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Minimum Analgesic Dose of Epidural Sufentanil for First-stage Labor Analgesia

A Comparison between Spontaneous and Prostaglandin-induced Labors in Nulliparous Women

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Background: **The aim of this prospective, double-blind, sequential allocation study was to compare the effects of spontaneous and prostaglandin-induced labor on the minimum analgesic dose of epidural sufentanil in the first stage of labor.**

Methods: **Seventy healthy, nulliparous women, at more than 37 weeks' gestation with cervical dilatation from 2 to 4 cm, requesting epidural pain relief in labor were enrolled. The subjects were assigned to two different groups according to whether labor was spontaneous or induced with dinoprostone 0.5 mg. Parturients received 10 ml of the study solution through a lumbar epidural catheter. The initial dose was sufentanil 25 μg, and subsequent doses were determined by the response of the previous patient in the same group using up–down sequential allocation. The analgesic effectiveness was assessed using 100-mm visual analog pain scores. The up–down sequences were analyzed using the method of independent paired reversals and probit regression.**

Results: **The minimum analgesic dose of sufentanil in spontaneous labor was 22.2 μg (95% CI: 19.6, 22.8) and 27.3 μg (95% CI: 23.8, 30.9) in induced labor. The minimum analgesic dose of sufentanil in induced labor was significantly greater (P = 0.0014) than that in spontaneous labor (95% CI difference: 2.9, 9.3) by a factor of 1.3 (95% CI: 1.1, 1.5).**

Conclusion: **Prostaglandin induction of labor produces a significantly greater analgesic requirement than does spontaneous labor.**

THERE is a perception among obstetric anesthesiologists that induced labor is more painful than spontaneous labor. Some support for this is found in the finding that women in whom labor is induced are more likely to choose epidural pain relief than are those who undergo spontaneous labor.[1] Also, when intrathecal fentanyl is given as the sole labor analgesic, it is more likely to be successful in spontaneous labor than if administered after induction with oxytocin.[2]

The minimum local analgesic concentration (MLAC) of local anesthetics has been developed to serve as a benchmark for epidural dosing in labor.[3–5] A meta-analysis of 14 studies suggests that oxytocin use did not influence the bupivacaine requirement. This analysis failed to distinguish between induction and augmentation, and induction techniques were not standardized. However, efficacy was inversely related to the initial visual analog pain score (VAPS).[6] The question remains unanswered.

Epidural opioid will provide pain relief in the first stage of labor as the sole analgesic.[7,8]

Sufentanil is effective in this role at doses between 5 and 50 μg,[9,10] but in some studies a test dose of lidocaine was used, and this may have contributed to the analgesia observed.[11]

The aim of this study was to apply the MLAC model to determine the median effective dose (ED_{50}) for epidural sufentanil as the sole labor analgesic and define this as the minimum analgesic dose (MAD). The MAD was used to compare the analgesic requirements of spontaneous and induced labors, using a prostaglandin induction technique, in the absence of oxytocic augmentation.

Methods

After institutional ethical approval (Fatebenefratelli Hospital, Rome, Italy) and written informed consent, 70 nulliparous women, American Society of Anesthesiology physical status I or II, at more than 37 weeks' gestation, requesting epidural pain relief in labor were recruited to this prospective, double-blind, sequential allocation study.

Women were enrolled in one of two groups according to whether labor was spontaneous or induced. Indications for induction were postterm pregnancy or premature rupture of membranes. All labors were induced using cervical prostaglandin E_2 (PGE_2), 0.5 mg dinoprostone (Prepidil; Pharmacia & Upjohn, Milan, Italy). No oxytocin was given during the duration of the study.

To standardize the progression of labor, only women with cervical dilatation from 2 to 4 cm at the last examination were enrolled. Women with presenting part below the ischial spines and those scoring less than 30 (0–100 mm) on a VAPS were excluded for obstetric reasons.

At some point in labor, the nature of pain changes from a first-stage distribution to a combination of first

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and second stage. To prevent this from interfering with the study, advanced fetal head descent was considered to be a reason for exclusion. Women who had previously received opioid analgesics were also excluded. All women had a vertex presentation.

While infusing intravenous lactated Ringer's solution, lumbar epidural analgesia was performed in a standardized manner at either L2–3 or L3–4 while the patient was in the left lateral position. Loss of resistance to saline was used, limiting injection to 2 ml to minimize dilution of the study drug. After removing the needle, the catheter was withdrawn until 3 cm remained in the epidural space and then was aspirated. For the purpose of the study, the test dose was omitted.

