Patient-controlled intravenous analgesia as an alternative to epidural analgesia during labor: Questioning the use of the short-acting opioid Remifentanil Survey in the French part of Belgium (Wallonia and Brussels)

P. Lavand’homme and F. Roelants

Abstract: Childbirth ranks among the most intense experiences of acute pain. Neuraxial analgesia (i.e. epidural or combined spinal-epidural technique) is the most effective way to relieve that pain but it is contraindicated or impossible to perform for some parturients. We designed a survey of the current use of analgesic alternatives to epidural analgesia (EA) for labor pain, specifically the use of opioid patient-controlled intravenous analgesia (PCIA), in the French part of Belgium (Wallonia and Brussels).

A questionnaire was mailed to the departmental chair of the hospitals with an obstetric unit, both in university and non-university centers (total of 53 centers). The questionnaire evaluated the availability of EA, the alternatives used when EA was contraindicated, the use of opioid-based PCIA for labor analgesia as well as opioid preference and doses, and finally the reasons for not using opioid PCIA.

The response rate was 67.5% (36 centers). Among the responding hospitals, EA was available for 68% (range 25-85%) of labors and deliveries. When EA was not available or contraindicated, a parenteral opioid (pirtiramide, tramadol or pethidine) was proposed in 19% (7/36) of the centers, Entonox in 11% (4/36), a pudendal block by obstetricians in 28% (10/36) and non-pharmacologic alternatives (i.e. hypnosis, sophrology, baths and massages) in 19% (7/36). In 28% (10/36) of the centers however, no analgesic alternative was proposed. Opioid PCIA was employed in 36% (13/36) of the centers and for an additional 11% (4/36) only in case of intrauterine death. Remifentanil was the first choice (76.5% of the PCIA), followed by sufentanil (23.5%). Other opioids (pirtiramide, morphine, fentanyl) and ketamine were also administered by PCIA. Forty-five percents of the centers reported never using opioid PCIA by either lack of knowledge (7%), fear of maternal or fetal side effects (48%) and inability to provide a correct supervision of the parturient during PCIA use (48%), opposition from the pediatricians or obstetricians (17%) or because they considered the technique as ineffective to relieve labor pain (17%).

In conclusion, the survey demonstrated that, when EA is contraindicated, systemic opioid administered by PCIA is used in almost half of the centers (47%) and that remifentanil is the first choice, particularly when a live birth is expected.

Key words: Patient-controlled intravenous analgesia (PCIA); systemic opioid analgesic; labor; survey.

Introduction

When compared to other forms of acute pain, childbirth ranks among the most intense (1). Although the pain experienced during labor and delivery varies from one person to another, for many women childbirth is the most painful experience encountered. To date, neuraxial analgesia (i.e. epidural or combined spinal-epidural technique) remains the most effective technique to relieve pain throughout the labor course (2). Nevertheless, there is a specific need for analgesia in a small population of laboring women for whom neuraxial techniques are contraindicated, unavailable or impossible to perform. Both non-pharmacologic options (e.g. hypnosis, sophrology, massage therapy...) and pharmacologic ones (e.g. parenteral opioid analgesics, nitrous oxide...) can be used for these parturients. Although parenteral opioids have been administered to laboring women for many years, their analgesic efficacy has been questioned and their use in parturients considered medically incorrect by certain (3). In 1998, Kan (4) was the first to suggest that the pharmacologic profile of the μ-opioid agonist remifentanil would allow easy titration and

© Acta Anesthesiologica Belgica, 2009, 60, n° 2
might provide satisfactory pain control during labor when administered by patient-controlled intravenous analgesia (PCIA). Since then, several clinical trials have evaluated PCIA with remifentanil in parturients but the real benefit remains subject to controversy because of limited efficacy and side effects in the mother and the fetus (2, 5, 6).

The present survey intended to obtain an overview of the analgesic techniques currently used as alternatives to epidural analgesia and particularly focused on the use of opioid PCIA for labor and delivery in the French part of Belgium (Wallonia and Brussels).

