Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section

C. Duale*, C. Frey, F. Bolandard, A. Barrière and P. Schoeffler

Département d’Anesthésie-Réanimation, CHU de Clermont-Ferrand, Rue Montalembert, BP69, F-63003 Clermont-Ferrand Cedex 1, France

*Corresponding author. E-mail: cduale@chu-clermontferrand.fr

Background. Perispinal anaesthesia for Caesarean section allows injection of epidural (ED) or intrathecal (i.t.) morphine to provide long-lasting postoperative analgesia. To compare these two routes, a prospective, randomized, double-blinded study of 53 patients undergoing elective Caesarean section was performed.

Methods. Combined spinal-epidural anaesthesia with 6 mg of i.t. hyperbaric bupivacaine plus sufentanil 5 μg, and additional ED lidocaine was used. Additionally, each patient received either 2 mg (2 ml) of ED morphine plus 1 ml of i.t. normal saline (ED group, n=28), or 0.075 mg (1 ml) of i.t. morphine plus 2 ml of ED normal saline (i.t. group, n=25). Additional postoperative analgesia was given in the form of propacetamol and ketoprofen, plus self-administered i.v. morphine.

Results. No major respiratory depression occurred. Time to first demand of morphine was similar in the ED (307.5 min) and i.t. (310 min) groups, as was the incidence of side-effects such as sedation, pruritis, nausea, and vomiting. During the first 24 postoperative hours, VAS pain scores were greater in the i.t. group (P=0.032), as was additional morphine consumption (4 vs 1.5 mg) (P=0.03).

Conclusions. The ED protocol was more effective than the i.t. protocol, whilst side-effects were similar.

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After Caesarean section, parenteral acetaminophen (propacetamol) and an NSAID (such as ketoprofen) are commonly used for postoperative analgesia. Their effectiveness is generally limited, however, leading to the need for opioid analgesia. Multiple regimens of administration have been proposed for opioids but perispinal morphine is one of the most widely used. This hydrophilic and long-acting drug can be effective for many hours after a single injection performed during perispinal anaesthesia (for review see ).

Side-effects (e.g. nausea, vomiting, and pruritis) and respiratory depression are possible with perispinal morphine, but the risk is lower with small doses.

Two routes of administration are possible for perispinal morphine, epidural (ED) or intrathecal (i.t.) injection. Choice is often influenced by the type of anaesthesia performed (i.e. epidural or spinal), but the recent technique of combined spinal-epidural anaesthesia makes either route of morphine administration possible. There is no clear evidence to recommend one technique over the other. Previous studies have shown that 3 mg of ED morphine (given alone) provide 18 h of postoperative analgesia without risk of respiratory depression, and that the same duration of analgesia can be provided by 0.1 mg of i.t. morphine (plus ketorolac). Also, these two doses appear to be equivalent in terms of 24-h morphine consumption, when administered without additional analgesic drugs.

For the current investigation they were thus considered to be equipotent. This study was designed to compare these two protocols but the doses of morphine were reduced to 2 and 0.075 mg, respectively, as additional analgesia by intrathecal sufentanil and parenteral acetaminophen and ketoprofen was delivered.
Therefore, the aim of the study was to compare the effectiveness of postoperative analgesia and side-effects of 2 mg ED morphine and 0.075 mg i.t. morphine after Caesarean section when associated with initial i.t. sufentanil and subsequent parenteral acetaminophen and ketoprofen.

Methods

This prospective, randomized, double-blind study was undertaken in two obstetric units of the same university hospital. After approval from the regional ethical committee (CCPPRB of Auvergne) and after written informed consent, patients undergoing Caesarean section were randomly assigned into two groups (ED or i.t. morphine). The inclusion criteria were: age 18–45 yr, ASA I–II and Caesarean section after a normal pregnancy. The exclusion criteria were: patient refusal, contra-indication for perispinal anaesthesia for haemodynamic, infectious, haemodynamic or neurological reasons, emergency Caesarean section, severe pre-eclampsia, contra-indication to any of the drugs used in the protocol, or failure of the perispinal anaesthesia for Caesarean section.