Each woman received 10 ml from a freshly prepared syringe containing sufentanil (Fentatienil; Angelini ACRAF SpA, Rome, Italy) diluted with 0.9% wt/vol saline to achieve the desired dose at room temperature. The dose of sufentanil in each syringe was determined by the response of the previous patient to a higher or lower dose according to up–down sequential allocation. The exception to this was the first woman in each group, for whom the starting dose was arbitrarily chosen to be 25 μg sufentanil. The syringes were prepared by an anesthesiologist who had no further role in the study. All observations were made by another anesthesiologist who was unaware of the dose in the syringe.

Efficacy was assessed using a 100-mm VAPS, where 0 represented "no pain" and 100 as "worst possible pain" at 0, 15, and 30 min after the injection of the test solution. VAPS was assessed at the height of contraction, using a slide rule; the patient's side was unmarked and the observer's side was marked from 0 to 100 mm. There were three possible outcomes:

Effective: This required a VAPS of 10 mm or less within 30 min and directed a decrement of 1 μg sufentanil for the next woman assigned to that group.

Ineffective: When the VAPS failed to reach 10 mm within 30 min, a rescue bolus of 15 ml bupivacaine (Marcaina, Astra-Zeneca, Milano, Italy), 0.125% wt/vol, was given. If the VAPS subsequently reached 10 mm or less within the next 30 min, a 1-μg sufentanil increment was directed for the next woman assigned to that group.

Repeat: If the rescue bolus failed to achieve a VAPS of 10 mm or less, indicating a failure of spread, this directed that the same dose be repeated for the next woman assigned to that group, and either the epidural site was changed or another technique was used.

Evidence of progression of labor beyond 4-cm cervical dilatation or descent of the fetal head below the ischial spines before an outcome was reached directed that the patient be withdrawn from the study and the dose be repeated for the next woman.

Maternal heart rate, noninvasive blood pressure, pulse oximetry, uterine contractions, and fetal heart rate were monitored. The occurrence of maternal side effects, such as drowsiness, pruritus, and nausea and vomiting, were recorded as a visual analog score (VAS) using a slide rule; the patient's side was unmarked and the observer's side was marked from 0 to 100 mm (0 = no effect, and 100 = worst effect). Fetal heart rate recordings were analyzed manually for variability by an obstetrician who was blind to the study group and dose allocations comparing the postinjection fetal heart rate tracing (at least 1-h duration) with the preinjection tracing (at least 30-min duration)

Table 1. Demographic and Obstetric Variables

Variable	Spontaneous	Induced	*P* Value
Age (yr)	30.0 (4.06)	31.5 (3.05)	0.11
Weight (kg)	69.8 (7.49)	71.1 (6.89)	> 0.2
Height (cm)	165.2 (6.13)	168.0 (5.34)	0.061
Gestation (week)	39.2 (1.05)	39.4 (1.43)	> 0.2
Cervical dilatation (cm)	3.0 [3, 4]	2.5 [2, 3]	0.002
VAPS (mm)	80 [70, 100]	85 [80, 90]	> 0.2

Data are presented as mean (SD) and median [interquartile range].
VAPS = visual analog pain score.

Statistical Analysis

Personal and obstetric characteristics were collected. Data were presented as mean (SD), median [interquartile range (IQR)], and count as appropriate and were analyzed using the Student *t* test, Mann-Whitney U test, or Kolmogorov-Smirnov test and the Fisher exact test. The median effective doses of sufentanil were estimated from the up–down sequences using the method of independent paired reversals and Wilcoxon–Litchfield probit regression analysis as a back-up or sensitivity test. This enabled the MAD, with 95% CI to be derived for each group. Analyses were performed using the following software: Microsoft Excel 95 (Microsoft Inc., Redmond, WA), Number Cruncher Statistical Systems (NCSS) 2000 (NCSS Inc., Kaysville, UT), GraphPad Prism 3.01 (GraphPad Software Inc., San Diego, CA), and Pharmacologic Calculation System 4.2 (PCS; University of Mississippi Medical Center, Microcomputer Specialists, Wynnewood, PA).

Results

Personal and Obstetric Characteristics

Women in whom labor was induced requested epidural pain relief earlier than those in whom labor was spontaneous (table 1).

Spontaneous Labor

Of 37 women enrolled, 6 were excluded for obstetric reasons and 1 because the epidural catheter accidentally dislodged during the first 30 min of the study, leaving 30 patients for analysis. The sequences of effective and

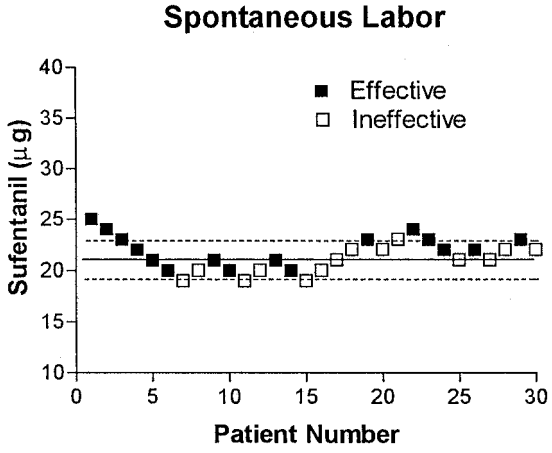

Fig. 1. Minimum analgesic dose of sufentanil in spontaneous labor was 21.2 μg (95% CI 19.6, 22.8).

ineffective analgesia are shown in figure 1. The MAD of sufentanil in spontaneously laboring women was 21.2 μg (95% CI 19.6, 22.8) using the method of independent paired reversals and was 21.2 μg (95% CI 20.0, 22.4) using probit regression.