MATERIALS AND METHODS

Following approval by the board of the Belgian Society of Anesthesiologists (SBAR-BVAR), a questionnaire was sent to the departmental chair of the hospitals with an obstetric unit in the French part of Belgium (Wallonia and Brussels). Both university hospitals (UH) and non-university hospitals (non-UH) were included, representing a total of 53 centers. The questionnaire (see Appendix) evaluated the following areas

1. availability of an epidural analgesia for vaginal delivery
2. what was considered as a contraindication to the use of epidural analgesia
3. the alternatives proposed to the parturients when epidural analgesia was contraindicated
4. if the anesthesiologists were familiar with opioid PCIA during labor, which opioid was preferred, the doses used, the side effects encountered
5. if the anesthesiologists were not using the PCIA technique, which were the principal reasons
6. what could be considered as an indication to use PCIA (parenteral opioid) for labor analgesia.

Four statements were proposed: (a) vaginal delivery in normal conditions (term > 37 weeks) in a parturient who can not benefit from an epidural analgesia; (b) vaginal delivery of a premature fetus in a parturient who can not benefit from an epidural analgesia; (c) vaginal delivery in case of intrauterine death in a parturient who can not benefit from an epidural analgesia; (d) vaginal delivery in normal conditions in a parturient who refuses an epidural analgesia without evident contraindication to the epidural technique.

A reminder was sent when no answer was received within two months. In the accompanying cover letter, mention was made that responses to the questionnaire should reflect team policy or procedure rather than individual practice.

Results were expressed as median values and percentiles or otherwise as specified.

RESULTS

A total of 36 questionnaires were returned giving a response rate of 67.5% (32 from non-UH and 4 from UH). The median number of deliveries per year was 1000 (IQR 573-1346) in non-UH and 2024 (IQR 2011-2126) in UH.

1. Availability of epidural analgesia

The median rate of epidural analgesia for vaginal delivery was 75% (IQR 56-80.5%) in non-UH and 84.5% (IQR 79-89%) in UH.

2. The contraindications to the use of epidural analgesia

The contraindications to the use of epidural analgesia were a low platelet count for 100% of the anesthesiologists who answered the questionnaire but acceptable lower value ranged from 50 000 to 120 000 platelets/mm³ (with an average value of 80 000), the intake of aspirine for 58% of the anesthesiologists (dose > 100 mg per day and when the last intake was within the last 5 days (from 2 days until 10 days), a history of spinal surgery for 25% of the anesthesiologists and a medical history of progressive neurologic disease for 37% of the anesthesiologists.

3. The alternatives proposed when epidural analgesia was contraindicated

28% (10/36) of the centers proposed no analgesic alternative (either pharmacologic or non-pharmacologic) to the parturients who could not benefit from epidural analgesia. Among the pharmacologic alternatives, intramuscular or intravenous administration of an opioid (piritramide, tramadol or pethidine) was proposed in 19% (7/36) of the centers. Opioid PCIA technique was available in 100% of the UH and in 36% (13/36) of the non-UH centers, and for an additional 11% (4/36) of them only in case of intrauterine death. Entonox (oxygen/nitrous oxide mixture) was used in 11% (4/36) of the centers.
A paracervical analgesia (pudendal block) made by obstetricians was considered in 28% (10/36) of all centers. Non-pharmacologic alternatives (i.e. hypnosis, sophrology, baths and massages) were proposed in 19% (7/36) of the centers.

4. The use of PCIA

In most of centers (both non-UH and UH) where PCIA was available, remifentanil was the first choice (76.5% of the PCIA) (Table 1) with a mode of administration highly variable from one hospital to another. The administration of other opioids as well as ketamine is described in Table 1. Morphine and ketamine were exclusively used in case of intrauterine death.

Nausea (the most frequent), dizziness, sedation but no harmful problem (e.g. major desaturation, apnea, loss of consciousness) were the side effects encountered with the use of PCIA.

5. Reasons for not using opioid PCIA:

Forty five percents of the non-UH reported that they had never used PCIA technique for the following reasons: lack of knowledge (7%), ineffectiveness to relieve labor pain (17.2%), fear of major maternal and/or fetal side effects (48.3%), opposition from the pediatricians or obstetricians (17.2%), lack of adequate supervision of the parturient (48.3%), PCA pump not available for such use (3.4%).

Finally, although it was not the principal reason for non using PCIA, the difficulty to get reimbursement for obstetric analgesia was mentioned by 20.7% of the centers (using the technique or not).

6. Indications for opioid PCIA for vaginal delivery

To question the opinion of the anesthesiologists on what could be considered an acceptable indication to use opioid PCIA as an alternative to epidural analgesia in the laboring parturient, four statements were proposed. The rate of agreement to the different indications which were suggested is shown in Table 2.

