The Dose–Response Relation of Intrathecal Fentanyl for Labor Analgesia

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Background: This study determined the dose–response relation of intrathecal fentanyl for labor analgesia and described the onset, duration, and quality of analgesia when used as the sole analgesic.

Methods: Eighty-four parturients in active labor who requested analgesia were randomized to one of seven treatment groups. They received 5–45 μg intrathecal fentanyl as part of a combined spinal–epidural technique. Visual analog pain scores were recorded before and at intervals after injection patients requested additional analgesia. The occurrence and severity of pruritus, nausea, and vomiting were also recorded. Maternal blood pressure was recorded before injection and at intervals after injection. Fetal heart rate was recorded before and 30 min after injection.

Results: By 5 min after injection, pain scores were significantly different among groups (P < 0.001). Mean duration of analgesia increased to 89 min as the dose increased to 25 μg. Maternal diastolic blood pressure was significantly lower 10 and 30 min after injection. There was no difference among groups in the incidence of pruritus; nausea and vomiting were uncommon. Fetal heart rates did not change after injection. A dose–response curve indicates that the median effective dose of intrathecal fentanyl for labor analgesia is 14 μg (95% confidence interval, 13–15 μg).

Conclusions: Intrathecal fentanyl produces rapid, profound labor analgesia with minimal side effects. These data indicate that there is little benefit to increasing the dose beyond 25 μg when it is used as the sole agent for intrathecal labor analgesia. (Key words: Obstetric anesthesia; opioids; parturition; subarachnoid.)

INTRATHecal opioids have become increasingly popular as an option for labor analgesia. Opioids that have been used for this purpose include morphine, meperidine, sufentanil, and fentanyl.1–3 The highly lipophilic opioids, sufentanil and fentanyl, have both been used widely as intrathecal analgesics for labor.

Intrathecal fentanyl has been reported by several authors to provide rapid, profound analgesia in laboring patients. The range of doses reported is 10–50 μg.1–3 In this study we determined the onset and duration of analgesia after a range of doses of intrathecal fentanyl and the incidence of side effects after each dose, and we constructed a dose–response curve to allow comparisons with other methods to provide labor analgesia.

Methods

Eighty-four nulliparous full-term parturients classified as American Society of Anesthesiologists physical status 1 and 2 who were in active labor and requested analgesia gave written informed consent and participated in this study that was approved by our institutional review board. After they were enrolled, patients were randomized to one of seven groups to receive either 5, 10, 15, 20, 25, 35, or 45 μg intrathecal fentanyl as part of a combined spinal–epidural analgesic technique. Parturients with significant coexisting disease (including pregnancy-induced hypertension, gestational diabetes, and so on) were excluded, as were parturients who had received any other form of labor analgesia (intravenous medications) within the preceding hour. Parturients were blinded as to their group assignment.

After hydration with 500–1,000 ml intravenous lactated Ringer’s solution, patients were positioned sitting for placement of a combined spinal–epidural block. An
18-gauge Tuohy needle was introduced into the epidural space at the L2-3, L3-4, or L4-5 interspace using the loss-of-resistance technique. A 24 g × 120 mm Sprotte needle was placed through the Tuohy needle into the subarachnoid space. After return of clear cerebrospinal fluid, patients received a single intrathecal injection of fentanyl as determined by their randomization. In all groups, the intrathecal injection was diluted with preservative-free normal saline to a total volume of 1.5 ml. After injection of the study solution, the Sprotte needle was withdrawn and an epidural catheter was threaded 3–5 cm into the epidural space. The Tuohy needle was withdrawn and the epidural catheter secured before the patient was repositioned supine with left uterine displacement. No medications were administered via the epidural catheter until the patient requested further analgesia.