Randomization was undertaken using computer-generated opaque envelopes. The patient was blinded to the protocol used. On arrival in the operating theatre, patients received 200 mg of oral effervescent cimetidine diluted in 10 ml of water. Routine non-invasive monitoring was performed throughout surgery and every 10 min during the immediate postoperative period. After 16-gauge antechrachovian venous catheterization, 500 ml of lactated Ringer’s solution was infused and pre-oxygenation performed with high-flow oxygen (8 litre min⁻¹). Then, with the patient in the sitting position, and after skin disinfection with iodine polyvidone and intradermal anaesthesia with lidocaine 1%, an 18-gauge Tuohy needle (Braun, Melsungen, Germany) was inserted through the L₃₋₄ interspace. The loss-of-resistance technique with normal saline was used to identify the epidural space. After the epidural space had been reached, dural puncture was performed with a 27-gauge, 12-cm needle for spinal anaesthesia (Pencil Point®, Braun, Melsungen, Germany) that was inserted into the Tuohy needle. After return of clear cerebrospinal fluid, a solution containing hyperbaric bupivacaine for spinal anaesthesia (6 mg in 1.2 ml), 5 μg of sufentanil diluted in 1 ml of normal saline and 1 ml of either normal saline (ED group) or morphine (i.t. group, 0.075 mg of preservative-free morphine, Pharmacie Centrale des Hôpitaux de l’Assistance Publique, Paris, France) were injected intrathecally over 30 s. Ephedrine was infused intravenously on initiating the i.t. injection (60 mg in 250 ml of normal saline, rate adapted to maintain preoperative values of arterial pressure). After the i.t. injection, an epidural catheter (Perifix®, Braun, Melsungen, Germany) was inserted for 3 cm. If it was not possible to thread the catheter, or if blood appeared in it, then the puncture was performed again at a higher level. As a test dose, 4 ml of lidocaine 1% plus epinephrine (5 μg ml⁻¹) were gradually injected into the catheter (30 s delay between each 1 ml injection). The test dose injection was stopped if signs of poor tolerance to the subarachnoid injection were noted.

The patient was then placed in the supine position (with a 10° left tilt), and the level of sensory loss (pinprick) was determined. Additional ED boluses of 2 ml of lidocaine 2% were injected until a bilateral T4 block was established. At the end of the procedure, 2 ml of either 2 mg of morphine diluted with 2 ml of normal saline (ED group, Morphine, Aguettant) or 2 ml of normal saline (i.t. group) were injected. Then, 2 ml of additional normal saline were injected to flush the system before removal of the catheter. The total dose of ED lidocaine needed for anaesthesia, as well as the volume of i.v. lactated Ringer’s solution and ephedrine needed for haemodynamic stability were noted, as well as the Apgar score for the newborn at 1, 5, and 10 min after birth.

After surgery, the patient was observed in the recovery room until the motor block resolved. On arrival, a first dose of propacetamol 2 g (Pro-Dafalgan®, UPSA; equivalent to acetaminophen 1 g) and ketoprofen 50 mg were infused intravenously. To ensure postoperative analgesia, the same doses of propacetamol and ketoprofen were infused every 8 h and additional analgesia was provided by i.v. morphine PCA (1 mg ml⁻¹ of normal saline, 1-ml bolus, 10-min lock-out period, 12 mg 2 h⁻¹ maximal dose, no continuous infusion). Observations were made by a nurse who was blinded to the procedure, but who was informed of the risks of opioid treatment. Every hour over 6 h, and every 4 h until the 24-h after the beginning of surgery, heart rate and arterial pressure were measured and pain was assessed by a 0–100 visual analogue scale (VAS). Side-effects of perispinal or systemic morphine were noted. Sedation was considered as clinically relevant if the patient was not easily awakened. In the case of nausea/vomiting, metoclopramide 10 mg was injected intravenously. In the case of unsuccessful treatment, unpleasant pruritis or a life-threatening event, an anaesthetist was to be called to administer i.v. naloxone 0.4 mg.