DISCUSSION

The present survey demonstrates that epidural analgesia for labor pain is widely available in Belgium, with a median rate of 68% in the French part (range from 25 to 92%) which is very similar to that of the Flemish part (Fig. 1). A previous survey in Flanders (7) reported a rate of neuraxial analgesia over 65% (84% of epidural technique) and a recent French survey (8) mentioned a rate close to 69% (range from 32 to 90%). Other European countries report a lower rate of locoregional analgesia for labor (9-11), a factor certainly related to cultural differences.

For decades, systemic administration of opioids, mainly intramuscular injection, has been the only way to relieve pain during labor and still remains a current practice. Of the available opioids, the most commonly used is pethidine. Parenteral opioid injection, however, seems less frequently used in Belgian obstetric units (22%) than in France (53%; nalbuphine and pethidine) (8) and in the United Kingdom where intramuscular pethidine is available in 99% of the centers (9). The analgesic efficacy of both intramuscular and intravenous pethidine for labor pain has often been questioned.

<table>
<thead>
<tr>
<th>Analgesic Drug</th>
<th>Frequency of use (%)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>76.5</td>
<td>Highly variable</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>23.5</td>
<td>bolus [3-5 µg with 10 min lockout]</td>
</tr>
<tr>
<td>Preritramide</td>
<td>18</td>
<td>bolus [1-1.5 mg, max 20-25 mg/4h]</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6</td>
<td>bolus [25 µg with 5-10 min lockout] + continuous infusion [0.02-0.05 µg/kg/min]</td>
</tr>
<tr>
<td>Morphine (*)</td>
<td>6</td>
<td>bolus [1 mg with 7 min lockout] + continuous infusion [3 mg/h]</td>
</tr>
<tr>
<td>Ketamine (*)</td>
<td>6</td>
<td>bolus [1-1.5 mg, max 20-25 mg/4h]</td>
</tr>
</tbody>
</table>

(*) only for induced labor for intrauterine death.

Some centers used more than one opioid, according to the situation and the choices made by the different members of the staff.
and intrapartum use of pethidine has been associated to neonatal respiratory depression and postnatal behavioral problems. Currently, some authors argue that it is ethically appropriate to administer systemic opioids, i.e. pethidine, to women requesting analgesia for labor pain (12, 13) while others conclude that pethidine should be avoided in this indication (8, 14).

Nitrous oxide (the mixture O\textsubscript{2}/N\textsubscript{2}O, Entonox/Kalinox\textsuperscript{®}) has been used for more than 100 years for labor analgesia, particularly in the United Kingdom where it is the standard inhaled analgesic. By consequence, it is not surprising that Entonox\textsuperscript{®} was readily available in 100% of the UK obstetric units (9). In France, nitrous oxide was proposed in only 12.4% of the centers (8) and our findings are very close (11.1%). Inhalational anesthetic agents have been recently evaluated for labor pain and self-administered sevoflurane at concentration of 0.8% seems effective and acceptable in that indication (15). The technique is still experimental and the use of sevoflurane very limited in the UK survey (9) where only 3% of the centers reported sevoflurane inhalation as an alternative to epidural analgesia.

PIC\textsubscript{A} is widely used to manage postoperative pain. The technique is simple, allows an individualized control of the pain and does not require the constant availability of an anesthesiologist. These attractive properties have lead to consider systemic opioid delivery by PIC\textsubscript{A} for labor pain when epidural analgesia is not available. Published data show a current use of the technique ranging from 25% to 49% in different European countries (8,9,16), including our survey (47%) (Fig. 2).

Different opioid analogesics are administered such as pethidine, nalbuphine, morphine, fentanyl, alfentanil, and sufentanil. Although morphine remains the gold standard for postoperative analgesia, the drug, whatever the route of administration, provides only poor relief of labor pain and induces pronounced sedation in the parturient (3). However, PIC\textsubscript{A} with morphine remains commonly used for deliveries involving intrauterine deaths (12% of PIC\textsubscript{A} in our survey and 35.5% in a recent UK survey (9)).