An investigator blinded to the dose of intrathecal fentanyl injected recorded all observations. Visual analog pain scores (VAS) were recorded immediately before injection and 2.5, 5, 7.5, and 10 min after injection, then every 30 min until the patient requested additional analgesia. The VAS consisted of an unmarked 10-cm line labeled on the left end with the words “no pain” and the right end with “worst pain imaginable”; parturients indicated their degree of discomfort by placing a mark on the scale. Visual analog scores were measured to the nearest 1 mm (range, 0–100). If a patient was not comfortable within 20 min after the intrathecal injection (i.e., a VAS pain score >20 or she requested further analgesia), the study was terminated and the epidural catheter was injected with a local anesthetic solution to provide adequate analgesia; in subsequent analysis of such patients, duration of analgesia was defined as 20 min. Maternal blood pressure was recorded immediately before injection and 10, 20, and 30 min after injection. Each parturient was questioned about the presence of any side effects (pruritus, nausea, or vomiting) at the same intervals as pain scores were determined; if a parturient responded affirmatively, she was asked to record the severity on a VAS (unmarked 10-cm line labeled “no [pruritus, nausea, vomiting|] or “worst [pruritus, nausea, vomiting|] imaginary”), and she was asked whether she wanted treatment for the side effect. Baseline fetal heart rate was recorded before and 30 min after injection. Use of oxytocin to induce or augment labor was recorded.

The duration of analgesia due to intrathecal fentanyl was recorded as the time from intrathecal injection until the patient’s first request for additional analgesia. If clear CSF was not obtained after placement of the Sprotte needle, the patient was dropped from the study and her group assignment was rerandomized; similarly, if a patient delivered or reached full cervical dilation (i.e., entered stage 2 of labor) before requesting additional analgesia, she was dropped from the study and her group assignment was rerandomized.

Aggregate data were analyzed with repeated measures analysis of variance; comparison of demographic and physiologic data among the seven dose groups was with repeated measures analysis of variance with dose group and time as factors. Dose–response data were analyzed with nonlinear analysis for best fit of the percentage of patients responding to log dose. A log-rank test for trend was used to compare continuing pain relief over time among dose groups. Pearson’s chi-square analysis was used to compare the incidence of side effects and oxytocin use.

Results

Eighty-four parturients were enrolled and completed the protocol of this study (n = 12 for each group). There were no significant differences among groups (table 1). Oxytocin use was frequent (79% of parturients overall), and there were no differences among groups (range, 67–100%).

Duration

Duration of analgesia differed significantly among groups (analysis of variance, P < 0.01). Five patients in the 5-μg group failed to obtain adequate pain relief from the initial injection and requested further analgesia at the earliest opportunity (20 min), as did one patient each in the 10-μg and 15-μg groups. The mean duration of analgesia increased as the dose of fentanyl increased from 5 μg to 25 μg; increasing the dose beyond 25 μg did not further prolong analgesia (fig. 1).

A posteriori comparison among groups indicated the duration of analgesia in the 5-μg group was significantly shorter than in groups 15 μg through 45 μg; the 10-μg group was significantly shorter than the 25-, 35-, and 45-μg groups (P < 0.05 for all comparisons). Results of other intergroup comparisons were not significant.

Figure 2 shows the percentage of parturients in each group with continuing pain relief as a function of time. A log-rank test for trend was highly significant (chi-square test = 20.979 with 6 degrees of freedom; P = 0.0019).
Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>5 µg</th>
<th>10 µg</th>
<th>15 µg</th>
<th>20 µg</th>
<th>25 µg</th>
<th>35 µg</th>
<th>45 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>25 (7)</td>
<td>22 (5)</td>
<td>23 (4)</td>
<td>23 (6)</td>
<td>24 (6)</td>
<td>25 (8)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (7)</td>
<td>163 (6)</td>
<td>160 (7)</td>
<td>164 (6)</td>
<td>164 (6)</td>
<td>162 (5)</td>
<td>161 (7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.2 (12.7)</td>
<td>75.2 (14.3)</td>
<td>78.9 (19.0)</td>
<td>72.5 (8.5)</td>
<td>86.5 (21.1)</td>
<td>80.0 (15.8)</td>
<td>85.0 (9.3)</td>
</tr>
<tr>
<td>Dilution (cm)</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Station (range, -3 to +3)</td>
<td>-1 (1)</td>
<td>-1 (1)</td>
<td>-1 (1)</td>
<td>-1 (1)</td>
<td>-2 (1)</td>
<td>-2 (1)</td>
<td>-2 (1)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Onset of Analgesia

Immediately before injection, the mean pain score in all groups was greater than 60 (scale, 0–100). Analysis of variance and *a posteriori* tests indicated the 5-, 25-, and 45-µg groups had slightly higher pain scores than did the other groups (P < 0.05 for all). Mean pain scores in all groups decreased in the 10 min after injection. Five minutes after injection, the VAS pain score was significantly higher in the 5-µg group than in the 15- through 45-µg groups, and the 10-µg group was significantly higher than the 25- to 45-µg groups (P < 0.05 for all).

