Epidural Neostigmine Combined with Sufentanil Provides Balanced and Selective Analgesia in Early Labor

Fabienne Roelants, M.D., Patricia M. Lavand’homme, M.D., Ph.D.

Methods: After informed consent, 125 healthy parturients were randomly allocated to receive, after a test dose, a single injection of either epidural sufentanil 20 μg (minimal analgesic dose) or 10 μg or a combination of sufentanil 10 μg with neostigmine 250, 500, or 750 μg in a total volume of 12 ml. Pain scores were recorded at regular intervals to determine onset and duration of analgesia. Maternal and fetal vital parameters as well as side effects were closely monitored.

Results: Parturients did not differ concerning demographic data. Epidural neostigmine 500 μg with sufentanil 10 μg produced effective analgesia (visual analog scale <30 mm within 10 min in 72% parturients and within 15 min in 85% parturients; average duration of 119 min, confidence interval 96–142 min) that was as effective as epidural sufentanil 20 μg. Epidural combination with neostigmine 250 μg was ineffective, whereas 750 μg did not produce higher effect than 500 μg. No motor block was recorded. Maternal and fetal vital parameters remained stable during labor.

Conclusions: Epidural combination of neostigmine 500 μg (e.g., 6–7 μg/kg) with sufentanil 10 μg provides similar duration of analgesia as epidural sufentanil 20 μg and allows effective and selective analgesia devoid of side effects in the first stage of labor.

BEYOND a rapid and effective analgesic effect, the permanent search for a better pain relief during labor also involves the reduction of motor impairment mostly associated with the neuraxial use of local anesthetics. Today, selective analgesia or “mobile epidural” is become extremely popular because reduced motor impairment has led to lower instrumentation rate, lower urinary catheterization, and higher degrees of satisfaction for the parturient.1 Neuraxial administration, either spinal2 or epidural,3 of potent liposoluble opioid alone achieves this goal. However, the use of “balanced analgesia,” i.e., spinal drug combinations, not only improves the efficacy through positive analgesic interactions but also reduces the side effects consecutive to the administration of high doses of a single drug.4

Epidural neostigmine, a cholinesterase inhibitor, potentiates opioids4,5 and provides analgesia without the severe gastrointestinal side effects (nausea and vomiting, diarrhea) consecutive to its intrathecal injection.6 Further, neostigmine does not induce respiratory depression, hypotension, or motor blockade.7 Hence, the characteristics of epidural neostigmine seem to meet those requested to achieve selective analgesia.

We have previously reported the administration of epidural neostigmine during labor8 but found no effect at the highest dose we used (4 μg/kg). This lack of analgesic effect might be related to the dose we used, which was too low because of the physical properties of neostigmine and the character of the pain throughout the labor.8 Thinking that epidural neostigmine deserved further investigation in the field of labor analgesia, especially in relation to a “mobile” epidural technique, we decided to investigate the effect of higher doses of neostigmine and to evaluate its combination with epidural sufentanil at the beginning of labor. We have combined increasing doses of epidural neostigmine (up to 10 μg/kg) with sufentanil, using the previously established minimum analgesic dose (20 μg) for epidural sufentanil in early labor.9

Materials and Methods

After approval by the Clinical Research Practices Committee and obtaining informed consent, 125 American Society of Anesthesiologists physical status I and II healthy parturients whose gestational age was greater than 36 weeks and who requested epidural analgesia during labor were enrolled in the study. Lumbar epidural puncture was performed with an 18-gauge Tuohy needle, and an epidural catheter was inserted 4 cm at the L3–L4 level in all parturients. Exclusion criteria included parturients with obstetric complications (multiple pregnancy, premature labor, or non-vertex presentation) or contraindications to regional analgesia. Accidental dural puncture when the epidural was performed also excluded patients from participation in the study. All parturients were in the established first stage of labor (cervical dilatation inferior to 5 cm) when the epidural technique was performed, and all received an oxytocin infusion during the course of labor.
Table 1. Demographic Data

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>30±5.3</td>
<td>29±6.8</td>
<td>32±6.2</td>
<td>31±5.7</td>
<td>31±5.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.0±17</td>
<td>77.8±16</td>
<td>77.1±18</td>
<td>79.4±17</td>
<td>74.0±18</td>
</tr>
<tr>
<td>Nulliparas (n)</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Cervical dilatation (cm)*</td>
<td>3.0 (2.9–4.0)</td>
<td>4.0 (3.0–4.0)</td>
<td>3.0 (2.8–4.0)</td>
<td>3.0 (3.0–4.0)</td>
<td>3.3 (3.0–4.0)</td>
</tr>
<tr>
<td>Cervical dilatation (cm)+</td>
<td>4.0 (4.0–5.5)</td>
<td>5.0 (4.1–6.0)</td>
<td>5.0 (4.0–7.0)</td>
<td>5.0 (4.0–5.6)</td>
<td>4.5 (4.0–5.5)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median (interquartile range).

