were compared using Fisher's exact testing. A result was considered statistically significant when the *P* value was 0.05 or less.

RESULTS

The four groups of patients did not differ in age, height, weight, ethnic background, or incidence of previous cesarean section (table 2). Twenty-three of the 40 patients received diazepam iv during cesarean section, five of whom received sufentanil 30 µg, six of whom received sufentanil 45 µg, eight of whom received sufentanil 60 µg, and four of whom received morphine epidurally. Of the sixteen patients who received fentanyl iv, three received sufentanil 30 µg, three received sufentanil 45 µg, seven received sufentanil 60 µg, and three received morphine epidurally. There were no significant differences in the administration of either diazepam or fentanyl among the four groups.

Figure 1 illustrates each patient's assessment of pain before and after the first administration of epidural opioid. All patients remained awake well after 90% pain relief was achieved. Times to onset of 50% and 90% pain relief, based on the visual linear analog scale, are presented in table 3. Patients who received epidural

TABLE 2. Characteristics of 40 Women Who Received Epidural Opioid Administration for Postoperative Analgesia after Cesarean Section*

	Morphine Sulfate 5 mg	Sufentanil 30 μ g	Sufentanil 45 μ g	Sufentanil 60 μ g
Age (years)	28 \pm 4.8	30 \pm 8.0	31 \pm 5.1	31 \pm 6.3
Height (inches)	64 \pm 5.2	64 \pm 3.5	65 \pm 3.3	62 \pm 2.7
Weight (kilograms)	80 \pm 13.4	80 \pm 19.6	80 \pm 10.4	79 \pm 15.9

Each value represents the mean \pm SD of ten patients.

* No significant differences between groups.

sufentanil obtained comparable analgesia significantly sooner than those who received morphine. Only one of the ten patients who received morphine reported 50% pain relief within 15 min of epidural administration. Among the groups who received 30, 45, or 60 μ g of sufentanil, eight, nine, and ten patients, respectively, reported 50% pain relief within 15 min. There were no significant differences in time to 90% pain relief among the three doses. Those given morphine obtained 90% pain relief between 45 to 420 min after administration (60–202 min semiquartile range), with a median time of 90 min. However, once peak analgesia was achieved, the quality of pain relief was similar with both opioids (fig. 2).

The duration of analgesia provided by sufentanil was significantly shorter than that provided by morphine

(table 3). The median time to request of additional analgesia among patients given morphine was 26.4 h. Median times to first request for additional analgesia among patients who received 30, 45, or 60 μ g of sufentanil were 3.9, 4.5, and 5.6 h, respectively. The differences in duration among the three sufentanil groups were not significant. Median times for onset and duration of analgesia after the second administration of sufentanil were not significantly different from those for the first dose (table 3).

Two of the 10 patients in the morphine group obtained pain relief for more than 2 h, but less than 10 h. Both requested a second administration of epidural opioid and received 2.0 mg of epidural morphine. One obtained analgesia for another 17 h, and the second for only another 90 min. All but one of the patients in the