By 10 min after injection, mean VAS pain scores were <10 in all groups except the 5- and 10-µg groups, which remained significantly higher (P < 0.05, fig. 3).

Maternal Blood Pressure

Assuming a standard deviation of 8 mmHg, analysis of variance of seven groups of blood pressures with 12

![Graph](image)

Fig. 1. Duration of analgesia (mean ± SD). Duration of analgesia (time to first request for additional analgesia) differed significantly among the groups (analysis of variance, P < 0.005). *P < 0.05 versus groups 15 through 45 µg; **P < 0.05 versus groups 25 through 45 µg.

Fig. 2. (A, B) Parturients with continuing analgesia *versus* time. Step graphs depicting the percentage of parturients in each group with continuing analgesia over time. Patients are assumed to have continued analgesia until their first request for additional analgesia. The curves are significantly different (log-rank test, P = 0.0019). The curves are presented as two figures only for clarity.
observations in each group would detect a 10% change in blood pressure with a power of 0.8.

Baseline maternal systolic and diastolic blood pressures were not significantly different among the groups. No differences were noted among groups in systolic or diastolic blood pressures 10, 20, or 30 min after injection. When all groups were combined for analysis of blood pressure effects over time, there was no significant difference in systolic blood pressure between preinjection and postinjection values. Diastolic blood pressure was slightly but significantly lower (all groups taken in aggregate) 10 and 30 min after injection ($P < 0.05$, table 2).

**Fetal Heart Rate**

Assuming a standard deviation of 10 beats/min, analysis of variance of seven groups of fetal heart rates with 12 observations in each group would detect a 10% change in fetal heart rate with a power of 0.89.

There was no difference among groups in baseline fetal heart rate or among groups 50 min after injection. Within each group there was no difference in fetal heart rate between baseline measurement and 30 min after injection; when taken in aggregate, there was no difference overall from baseline to 30 min after injection.

**Side Effects**

Nausea and vomiting were uncommon in all groups, occurring too infrequently for any meaningful comparisons to be made.

Pruritus was common in all groups. There was no difference among groups in the incidence of pruritus. Mean maximal pruritus scores differed significantly among groups (analysis of variance, $P < 0.01$); intergroup comparisons indicated the 5-µg and 10-µg groups tended to have lower pruritus scores, but no clear trend was evident (table 3). Only two parturients in this series requested treatment for pruritus (one each in the 15- and 20-µg groups); satisfactory relief was obtained in both using 5 mg intravenous nalbuphine.

**Pharmacodynamics**

When pain relief is defined as a VAS pain score of 20 or less at both 10 and 40 min after injection, a log dose–percentage curve can be constructed (fig. 4). "Percent" refers to the proportion of parturients in each group who met this criterion. Using nonlinear analysis, the data can be fit to an equation in the form:

$$\%\text{Relief} = \text{Low}\% + \frac{\text{High}\% - \text{Low}\%}{1 + 10^{(\log D[50] - \log \text{dose} / \text{Hill slope})}}$$

**Table 2. Maternal Blood Pressure: Aggregate Data (All Groups Combined)**

<table>
<thead>
<tr>
<th></th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>120 (12)</td>
<td>123 (13)</td>
<td>121 (11)</td>
</tr>
<tr>
<td>Postinjection</td>
<td>123 (13)</td>
<td>68* (10)</td>
<td>67* (10)</td>
</tr>
<tr>
<td><strong>Diastolic (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>71 (9)</td>
<td>68* (10)</td>
<td></td>
</tr>
<tr>
<td>Postinjection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD).