Cervical dilatation was recorded * before administration of the first epidural injection and † when the parturient requested a second epidural dose because VAS was > 30.

Legend for the different groups: epidural sufentanil 10 µg (S10) or 20 µg (S20), epidural sufentanil 10 µg combined with neostigmine 250, 500, and 750 µg (S10 N250, S10 N500 and S10 N750).

Pain was assessed with a 100-mm visual analog scale (VAS; 0–100). When the VAS score reached 30, a test dose of 3 ml of lidocaine 2% with epinephrine 1:200,000 was administered via the catheter, and the parturients were randomly allocated to one of the study groups. Patients in the two first groups received sufentanil 10 µg (S10; n=25) and sufentanil 20 µg (S20; n=25), respectively. In the other groups, sufentanil 10 µg was combined with neostigmine 250 µg (S10 N250; n=25), neostigmine 500 µg (S10 N500; n=25), or neostigmine 750 µg (S10 N750; n=25). Neostigmine was provided from the commercial solution of neostigmine methylsulfate (Prostigmine®, 0.5 mg/ml; Roche, Somerville, NJ), for which intrathecal safety assessment has been reported. All the parturients received the first epidural bolus in a total volume of 12 ml. The data were collected by an anesthesiologist, either a resident or an attending blinded to the patient group and to the epidural drugs.

Maternal noninvasive blood pressure, heart rate, and oxygen saturation were monitored. Fetal heart rate was also continuously recorded on a cardiotocograph. Pain score (VAS) was recorded 3, 5, 10, 15, 20, and 30 min after the epidural injection. Level of sensory block was evaluated by using the ether test and motor block in the lower limb was evaluated by using a modified Bromage scale (1 = complete motor block; 2 = almost complete motor block: the patient is able only to move the feet; 3 = partial motor block: patient is able to move the knees; 4 = detectable weakness of hip flexion: the patient is able to raise the leg but is unable to keep it raised; 5 = no detectable weakness of hip flexion: the patient is able to keep the leg raised during 10 s at least; 6 = no weakness at all) were recorded 15 and 30 min after the epidural injection as well as maternal and fetal vital parameters. The duration of analgesia was considered as the time elapsed to the patient’s first request for further analgesia (new epidural injection). From that second epidural injection until delivery, the mode of delivery (operative, vaginal instrumental, or spontaneous), and cervical dilatation at the time of second epidural injection were recorded. Maternal adverse events (nausea and vomiting, pruritus, sedation) and fetal side effects (bradycardia during labor, low Apgar score) were also closely monitored.

Statistical Analysis

Results were expressed as mean ± SD, 95% confidence interval, or median (interquartile range), as indicated. Demographic data and continuous variables were compared among the groups by analysis of variance and repeated measures, followed, if appropriate, by multiple comparison with the Tukey HSD test (Statistica; StatSoft, Tulsa, OK). Comparison of ordinal categorical data among groups was realized by application of the Kruskal-Wallis test followed by the Wilcoxon rank sum test for multiple comparisons. Incidence of adverse effects and installation of satisfactory analgesia were compared among the groups by chi-square analysis corrected for multiple tests. A P < 0.05 was considered significant.

The number of patients assigned to the different groups was based on preliminary data based on the duration of analgesia resulting from a first epidural bolus of sufentanil 20 µg. A prospective sample size calculation (SigmaStat; SPSS Science Software, Surrey, UK) indicated that 20 subjects were required in each group to have 80% power to detect a 25% difference at α-level of 0.05 in the duration of analgesic effect.