### Table 2

<table>
<thead>
<tr>
<th>Statement</th>
<th>UH (n = 4)</th>
<th>Non-UH (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. vaginal delivery in normal conditions (term &gt; 37 weeks) in a parturient who can not benefit from an epidural analgesia</td>
<td>75%</td>
<td>35%</td>
</tr>
<tr>
<td>b. vaginal delivery of a premature fetus in a parturient who can not benefit from an epidural analgesia</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>c. vaginal delivery in a case of intrauterine death in a parturient who can not benefit from an epidural analgesia</td>
<td>75%</td>
<td>56%</td>
</tr>
<tr>
<td>d. vaginal delivery in normal conditions in a parturient who refuses an epidural analgesia without evident contraindication to the epidural technique.</td>
<td>0%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Data are expressed as percentage of agreements to four different statements:

a. vaginal delivery in normal conditions (term > 37 weeks) in a parturient who can not benefit from an epidural analgesia
b. vaginal delivery of a premature fetus in a parturient who can not benefit from an epidural analgesia
c. vaginal delivery in a case of intrauterine death in a parturient who can not benefit from an epidural analgesia
d. vaginal delivery in normal conditions in a parturient who refuses an epidural analgesia without evident contraindication to the epidural technique.

Data are expressed as the average percentage of parturients delivering under epidural analgesia in different European countries (extreme values are indicated when available): Germany (G) (from 10-30%) (11); Netherlands (N) (7); Scandinavian countries (Scand) (from 20-60%) (10); United Kingdom (UK) (maximum 56%) (9); France (F) (from 32-90%) (8); Belgium Flanders part (Belgium FL) (7); Belgium French part (Belgium FR) (from 25-90%, present survey).

Fig. 1. — Usage of epidural analgesia for labor pain and delivery in different European countries (data from 2000-2007)
In obstetrics, PCIA with fentanyl is safer than pethidine because no neurobehavioral changes are noted in the neonates. Fentanyl also provides superior labor analgesia than alfentanil with no difference in maternal side effects (17). Fentanyl was chosen for 31.7% of the PCIA during labor and delivery in a recent UK survey. Surprisingly, although no clinical studies evaluated sufentanil for labor analgesia, 23.5% of PCIA were set to deliver sufentanil in our survey and sufentanil was the preferred opioid (70% of PCIA) in two recent French surveys (8, 18). Table 3 presents the dosages currently recommended for the administration of different opioids by PCIA during labor.

Labor pain has gained popularity as an indication for PCIA since the potent and ultra-short acting µ-opioid analgesic, remifentanil, became available. The findings of the present survey which reports the use of remifentanil as first choice among opioid analgesics for PCIA in obstetrics are in agreement with current medical literature and practice.

The challenge was to find a systemic opioid which could match the time course of labor pain, i.e. intermittent and increasing in intensity over time. The pharmacologic properties of remifentanil, which is quickly metabolized by non specific esterases in blood and tissues, allow a rapid onset and a rapid offset of action, independently of the doses and the duration of administration (4, 17). Further, although remifentanil as other opioids easily crosses the placenta, it is quickly metabolized and redistributed in the fetus, this limits but does not exclude the risk for side effects in the neonate (4, 17). Today, remifentanil is the most commonly used opioid for live births in the United Kingdom (34.6%) (9) as well as in our survey (76.5%). It seems to be the most suitable opioid in the indication of labor pain. Clinical trials have demonstrated that PCIA with remifentanil is more effective and induces less side effects than pethidine (19, 20), and provides superior pain relief than nitrous oxide during labor (21).

However, two points still raise concerns and preclude a larger use of systemic analgesia, i.e. PCIA, in parturients: the efficacy of the technique and the side effects in both the mother and the future newborn. By definition, pain is subjective and the experience of labor pain varies considerably from one parturient to another. When women were questioned about the level of pain they would consider acceptable during their labor (16), the answers ranged from 0 to 7, with a median score of
A majority of the studies having assessed the efficacy of systemic opioids for labor pain have reported a reduction of pain scores to a median VAS value of 5 to 6 after opioid administration (Fig. 3). Although the reduction of pain scores is less than that provided by neuraxial analgesia, the average decline in pain intensity usually reaches 25 to 30% after systemic opioids and specifically after PCIA use (Fig. 3). In patients suffering from acute postoperative pain, the minimal decline in pain intensity that patients could discern is a 20% decrease and a 35% reduction is considered as a clear improvement (22). Furthermore, pain associates both a sensory and an emotional experience and opioids are known to also reduce the affective response to pain. NELSON et al. (12) have demonstrated a significant correlation between the reduction in labor pain intensity and in affective magnitude following intravenous meperidine in parturients. By consequence, the results from BALKI (23), who reported high satisfaction scores (average 8.2 ± 0.4 on a 10-point scale) in women using PCIA for labor pain are not so surprising. More recently, VOLMENEN et al. (24) compared PCIA with remifentanil to

Data are expressed as average values on a Visual Analog Scale (VAS from 0 = no pain to 10 = the worst pain) before (VAS pre) and after (VAS post) opioid administration. Only two studies reported the effect of opioid administration as ineffective (NS: non significant effect).