$^* P < 0.05$ versus preinjection value.
INTRATHecal FENTANYl FOR LABOR ANALGESIA

Table 3. Mean Maximal Pruritus Score (Scale 0–100)

<table>
<thead>
<tr>
<th>Score</th>
<th>5 µg</th>
<th>10 µg</th>
<th>15 µg</th>
<th>20 µg</th>
<th>25 µg</th>
<th>35 µg</th>
<th>45 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>67</td>
<td>75</td>
<td>92</td>
<td>100</td>
<td>92</td>
<td>100</td>
<td>92</td>
</tr>
</tbody>
</table>

Values for score are mean (SD).
* P < 0.05 versus 20 µg and 35 µg groups.
† P < 0.05 versus 20 µg group.
‡ Not significant (Pearson’s chi-square).

where High% is the estimated best response, Low% is the estimated lowest response, Hillslope is a constant describing variability of slope, and ED_{50} is the estimated dose resulting in pain relief in 50% of patients. Assuming a Hillslope of 10, the estimated variables, their SEM, and their 95% confidence intervals are:

\[
\text{High\%} = 90 +/− 2\% (84\% \text{ to } 97\%)
\]

\[
\text{Low\%} = 6 +/− 3\% (−3\% \text{ to } 16\%)
\]

\[
\text{ED}_{50} = 14 +/− 1 \mu g (13 \text{ to } 15 \mu g)
\]

Discussion

Fentanyl is used widely as an intrathecal agent for labor analgesia, often as part of a combined spinal-epidural technique. Advantages ascribed to the use of intrathecal fentanyl include the ease of use, low cost, and the rapid onset and relatively long duration of profound analgesia without significant motor blockade. The use of intrathecal fentanyl for labor analgesia has been reported in combination with other agents, including morphine\textsuperscript{1,2,5} and bupivacaine.\textsuperscript{6,7} Relatively few series have described the use of intrathecal fentanyl alone for labor analgesia; those that do focus on a single dose of the opioid\textsuperscript{8,9} or rely on a technique (continuous spinal analgesia) not widely used for labor.\textsuperscript{3} As a sole agent, doses of intrathecal fentanyl reportedly used for labor analgesia range from 10 – 50 µg.\textsuperscript{3,4} Our primary purpose with this series was to define the relation between fentanyl dose and the duration and onset of labor analgesia; the dose range chosen for this series was based on previous reports and our clinical experience in anticipation of defining a “ceiling” effect in the duration of analgesia. We used these data in combination with VAS pain scores to construct a dose–response curve that incorporates both quality and duration as endpoints.

Our data confirm that intrathecal fentanyl provides excellent analgesia over a wide dose range. We prospectively defined a VAS pain score of 20 (on a scale of 0–100) to be the highest pain score consistent with adequate analgesia. Despite random allocation of parturients, there were significant differences among the groups with respect to preinjection pain scores; we believe this difference was due to chance and do not believe it affected the outcome of the study. With all but the lowest dose in this series (5 µg), mean VAS pain score decreased to < 20 within 10 min of injection and was < 20 within 5 min in all but the two lowest doses (5 and 10 µg; fig. 3). This indicates that onset of analgesia is reliably rapid even at low doses (as low as 15 µg).

The second important component of labor analgesia is duration, and in this regard the dose–response relation is less steep. Mean duration of analgesia increased as dose increased to 25 µg, up to 89 min, but did not

Fig. 4. Dose–response curve. Dose–response curve for intrathecal fentanyl for intrathecal labor analgesia. Effective analgesia (“pain relief”) was defined as a VAS pain score < 20 at both 10 and 40 min after injection. The line is defined by the equation:

\[
\text{%Relief} = \text{Low\%} + \frac{\text{High\%} - \text{Low\%}}{1 + 10^{\left(\log \text{ED}_{50} - \log \text{dose}[\text{Hillslope}]\right)}}
\]

The ED_{50} of intrathecal fentanyl for labor analgesia is 14 µg (95% confidence interval, 13–15 µg).

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further increase with increasing dose (fig. 1). The number of parturients in each group with continuing analgesia can also be viewed as a function of time (fig. 2).

Serious maternal side effects of intrathecal fentanyl were infrequent. The incidence of nausea and vomiting was low in all groups, too low to allow any meaningful comparisons, and no parturient requested or required treatment for these side effects. Pruritus was frequent in all groups regardless of dose, indicating that the threshold for inducing pruritus is lower than the threshold for producing clinically effective analgesia. Despite mean pruritus scores as high as 55 in the 20-µg group, few parturients requested treatment when it was offered (only 2 of 84 women), and those who did required only minimal intervention (5 mg nalbuphine). Our clinical impression is that the pruritus is transient and resolves rapidly, with pruritus scores decreasing more rapidly than pain scores increase.