Results

One hundred and twenty-five patients were enrolled in the study. Variables measured included age, weight and parity were similar among the groups, as well as cervical dilatation at the first injection, and when a second epidural injection was required (table 1). Maternal hemodynamic variables did not differ between groups and did not change into the group after epidural injection. Epidural neostigmine, 250 to 750 µg, was devoid of significant effect on maternal blood pressure and heart rate.
EPIDURAL NEOSTIGMINE-SUFENTANIL IN EARLY LABOR

Table 2. Maternal Hemodynamic Variables Before and After Single Epidural Injection

<table>
<thead>
<tr>
<th></th>
<th>S10</th>
<th>S20</th>
<th>S10 N250</th>
<th>S10 N500</th>
<th>S10 N750</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP 0</td>
<td>116 ± 15</td>
<td>121 ± 17</td>
<td>113 ± 14</td>
<td>120 ± 14</td>
<td>116 ± 21</td>
</tr>
<tr>
<td>DBP 0</td>
<td>66 ± 11</td>
<td>67 ± 12</td>
<td>67 ± 12</td>
<td>72 ± 11</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>HR 0</td>
<td>80 ± 11</td>
<td>81 ± 11</td>
<td>83 ± 10</td>
<td>79 ± 10</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>SBP 30</td>
<td>113 ± 11</td>
<td>118 ± 14</td>
<td>111 ± 13</td>
<td>116 ± 16</td>
<td>117 ± 21</td>
</tr>
<tr>
<td>DBP 30</td>
<td>67 ± 10</td>
<td>65 ± 10</td>
<td>60 ± 11</td>
<td>67 ± 14</td>
<td>68 ± 17</td>
</tr>
<tr>
<td>HR 30</td>
<td>80 ± 13</td>
<td>79 ± 12</td>
<td>79 ± 9</td>
<td>76 ± 11</td>
<td>76 ± 12</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

SBP0–SBP30 = systolic blood pressure (mmHg) at the beginning of the procedure and 30 minutes after epidural injection; DBP0–DBP30 = diastolic blood pressure (mmHg) before and 30 minutes after injection; HR0–HR30 = heart rate (beats/min) at the beginning of the procedure and 30 minutes after injection. Legend for the different groups: epidural sufentanil 10 μg (S10) or 20 μg (S20), epidural sufentanil 10 μg combined with neostigmine 250, 500, and 750 μg (S10 N250, S10 N500, and S10 N750).

DBP = diastolic blood pressure; HR = heart rate; N = neostigmine; S = sufentanil; SBP = systolic blood pressure.

during the first 30 min postinjection (table 2) as well as during the rest of labor (unshown data).

All epidural solutions provided efficient analgesia and significantly reduced the initial VAS. From a similar initial pain score, epidural sufentanil 10 and 20 μg provided a significant VAS reduction after 20 min, whereas such a significant effect was recorded after 15 min in the S10 N250 and S10 N 750 groups and after 10 min in the S10 N500 group (fig. 1). At 30 min postinjection, only the S10 group presented a pain score statistically higher than all the other groups that did not differ from the initial VAS within the group. To better compare the effectiveness of the various epidural solutions, we recorded the percentage of parturients presenting a satisfactory analgesia (defined as a VAS strictly <30) at different time scores postinjection (fig. 2). At first sight, the S20 and S10 N500 groups displayed a very similar time course of effectiveness. The duration of analgesia resulting from this first top-up dose was significantly longer in the S20, S10 N500, and S10 N750 groups than in the S10 and S10 N250 groups (table 3). Epidural neostigmine 250 μg did not prolong sufentanil duration of action (S 10–S10 N250, P = 0.15). Further, neostigmine 750 μg was no more effective than neostigmine 500 μg (S10 N500–S10 N750, P = 0.09). The level of sensory block assessed at 30 min after epidural injection was similar between all the groups (median value, T10; T9 – 12), as was the degree of motor block. No significant motor impairment was observed (table 3).

Epidural administration of neostigmine neither significantly modified the total duration of labor nor interfered with the mode of delivery (table 4). No harmful fetal side effects, e.g., bradycardia, were noted during labor and Apgar scores did not differ between the groups. Cesarean delivery was required for two parturients in the S10 group, two parturients in the S10 N500 group, and one parturient in the S10 N750 group.

Discussion

Our results provide evidence that epidural neostigmine 500 μg combined with sufentanil 10 μg produces effective analgesia in early labor (VAS <30 within 10 min in 72% of parturients and within 15 min in 85% parturients, average duration of 119 min, confidence interval,
96–142 min) without motor block or other side effect in mother and fetus. These results match the current definition of selective analgesia during the first stage of labor, also called “mobile epidural.” The term, which is becoming popular, does not necessarily imply maternal ambulation but rather refers to a regional analgesic technique that interferes least with the normal mechanism of labor.\(^1\)