a) Morphine 5 mg

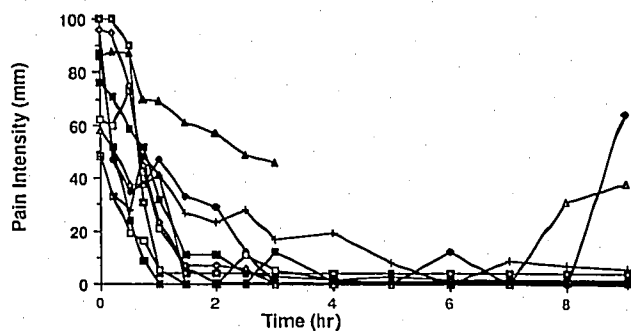
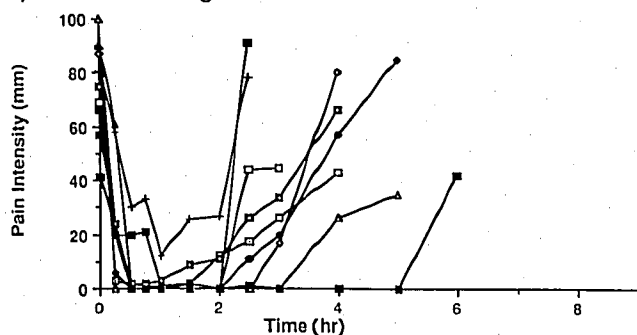
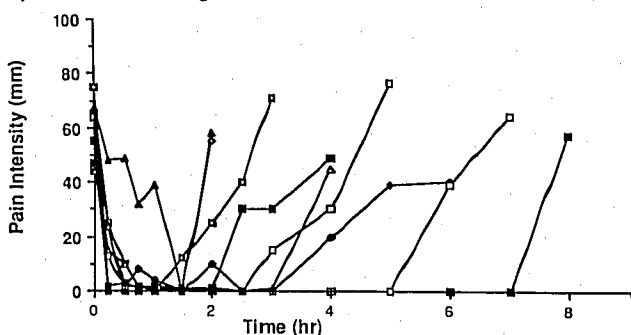
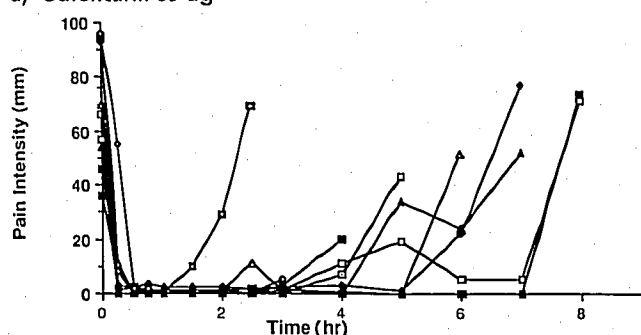
b) Sufentanil 30 μ gc) Sufentanil 45 μ gd) Sufentanil 60 μ g

FIG. 1. Maternal assessment of pain, as measured from the visual linear analog scales, before (time zero) and after epidural administration of: a) morphine sulfate 5 mg; b) sufentanil 30 μ g; c) sufentanil 45 μ g; and d) sufentanil 60 μ g. The patient represented her pain by placing a point somewhere between "no pain" (0 mm) and "the worst pain I have ever experienced" (100 mm).

TABLE 3. Onset and Duration of Analgesia with Epidural Morphine and Sufentanil

	Morphine Sulfate 5 mg	Sufentanil 30 µg	Sufentanil 45 µg	Sufentanil 60 µg
Onset of 50% pain relief (min)	52* (24-80)	15 (15-19)	15 (15-15)	15 (15-15)
Onset of 90% pain relief (min)	90* (60-202)	30 (15-38)	30 (15-45)	15 (15-19)
Duration of first dose (h)	26.4* (17.3-31.5)	3.9 (2.8-5.2)	4.5 (2.7-6.2)	5.6 (4.4-7.2)
Duration of second dose (h)	see text	3.5 (2.5-5.9)	5.5 (3.9-7.0)	5.2 (4.1-6.6)

There are ten patients in each group. Values are median with semi-quartile range in parentheses.

* $P < 0.05$ compared to each sufentanil group.

three sufentanil groups had pain relief > 2 h but < 10 h, and received the same epidural dose of sufentanil a second time. One patient who had received 45 µg of sufentanil obtained analgesia of less than 2-h duration (110 min), and, therefore, did not receive a second epidural dose. The analgesia achieved was similar for all dosages.

Patients who received morphine required significantly less analgesics in the first 72 postoperative hours than patients in the 30- and 45-µg sufentanil groups (table 4). Comparison of morphine with the 60-µg sufentanil group did not reach statistical significance. However, requirements for analgesics among the three sufentanil groups did not differ significantly.