References: IV morphine, OLOFSSON et al. (3, 14); IM pethidine/placebo, TSUI et al. (13); IV pethidine US, NELSON et al. (12); IV pethidine FR, BERGERET et al. (8); PCIA Sufentanil, BERGERET et al. (8); PCIA Remifentanil, VOLKAS et al. (19); PCIA Remifentanil, EVRON et al. (20); PCIA Remifentanil, BALKI et al. (23); PCIA Remifentanil, VOLMENEN et al. (24).

Fig. 3. — Reduction of pain scores provided by the administration of systemic opioids during labor according to different clinical studies
epidural analgesia in parturients. The median pain scores were lower with epidural analgesia (5.2) than intravenous remifentanil (7.3) but there was no difference in the scores assessing pain relief (2.8 versus 2.5 on a scale 0-4). In this study, the authors adapted the doses of remifentanil following a dose escalation scheme up until the individual-effective dose was reached. The wide interindividual variability in the dose of systemic analgesics needed to obtain postoperative pain relief is well known. A similar variability, and even higher, does exist for labor analgesia, explaining the differences in the doses of remifentanil used throughout labor course (median dose 0.066 µg/kg/min, range from 0.046 to 0.1 µg/kg/min) (17). To date, the ideal dose regimen of remifentanil for labor pain remains to be determined and requires a dose titration to meet the needs of each parturient. Adaptative changes can be made either on the background infusion or on the bolus doses. Balki et al. (23) have recently compared the stepwise increase of a background infusion rate (from 0.025 to 0.1 µg/kg/min) associated with a constant bolus dose of 0.25 µg/kg, and a constant background 0.025 µg/kg/min infusion rate associated with a stepwise increase of the bolus dose from 0.25 to 1.0 µg/kg. They concluded that, for similar pain scores and satisfaction, the later regimen was associated with more side effects (i.e. drowsiness: 100% vs 30%; nausea: 60% vs 20%; desaturation < 90%: 20% vs 10%).

Systemic opioids are associated with adverse effects in both the mother and the neonate. For the mother, they include sedation, respiratory depression and oxygen desaturation, nausea and vomiting, delayed gastric emptying, pruritus and sometimes dysphoria. The side effects of remifentanil are similar to those of other opioids. Sedation and dizziness usually occur in 30-58% of the parturients although they remain alert to voice (23, 25). Decreased peripheral oxygen saturation (SpO₂) < 95% is observed in 40-50% and < 90% in 10-25% of the parturients breathing room air (16, 23). This side effect is easily corrected with supplemental oxygen administration. By consequence, opioid PCA during labor imperatively requires close patient’s monitoring (SpO₂) as well as oxygen availability. Hemodynamic stability is generally preserved (23, 25). Appgar scores of the neonates do not seem to be a concern although several studies mention alterations of fetal heart rate tracings (around 20% of the cases) during remifentanil analgesia (16, 23, 25) as it is also reported for other opioids.

In conclusion, the present survey demonstrates that, in the French part of Belgium, epidural analgesia is widely available and opioid PCA is available in almost 50% of the obstetric units when epidural analgesia can not be provided for different reasons. Remifentanil was found to be the opioid of choice for PCA in laboring parturients, and this is in agreement with the current literature. Moreover, the indications for remifentanil PCA during labor are now increasing. Besides its use when epidural is contraindicated, some studies report its use when the parturients refuse EA (Indications for PCA: contraindication to regional technique in 18.8% and refusal of regional technique in 24.5%) (26). However, it is worth noting that further studies are still needed to optimize the technique and that careful monitoring of the parturient and the neonate is mandatory.

Acknowledgements

The authors thank Pr. J. F. Brichant (President of the Belgian Society of Anesthesiology and Reanimation) and Pr. F. Veyckemans for their support and for the advices provided in the design of the questionnaire.

References