Induced Labor

Of 33 women enrolled, 3 were excluded because of obstetric reasons, leaving 30 patients for analysis. The sequences of effective and ineffective analgesia are shown in figure 2. The MAD of sufentanil in induced-laboring women was 27.3 μg (95% CI 23.8, 30.9) using the method of independent paired reversals and was 26.8 μg (95% CI 22.9, 31.3) using probit regression. The MAD of sufentanil in induced labor was significantly greater than that in spontaneous labor ($P = 0.0014$). Probit regression showed that induction of labor significantly increased the requirement for sufentanil by a factor of 1.3 (95% CI 1.1, 1.5).

Estimates for the ninety-fifth percentile for efficacy were 24.0 and 32.9 μg for the spontaneous and induced groups.

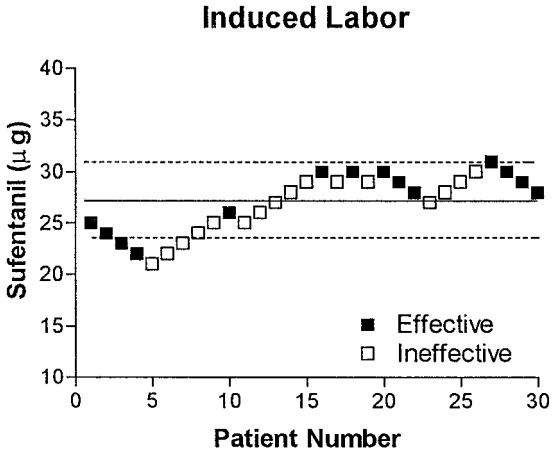

Fig. 2. Minimum analgesic dose of sufentanil in induced labor was 27.3 μg (95% CI 23.8, 30.9).

Table 2. Distribution of Repeat Doses (μg)

Spontaneous	Induced
21	25
19	31
21	28
21	—
19	—
21	—
22	—

Significant ($P = 0.016$) difference in distributions.

Intention to Treat

The distributions of doses tested for all subjects (N = 70, intention to treat) enrolled in the spontaneous and induced groups were significantly different ($P < 0.0001$) when evaluated using the Kolmogorov–Smirnov test. The median doses tested were 21 [IQR 20, 22] and 28 μg [IQR 25, 29]. In addition the distributions of patients who required subsequent doses because the study dose was ineffective were significantly different ($P = 0.017$) among the groups. The distributions of subjects who were rejected from analysis necessitating subsequent testing are shown in table 2. All women had satisfactory analgesia after administration of the rescue bolus.

Other Effects

The duration of analgesia in "effective" subjects was 88.3 min (SD, 25.47) in the spontaneous, and 95.2 (SD, 36.15) in the induced-labor group (NS). Maximum sensory height to pin prick also was similar in the groups. The VAS for pruritus was similar in the groups, but there was a significant increase ($P = 0.024$) in sedation as assessed by VAS in the induced group. (Table 3).

Three (10%) women in the induced group had hypotension (systolic pressure < 90 mmHg) and one (3%) reported nausea. A transient reduction in fetal heart rate variability was noted in 53% of spontaneous and in 63% of induced-labor groups within 10 min (7.6 min; SD, 2.33) after the administration of epidural sufentanil. These cardiotocographic changes lasted approximately 0.5 h (31.8 min; SD, 7.45). In four patients in the induced group, mild variable deceleration was also noted. These changes resolved spontaneously without obstetric intervention or treatment (table 3).

Discussion

We have shown that women in spontaneous labor require a significantly smaller median effective dose of epidural sufentanil compared with women after prostaglandin induction. There is no accepted explanation for this. Animal studies have shown that peripherally applied prostaglandin E_2 is pronociceptive,[12-14] and our findings could be interpreted as a clinical manifestation of this mechanism.