To meet such a goal, potent opioids such as fentanyl and sufentanil are mainly used by either the intrathecal or the epidural route. Most studies refer to the use of the combined spinal-epidural technique with the injection of intrathecal sufentanil,\(^2\) which results in quick and almost complete pain relief (within 5 to 10 min) lasting approximately 90 min (SD, 40 min).\(^10,11\) However, many anesthesiologists still prefer the traditional epidural technique, which is less expensive than the combined spinal-epidural technique with the injection during labor analgesia, the incidence of major gastrointestinal side effects (nausea and vomiting, diarrhea) concerning a satisfactory level of analgesia (defined as a score strictly $<30/100$ on visual analog scale) at different times after injection of the different analgesic solutions. Legend for the groups: epidural sufentanil 10 µg (S10) or 20 µg (S20), epidural sufentanil 10 µg combined with neostigmine 250, 500 and 750 µg (S10/N250, S10/N500 and S10/N750). \(^* P < 0.05\) with the groups Sufentanil 20 µg and Sufentanil 10 µg combined with Neostigmine 500 µg. \(† P < 0.05\) with the group receiving epidural Sufentanil 20 µg.

To achieve better pain control associated with a reduction of side effects, the principle of balanced analgesia has been applied in obstetric analgesia using spinal drugs combinations which target different mechanisms.\(^4\) Neostigmine inhibits the breakdown of endogenous acetylcholine, and its intrathecal injection induces selective analgesia devoid of sympathetic and motor block. However, despite a positive interaction with spinal opioids during labor analgesia, the incidence of major gastrointestinal side effects (nausea and vomiting, diarrhea) consecutive to the intrathecal administration, even at doses

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Table 3. Assessment of the Analgesic Effect Resulting from a Single Epidural Injection

<table>
<thead>
<tr>
<th>Groups</th>
<th>S10</th>
<th>S20</th>
<th>S10 N250</th>
<th>S10 N500</th>
<th>S10 N750</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS(^*)</td>
<td>53 ± 19</td>
<td>54 ± 16</td>
<td>58 ± 21</td>
<td>47 ± 18</td>
<td>54 ± 21</td>
<td>n.s.</td>
</tr>
<tr>
<td>VAS(†)</td>
<td>50 ± 22</td>
<td>53 ± 19</td>
<td>47 ± 22</td>
<td>55 ± 23</td>
<td>59 ± 19</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sensory level</td>
<td>Th 10 (10–12)</td>
<td>Th 10 (9–10)</td>
<td>Th 10 (10–12)</td>
<td>Th 10 (9–11)</td>
<td>Th 9 (9–10)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Motor block</td>
<td>5 (4–5.5)</td>
<td>6 (6–6)</td>
<td>6 (6–6)</td>
<td>6 (6–6)</td>
<td>6 (6–6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>69 ± 38(‡) (53–86)</td>
<td>118 ± 45 (97–139)</td>
<td>72 ± 23(‡) (60–84)</td>
<td>119 ± 56 (106–135)</td>
<td>103 ± 41 (58–94)</td>
<td>(‡)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD and (95% CI) or median value (interquartile range).

VAS represent an evaluation of pain score (0–100) by the parturients\(^*\) before administration of the first epidural injection and \(†\) when the parturient requested a second epidural dose. The duration of epidural analgesia was calculated as the time elapsed between these two injections (mean value [95% CI]). Sensory thoracic (Th) level (ether test) and motor block (modified Bromage’s scale) are assessed at 30 min after epidural injection (median value [interquartile range]).

Legend for the different groups: epidural sufentanil 10 µg (S10) or 20 µg (S20), epidural sufentanil 10 µg combined with neostigmine 250, 500, and 750 µg (S10 N250, S10 N500, and S10 N750).

\(VAS = \) visual analog scale.

\(‡ P < 0.05\) with S20.
as low as 10 \mu g, has precluded any routine use of the
drug.\textsuperscript{11}

Recently, several studies in postoperative patients
have reported an analgesic effect of epidural neostig-
mine that, interestingly, was devoid of unacceptable side
effects,\textsuperscript{8} and we made the first report about the use of
epidural neostigmine in labor.\textsuperscript{9} However, at doses up to
4 \mu g/kg, that provided analgesia and opioid-sparing ef-
effects in postoperative conditions involving somatic pain,
we did not observe a significant benefit nor did we note
relevant side effects in our parturients. One explanation
might be that the dose we used was too low, especially in
laboring parturients with potent painful stimuli from a
visceral origin. In a previous study, Lauretti and Lima
observed that intrathecal neostigmine was more effec-
tive to relieve somatic than visceral pain.\textsuperscript{13} Effectively,
in contrast with somatic fibers, the central terminal of vis-
ceral afferents display an extensive and deeply located
intraspinal arborization,\textsuperscript{14} and neostigmine is a quater-
ary ammonium compound, ionized at physiologic pH
and with a low lipid solubility that crosses biologic
membranes to a limited extent.\textsuperscript{15} It is thus conceivable
that the dose of neostigmine that really accessed the
spinal cord was ineffective. Therefore, in this study, we
decided to test higher doses of epidural neostigmine:
500 \mu g (equivalent to 6–7 \mu g/kg) and up to 750 \mu g
(10 \mu g/kg). Besides, others have previously used such
doses: Nakayama \textit{et al.} found that a dose of 10 \mu g/kg of
epidural neostigmine was necessary to prolong the du-
ration of postoperative analgesia after abdominal hyster-
ectomy; 5 \mu g/kg was ineffective.\textsuperscript{16}