For the 24-h observation period, the area under the curve (AUC) for pain was calculated, as the sum of the VAS values [(pain at tᵢ+1 + pain at tᵢ)/2]×[time (h) between tᵢ and tᵢ+1] calculated for each interval between observations. Numerical data were expressed as median values and (CI25– CI75). Comparisons between the ED and i.t. groups for patient characteristics, anaesthetic, surgical, and newborn data, as well as for the time of first demand of morphine and morphine consumption, were made using the Mann–Whitney U-test. For comparisons of haemodynamic data in the same group with preoperative values, ANOVA for repeated measures was used, followed by the Dunnett’s test in case of a difference. The χ²-test was used for nominal data.
According to previously published data, the sample size for this study was based on an expected difference of 6.5 mg of morphine per 24 h (\(\sigma=6\), bilateral comparison of means, risk \(\alpha=0.05\) and \(\beta=0.1\)) and was calculated to be 25 patients per group.

### Results

Twenty-eight patients were included in the ED group and 25 in the i.t. group, as three patients in the i.t. group were withdrawn from the study (post-operative haemorrhage). There was no difference between groups with respect to characteristics, perioperative events, and Apgar scores (Table 1).

![Graph A](https://example.com/graphA.png)  
**Fig 1** Time course of postoperative pain expressed as VAS score out of 100 (A) and consumption of i.v. morphine in mg h\(^{-1}\) (B). VAS pain scores and morphine consumption (mg h\(^{-1}\)). Data expressed as median, range, CI 25–75. *P<0.04.

![Graph B](https://example.com/graphB.png)  

According to previously published data, the sample size for this study was based on an expected difference of 6.5 mg of morphine per 24 h (\(\sigma=6\), bilateral comparison of means, risk \(\alpha=0.05\) and \(\beta=0.1\)) and was calculated to be 25 patients per group.

### Table 1

Patient characteristics and surgical, anaesthetic, and Apgar scores. No significant differences. Data are expressed as median and (CI 25–75)

<table>
<thead>
<tr>
<th></th>
<th>ED (n=28)</th>
<th>i.t. (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.5 (28–35.5)</td>
<td>32 (29–32)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.5 (62.5–79.5)</td>
<td>65 (61.5–72.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (155.5–165.5)</td>
<td>160 (157–164)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0–2)</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39 (38–39)</td>
<td>39 (39–39)</td>
</tr>
<tr>
<td>Previous history of Caesarean section (%)</td>
<td>12 (42)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Epidural lidocaine consumption (mg)</td>
<td>140 (80–170)</td>
<td>160 (80–160)</td>
</tr>
<tr>
<td>Lactated Ringer’s consumption (ml)</td>
<td>1500 (1000–2000)</td>
<td>1650 (1500–2000)</td>
</tr>
<tr>
<td>Intravenous ephedrine consumption (mg)</td>
<td>60 (50–64)</td>
<td>60 (49.5–61.5)</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>150 (130–180)</td>
<td>150 (150–180)</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>9 (4–10)</td>
<td>9 (8–10)</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>10 (6–10)</td>
<td>10 (6–10)</td>
</tr>
<tr>
<td>Apgar score at 10 min</td>
<td>10 (8–10)</td>
<td>10 (9–10)</td>
</tr>
</tbody>
</table>

### Table 2

Consumption of i.v. morphine (PCA) after Caesarean section. Numerical data are expressed as median and (CI 25–75). *P<0.05

<table>
<thead>
<tr>
<th></th>
<th>ED (n=28)</th>
<th>i.t. (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for first demand of morphine (min)</td>
<td>307.5 (240–715)</td>
<td>310 (260–781)</td>
</tr>
<tr>
<td>24-h morphine consumption (mg)</td>
<td>1.5 (0–5)</td>
<td>4 (1.8–10.7)*</td>
</tr>
<tr>
<td>Patients who never asked for morphine, n (%)</td>
<td>9 (32)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

![Graph C](https://example.com/graphC.png)  
**Fig 2** Haemodynamic effect of perispinal morphine. Percentage of the control value (i.e. the beginning of the procedure) is plotted against time. Data are expressed as mean (SEM). No significant differences.

In both groups, a significant decrease in heart rate and arterial pressure after the 4 h was observed (compared with baseline) but, at all times, these values were similar in the two groups (Fig. 2). No life-threatening haemodynamic or respiratory events occurred during the study, and no injection of naloxone was necessary. Side-effects of morphine were reported in both groups, and the time course of
their incidence is shown in Figure 3. The incidence of side-effects was similar (Tables 3 and 4).