The hemodynamic effects of intrathecal fentanyl have been investigated in full-term parturients, both laboring and nonlaboring. Grant et al.10 studied the effects of 25 µg intrathecal fentanyl in nonlaboring parturients, both with and without previous intravenous hydration, and they did not observe any significant hemodynamic changes in either group. Mandell et al.9 investigated the maternal hemodynamic effects of 25 µg intrathecal fentanyl in laboring patients; compared with preinjection values, they noted a significant decrease in systolic and diastolic blood pressure within 5 min after injection. Based on the observed decrease in heart rate and cardiac index, they concluded that the decrease in blood pressure was due not to vasodilation but to the onset of effective analgesia. Cascio et al.8 reported a significant decrease in maternal plasma epinephrine levels and VAS scores after the intrathecal injection of 25 µg fentanyl in laboring parturients. We did not find a dose-related difference in maternal blood pressures among groups, but when all groups were pooled, we noted a significant decline in maternal diastolic blood pressure was noted (table 2). Systolic blood pressure did not change. This modest decrease in maternal blood pressure is also consistent with the onset of analgesia.

Intrathecal fentanyl was recently implicated as a cause of fetal bradycardia in laboring parturients.1 Unfortunately, this report appeared after the protocol for our series had been defined, and although we did not continuously evaluate fetal heart rate tracings, we did not observe any instances of significant fetal bradycardia.

The dose–response curve we have defined in this series can be used to compare intrathecal fentanyl to other labor analgesics that have been similarly studied. No single standard for the definition of labor analgesia has been defined, which makes comparison with other series challenging. We chose to define effective labor analgesia in terms of both quality and duration, on the premise that a single-dose technique cannot be considered effective if the analgesia does not last for at least a certain minimum amount of time. In this series we defined effective analgesia as a VAS score < 20 at both 10 and 40 min after injection. Further, because the sensory and pain pathways of the first and second stages of labor are distinct and different,11,12 we limited our observations to parturients in the first stage of labor. This limitation would be expected to result in a conservative estimate of duration, because our sample is skewed toward parturients likely to request analgesia earlier in labor and those with longer labors.

Sufentanil has also been used widely for intrathecal labor analgesia and is often compared with fentanyl for this purpose. Foss et al.13 used the Dixon up-down method and probit analysis to determine the ED_{50} of intrathecal sufentanil; their criteria of analgesia within 20 min of injection that persisted for at least 60 min and exclusion of patients in advanced labor are similar to those that we used in this series. They determined that the ED_{50} of intrathecal sufentanil is 4.1 ± 0.3 µg (compared with the ED_{50} of intrathecal fentanyl of 14 µg in this series), for a calculated potency ratio of 3.4:1 (fentanyl:sufentanil).

Herman et al.14 studied several doses of intrathecal sufentanil from 2.5 to 15 µg; the criteria for effective analgesia was defined as achieving a VAS pain score of 25 or less, without respect to duration of analgesia. This less stringent criteria results in a lower calculated ED_{50} for intrathecal sufentanil of 2.6 µg. Only at the highest dose reported in their series (15 µg) did the mean duration of analgesia appear to exceed the mean maximal duration of analgesia that we found with intrathecal fentanyl. Surprisingly, the onset of analgesia was slower even at the highest doses of sufentanil than we observed with intrathecal fentanyl; 5 min after injection, mean pain score had not decreased to < 20 at any dose of intrathecal sufentanil, as compared with all but the 5- and 10-µg fentanyl groups in this series. These comparisons indicate that at equivalent doses, there are only modest differences between the two opioids for intrathecal labor analgesia.

In conclusion, this series indicates that intrathecal fentanyl is an effective labor analgesic. It provides a rapid onset of profound analgesia of relatively long duration.
when administered at an appropriate dose. It has few significant side effects. A dose–response curve derived from these data indicates the ED$_{50}$ for labor analgesia is $14 \pm 1$ µg. Based on our observations of mean duration of analgesia, when used as the sole intrathecal agent for labor analgesia, there does not appear to be any benefit to increasing the dose beyond 25 µg.

References