Table 3. Block Characteristics and Maternal and Fetal Observations

Variable	Spontaneous	Induced	*P* Value
Duration of analgesia (min)	88.3 (25.47)	95.2 (36.15)	> 0.2
Maximum sensory level	T5 [T12, T4]	T5 [T9, T4]	> 0.2
Pruritus (mm)	19 [0, 32.5]	0 [0, 46.3]	> 0.2
Sedation (mm)	55 [34, 70]	70 [50, 80]	0.024
Nausea	0	1	> 0.2
Maternal hypotension	0	3	> 0.2
FHRV onset (min)	7.6 (2.42)	7.5 (2.31)	> 0.2
FHRV duration (min)	32.0 (5.87)	32.7 (8.72)	> 0.2

Data are presented as mean (SD), median [interquartile range] and count.
FHRV = fetal heart rate variability.

The use of the MLAC for epidural local anesthetics has become established as a research tool in the investigation of analgesic requirements in labor. The concept of MAD may be used in a similar way, but differences must be acknowledged. Epidural local anesthetics can be used effectively during labor, but the required dose is likely to increase with cervical dilatation.[15] Opioid analgesics similarly are more effective in the first stage, but tend to fail with the onset of the second stage of labor.[7,8,16,17] Because the opioid analgesics are more effective at blocking nociceptive discharge from C fibers than Aδ fibers,[18] we speculated that first-stage pain is transmitted mainly *via* C fibers.[15] Although some opioids have local anesthetic actions, their effects are largely achieved by μ-receptor agonism. Although systemic absorption might contribute to this, there is evidence that the greater effect comes from action within the umbilical cord.[19] This is in contrast with epidural local anesthetics, which work through ion channel blockade of nerve root axons.

For these reasons, it cannot be automatically assumed that MAD will behave in a manner identical to MLAC. Such doubts are balanced by the expectation that epidural opioids will follow conventional patterns of dose and response. The previously reported dose-dependent depression of bupivacaine by epidural opioids would support this expectation.[5,20] It seems reasonable to extend the use of this methodology to estimate the effect of opioid alone.

A meta-analysis of 14 studies using the MLAC model failed to register oxytocin augmentation as an important influence on the analgesic requirement of labor.[6] None of the women in our study received oxytocin before the end of the study period. The meta-analysis provided no information regarding the role of prostaglandin but tells us that cervical dilatation is an important influence on analgesic requirement.[15] In this study, women in whom labor was induced opted for epidural analgesia earlier in labor, resulting in a significant difference in cervical dilatation in the groups. Despite the significant difference in cervical dilatation in this study, this did not offset the increased requirement for sufentanil in the prostaglandin group. If cervical dilatation at the start of the study had been the same in both groups, it would have been probable that an even larger difference in analgesic requirement would have been seen.

The distribution of repeated cases between the groups was different. Every repeated syringe represents a situation in which either the outcome was impossible to achieve or was influenced by a confounding factor. If one took the view that there were possible therapeutic failures because of a second opportunity to be successful, then repeated syringes would tend to underestimate the median effective dose to a small degree. This is purely a theoretical consideration, and it is unlikely to have made an important difference given the margin involved in this study.

Changes in fetal heart rate variability were observed in more than half the subjects. One explanation for this might be a direct depressant effect of sufentanil.[21] It is possible to detect sufentanil, when given by the epidural route in labor, in therapeutic doses, in the maternal circulation.[22] One attempt to measure maternal systemic absorption found that the assay was unable to detect doses between 5 and 50 μg, suggesting concentrations of less than 0.1 ng/ml[9]. Very high doses, in the range of 80 μg/ml, seem to be necessary to produce measurable effects,[23] and the doses reported herein are unlikely to have any important systemic influence by comparison. For these reasons, although systemic absorption occurs, it is unlikely to be of a magnitude sufficient to influence fetal heart rate variability, and other causes should be sought.

Another possible explanation for fetal heart rate variability changes might be found in changes in circulating catecholamines. Segal *et al.*[24] showed, using gravid rat uteri, that epinephrine and norepinephrine together are tocolytic, an effect opposed by oxytocin. Norepinephrine without epinephrine stimulates increased uterine activity.[24] After effective labor analgesia, maternal epinephrine concentrations decrease, but norepinephrine concentrations are little changed.[25,26] Similar to oxytocin, prostaglandin promotes contraction of uterine smooth muscle and might lead to an increase in uterine activity after the onset of effective analgesia. Changes in fetal heart rate could be a consequence of this. However, this study was not designed to detect uterine activity changes, and an external cardiotocograghic monitor was used.

The MAD represents the median effective dose of epidural sufentanil in labor. It is not a dose recommendation, but, because the target VAPS was set at 10 mm, a more exacting test of analgesia than is necessary for clinical comfort, it may reflect the lower end of the therapeutic range. In conclusion, we have shown that women in whom labor is induced with prostaglandin show a significantly greater requirement for epidural

sufentanil than those in spontaneous labor by a factor of 1.3 (95% CI: 1.1, 1.5).

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