### Discussion

The present study was designed to compare the effects of ED morphine 2 mg with those of i.t. morphine 0.075 mg for postoperative analgesia after Caesarean section. Both ED and i.t. protocols provided effective analgesia of similar duration (median time 5 h without any need for additional morphine). Both protocols were associated with a similar incidence of side-effects. Patients undergoing i.t. morphine experienced more postoperative pain, however, and required more additional morphine than those in the ED group. The only other study comparing ED and i.t. morphine (with ketoprofen) for postoperative pain after Caesarean section was published recently. The authors used larger doses of morphine (3 mg ED or 0.1 mg i.t.) as propacetamol was not used in addition to the NSAID for supplemental analgesia. Both techniques were reported to be equally effective and led to a similar incidence of side-effects. Greater quantities of additional analgesics (oxycodone) were needed, however, in the i.t. group. The current study thus confirms previous findings that i.t. morphine seems to be less effective than ED, although this difference is not marked. However, the injection of larger doses of i.t. morphine to provide better analgesia is likely to be associated with more side-effects. It is hypothesized that i.t. morphine may be less effective as a result of more extensive rostral spread of the drug, but this theory needs to be tested further.

The present study also found that the consumption of PCA morphine is significantly reduced by additional analgesia (in this case initial i.t. sufentanil, then propacetamol and ketoprofen), when compared with the results in the literature after perispinal morphine alone. Indeed, Palmer and colleagues showed that 2.5 and 3.75 mg of ED morphine alone provided poor analgesia if compared with the results of the ED group presented here, as a mean dose of 33 and 18 mg of morphine over 24 h (respectively) were required. The same conclusions can be drawn for i.t. morphine, as 25 mg of additional morphine over 24 h were needed after 0.1 mg of i.t. morphine. The addition of an NSAID may have sparing effects for additional morphine, reducing the need to 6.4 mg over 24 h after the same i.t. dose.

Data from the literature with respect to the same postoperative model have shown that the use of larger doses of morphine may provide better analgesia but leads to
a greater incidence of side-effects. Indeed, doses from 2 to 5 mg (ED)\textsuperscript{10} and from 0.025 to 0.5 mg (i.t.)\textsuperscript{3} have been used previously. The duration and effectiveness of the analgesia have been shown to be dose-dependent, although a ceiling-effect is observed above 3.75 mg (ED) and 0.1 mg (i.t.).\textsuperscript{8} Conversely, the incidence of side-effects always increases above these doses and may limit the quantity of morphine that can be given. For example, a significant incidence of respiratory depression above 4 mg of ED morphine\textsuperscript{6,12} and 0.2 mg of i.t. morphine\textsuperscript{12} has been described, while no similar event has been described with 3 mg of ED or 0.1 mg of i.t. morphine.\textsuperscript{5,9} This is also true of pruritis, for which little preventive treatment is available.\textsuperscript{5} For example, a 60–65\% incidence of itching has been reported after 0.1±0.2 mg of i.t. morphine\textsuperscript{9,10} and a 70\% incidence after 2 mg ED morphine.\textsuperscript{10} Reducing the doses of perispinal morphine may reduce the incidence of side-effects and is possible without impairing the analgesic efficacy by the addition of other analgesic drugs. This is demonstrated in the current study, as the incidence of pruritis was lower than that in studies using larger doses of morphine.\textsuperscript{1,13–16}

Nausea and vomiting are less frequent and more easily treated side-effects, as antiemetic treatments that do not interact with analgesia are now available.\textsuperscript{17,18} In addition, nausea and vomiting have also been reported in control groups without perispinal morphine, showing that they can also be induced by the surgical procedure itself or by the use of i.v. morphine. It should also be noted that for the study protocol described here, some of the early side-effects (during the first 4 h; Fig. 3) might be a result of initial treatment with i.t. sufentanil. This drug is recommended, however, as it improves the quality of perispinal analgesia.\textsuperscript{19,20}

In conclusion, the results of this study suggest that ED morphine 2 mg, in addition to systematic i.v. propacetamol, ketoprofen, and i.t. sufentanil 5 μg provide effective long-lasting analgesia after Caesarean section. Analgesia provided by i.t. morphine 0.075 mg was slightly less effective. Both techniques were associated with a similar incidence of side-effects. The importance of concomitant non-opioid analgesia to limit the dose and associated side-effects of morphine, is confirmed.

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