Across all study intervals, blood pressure, pulse, and respiratory rates did not differ significantly in any of the four groups. The lowest respiratory rate observed was 12 breaths/min, and this occurred in two patients who had received 60 µg of sufentanil. One of these patients had a respiratory rate of 12 breaths/min prior to sufentanil administration, and at several times thereafter, up to 5 h into the study. The other patient had a respiratory rate of 12 breaths/min at 30 and 45 min after the administration of sufentanil. There was no significant difference in the incidence of pruritus, nausea, or vomiting between groups. At least 80% of patients in each group experienced some degree of pruritus. However, when all patients who received sufentanil were compared to the patients who received morphine, those given morphine had a significantly higher incidence of generalized pruritus than those given sufentanil, 50% versus 17%, respectively ($P < 0.05$). The highest incidence of nausea and/or vomiting was 20%. This occurred in both the morphine and sufentanil 60-µg groups. None of the patients who received 30 µg of sufentanil had nausea and/or vomiting. No patients required naloxone during the study period for treatment of side effects.

DISCUSSION

Epidural administration of sufentanil at three different doses rapidly produced analgesia. Onset was evident within 15 min of administration and near maximal (90% pain relief) effect was reliably obtained within 45 min. In contrast, the median time to onset of analgesia (50% pain relief) after epidural morphine was 52 min and 90 min for near maximal pain relief. The quality of pain relief was similar with both narcotics once analgesia was achieved. The duration of action of sufentanil

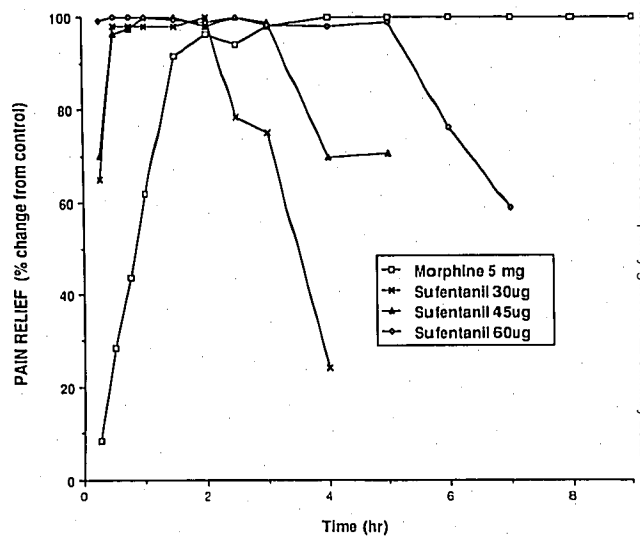


FIG. 2. Maternal pain relief (expressed as % change from assessment before morphine or sufentanil) for 40 patients after the first epidural administration of morphine sulfate (5 mg) or sufentanil (30, 45, or 60 µg) after cesarean section. Data points represent median values for those patients who had not requested additional analgesia. Data were not plotted when less than four patients remained. Four hours after administration, nine patients remained in the morphine group and six, seven, and eight patients who received sufentanil 30, 45, and 60 µg, respectively, remained. At 9 h, nine patients remained in the morphine group and none remained who received sufentanil.

TABLE 4. Oral and Parenteral Postoperative Analgesics Administered in First 72 h after Recovery Room Entry

	Morphine Sulfate 5 mg	Sufentanil 30 µg	Sufentanil 45 µg	Sufentanil 60 µg
Morphine equivalents (mg)	15 (4.4-34.8)	48.9* (33.9-103.5)	46.0* (28.3-78.8)	45.2 (24.0-79.0)

There are ten patients in each group. Values are median with semi-quartile range in parentheses.

* $P < 0.05$ when compared to epidural morphine.

was limited (3.5-5.6 h) compared to that of morphine (26.4 h). A review of over 1000 patients in our institution who have received 5 mg of epidural morphine for post-cesarean section pain demonstrated a similar duration of action (23 ± 0.4 h, mean \pm SEM).⁶

The higher lipid solubility of sufentanil compared to morphine (octanol-water partition coefficient 1727 and 1.4, respectively)⁷ probably results in a faster onset by more rapid movement of sufentanil into the subarachnoid space with nearly immediate diffusion into the dorsal horn. Alternatively, the faster onset of sufentanil in this study could have been due to the relatively larger doses administered, compared to morphine. We did not assess the onset of pain relief until 15 min after administration of the epidural opiates. Had we performed pain assessments within the first 15 min, we might have seen a difference between the onset of the different doses of sufentanil. Verborgh *et al.* demonstrated that higher doses of epidural sufentanil (75 µg) achieves analgesia within 5 min when compared to the slower onset of analgesia following 30 and 50 µg of epidural sufentanil.⁸