In our parturients, the best effect was obtained with a
dose of 500 \mu g combined with sufentanil 10 \mu g. A dose
of 750 \mu g was no more efficient and even seemed to
produce a plateau effect. However, such an observation
might also result from a bias caused by the small number
of parturients included.

At the effective dose, we have observed that the epidi-
ral combination of neostigmine with sufentanil de-
creases the previously established sufentanil ED50 by
50%. A positive interaction between cholinesterase
inhibitors and opioid derivatives has been described in
several studies involving visceral pain, particularly after
intrathecal administration, both in gynecologic sur-
gery\textsuperscript{17,18} and during labor,\textsuperscript{11} although nausea limited
clinical usefulness. Nelson \textit{et al.} have found a 25% re-
duction of intrathecal sufentanil ED50 with 10 \mu g
neostigmine, the combination of both resulting in ap-
proximately 100 min (SD, 40 min) of analgesia.\textsuperscript{11}

In agreement with our previous study and other pub-
lished reports, we did not observe undesirable side ef-
effects after epidural neostigmine, even when increasing
the doses. Particularly the lack of nausea and vomiting
strongly contrasts with the reports about intrathecal
administration in which side effects are correlated to the
dose.\textsuperscript{9} The role played by the meninges, which express
both acetylcholinesterases and butyrylcholinesterases,
probably prevents the diffusion of high doses of neostig-
mine into the cerebrospinal fluid as well as its spread
to supraspinal levels.\textsuperscript{19} The risk of maternal hypoten-
sion is not a concern with neostigmine. Further, after epidural
administration the chemical characteristics of the drug
certainly limit its transfer to the maternal circulation
and hence to the fetus, decreasing the risk for direct and
indirect fetal bradycardia, which was observed after in-
travenous administration of the drug to reverse muscle
relaxants.\textsuperscript{15} Finally, because muscarinic receptors medi-
ate uterine tone,\textsuperscript{20} although we did not observe bother-
some side effects in parturients, a potential effect of
epidural neostigmine on basal tone, intensity, and fre-
quency of uterine contractions can not be excluded.

In conclusion, in the context of “mobile epidural”
involving a selective block of pain by spinal opioids in
the absence of sympathetic and motor block, epidural
neostigmine represents a useful tool. Combination with
epidural sufentanil provides very effective pain relief,
similar in duration to what is usually reported with
intrathecal analgesics. Results from this study show that
a dose of neostigmine 6 to 7 \mu g/kg (around 500 \mu g) is
mandatory to be effective in the first stage of labor.

\section*{References}

Mobile Epidural Trial (COMET) Study Group UK: Randomized controlled trial
comparing traditional with two "mobile" epidural techniques: anesthetic and
analgesic efficacy. \textit{Anesthesiology} 2002; 97:1567–75

2. Eisenach JC: Combined spinal-epidural analgesia in obstetrics. \textit{Anesthesiol-
ogy} 1999; 91:299–302

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\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Groups & S10 (n = 25) & S20 (n = 25) & S10 N250 (n = 25) & S10 N500 (n = 25) & S10 N750 (n = 25) \\
\hline
Labor (min) & 245 ± 105 & 225 ± 108 & 225 ± 137 & 239 ± 65 & 285 ± 127 \\
Instrumental delivery (%) & 12 & 8 & 0 & 4 & 12 \\
Maternal nausea and vomiting (n) & 0 & 3 & 0 & 0 & 4 \\
Maternal pruritus (n) & 0 & 5 & 0 & 0 & 0 \\
Apgar Scores < 7 (n) at 3; 5; 10 min & 1; 0; 0 & 2; 0; 0 & 3; 0; 0 & 1; 1; 1 & 2; 1; 0 \\
\hline
\end{tabular}
\caption{Details on Labor: Delivery Mode, Rate of Maternal Side Effects and Apgar Scores}
\end{table}