It should be noted that relatively large doses of sufentanil were compared to morphine for postoperative analgesia. This study did not identify the minimum effective dose of epidural sufentanil to achieve postoperative analgesia after cesarean section. Our subsequent experience suggests that effective analgesia can be achieved with smaller doses of epidural sufentanil, 10 or 15 µg. However, while one report suggested that 25 µg of sufentanil was effective for cesarean section patients,⁹ others have suggested that 15 µg was ineffective and that the optimal dose for abdominal surgery and lower extremity postoperative pain relief was 50 µg.^{8,10} In another study, 50 µg of sufentanil was shown to be effective in cesarean section patients.¹¹ It is possible that larger doses of sufentanil may be required to achieve analgesia due to the greater uptake of sufentanil by adjacent non-neural tissues, with less drug reaching the dorsal horn. In support of this, after intraventricular injection of ¹⁴C-morphine and ³H-fentanyl in animal models, the much more lipophilic fentanyl was quickly removed from neural tissue, while the hydrophilic mor-

phine could be detected for up to 4 h.¹² However, our more recent experience suggests that the large doses of epidural sufentanil evaluated in this study are not necessary to achieve analgesia after cesarean section.

The duration of action of epidural sufentanil was disappointing. Although no significant differences in duration of analgesia were found among the three doses of sufentanil studied, it is possible that a larger sample size or a wider dose range would have demonstrated longer duration of analgesia from larger doses. Despite the high degree of opiate receptor binding, the lipid solubility of sufentanil may have a greater effect on limiting the duration of action. Epidural sufentanil appears to be similar in duration of analgesia provided to epidural fentanyl. It has been demonstrated that 50 µg of fentanyl after 0.75% bupivacaine for cesarean section patients provided analgesia of approximately 5 h.¹³ The shorter duration of action of relatively larger doses of sufentanil may be due to rapid uptake of this agent by adjacent tissues, particularly the vasculature. As a result, sufentanil is a "fast-in and fast-out" drug when applied to the epidural space.

We suspected that the higher lipid solubility would confer some advantage for sufentanil over morphine with regard to side effects. With less sufentanil remaining in the cerebrospinal fluid (CSF), there should be less available for cephalad spread in the CSF. Unfortunately, we did not see a decreased incidence of side effects with sufentanil compared to morphine with the exception of generalized pruritus, which occurred more frequently among patients who received morphine (50% versus 17%). Pruritus has been attributed to the cephalad spread of morphine.³

The principal risk of epidural administration of opioids is life-threatening delayed respiratory depression. Although no patient given sufentanil experienced decreased respiratory rate, our study involved too few patients and only employed a relatively insensitive measurement for complete evaluation of the potential for epidural sufentanil to cause respiratory depression. Severe respiratory depression has been seen within 10 min after the epidural administration of 75 µg sufentanil, and respiratory depression has been reported after epi-

dural fentanyl, alfentanil, and other lipid soluble agents.^{8,14} ** In addition, if such large doses of sufentanil are accidentally injected intravenously, there is a high potential of adverse effects, including respiratory depression. Morphine has been evaluated extensively with regard to respiratory depression. Our previous work suggests a 0.1% incidence of severe respiratory depression after epidural morphine 5.0 mg in cesarean section patients.⁶ Others have reported an incidence of 0.09–0.9% in large series of general surgical patients.^{15,16} All patients in these series responded well to naloxone given intravenously. The estimates of respiratory depression with epidural morphine compare with an incidence of life-threatening respiratory depression of 0.9% after systemic narcotics given for postoperative pain.¹⁷ If less sufentanil is available for cephalad spread, it is possible that this agent would result in a lower incidence of respiratory depression than epidural morphine. However, if the relatively large doses of sufentanil evaluated in this study are accidentally injected intravenously, there is a high likelihood of adverse effects, particularly respiratory depression. Since the incidence of intravenous placement of epidural catheters is relatively high¹⁸ and the possibility exists that epidural catheters can migrate into an epidural vein, the risk of intravenous injection must be carefully considered. Further evaluation of epidural sufentanil is needed to fully assess the risk of respiratory depression.

Sufentanil 30 µg is highly effective for postoperative pain relief in the cesarean section patient. Sufentanil may be superior to morphine for epidural analgesia in clinical settings in which rapid onset is desired; however, this may be limited by the predictably short duration of analgesia provided. The analgesic effect of sufentanil does not appear to be cumulative, since the onset and duration of the second dose were similar to those of the first dose. Similarly, acute tolerance does not seem to occur for the second dose. This suggests that administration of small, repetitive doses may be one method of achieving good postoperative analgesia. A second approach may be the continuous epidural infusion of very small doses of sufentanil, which we are currently investigating. A third possibility may be to combine the benefits of sufentanil and morphine by administering both a small dose of epidural sufentanil to obtain rapid onset of analgesia, and epidural morphine to achieve prolonged duration of action. Further inves-

tigation is required to evaluate these various approaches to pain relief using epidural opioids.

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Epidural Narcotic and Patient-controlled Analgesia for Post-cesarean Section Pain Relief

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The recognition of inadequacies of traditional on demand intramuscular narcotic administration for postoperative analgesia,¹ together with the desire to reduce the side effects traditionally associated with opioids, has led to the development of alternative techniques of narcotic administration. Both the epidural administration of narcotics and patient-controlled analgesia (PCA) apparently are superior to intramuscular (im) administration of narcotics.^{2,3} However, no published studies have directly compared epidural narcotics, patient-controlled analgesia, and intramuscular narcotics in a controlled, randomized fashion.

The present investigation was designed to compare these modalities of postoperative analgesia in a randomized prospective study in 60 patients following cesarean delivery.

MATERIALS AND METHODS

Following protocol approval by our Human Investigation Committee, 60 patients undergoing elective cesarean delivery under regional anesthesia were enrolled, and written informed consent obtained. All patients were free of any significant pre-existing disease and had no history of drug or alcohol abuse (ASA I or II). Anesthesia for cesarean delivery was administered

via an epidural catheter using 2% lidocaine with epinephrine 1:200,000 in a volume sufficient to achieve a T4 sensory level.

Upon enrollment in the study, patients were randomized into three groups for postoperative analgesia. Group A (N = 22) received epidural morphine; this was administered as 5 mg morphine in 10 ml preservative-free saline (Duramorph®) via the epidural catheter at the time of clamping of the umbilical cord. Group B (N = 18) patients received PCA. An "analgesic base" of narcotic was provided by iv titration of 5-mg increments of morphine at 15 and 30 min following umbilical cord clamp. Further iv increments were provided, if a request was made, in the recovery room. The patient then received PCA using the Abbott Lifecare® PCA Infuser. The PCA pump was set to administer 2 mg morphine with a lockout interval of 6 min in between doses. The need for an early loading dose of morphine, together with the dose and lockout interval selected, were determined to provide optimal analgesia in a pilot study which preceded this study.

Group C (N = 20) patients received im morphine, 10-15 mg, every 4 h, as requested. In our institution, this dose is routinely ordered by the obstetricians for patients following cesarean delivery.

Patients were observed for 24 h following delivery. A visual analog scale (VAS) was used to evaluate pain; patients were asked to evaluate the intensity of their pain by marking the degree of pain they were experiencing on an unmarked 10-cm line, with 0 representing no pain and 10 worst pain imaginable. Scores were obtained at 2 and 4 h following delivery and 4 h thereafter. Pain scores thus obtained were graded as "mild" (VAS 0-3), "moderate" (VAS 4-7), and "severe" (VAS 8-10). Other observations included presence of pruritus and its treatment, nausea and vomiting, and respiratory rates. Patient comments regarding the level of satisfaction with their analgesic regimen were noted and,

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