Analgesic Effect of Low-dose Intrathecal Morphine after Spinal Fusion in Children

Olivier Gall, M.D., Ph.D.,* Jean-Vincent Aubineau, M.D.,* Josée Bernière, M.D.,* Luc Desjeux, M.D.,* Isabelle Murat, M.D., Ph.D†

Background: This study was designed to assess the postoperative analgesic effect of low-dose intrathecal morphine after scoliosis surgery in children.

Methods: Thirty children, 9–19 yr of age, scheduled for spinal fusion, were randomly allocated into three groups to receive a single dose of 0 (saline injection), 2, or 5 μg/kg intrathecal morphine. After surgery, a patient-controlled analgesia device (PCA) provided free access to additional intravenous morphine. Children were monitored for 24 h in the postanesthesia care unit.

Results: The three groups were similar for age, weight, duration of surgery, and time to extubation. The time to first PCA demand was dose-dependently delayed by intrathecal morphine. The first 24 h of PCA morphine consumption was 49 ± 17, 19 ± 10, and 12 ± 12 mg (mean ± SD) in the saline, 2 μg/kg morphine, and 5 μg/kg morphine groups, respectively. Pain scores at rest were significantly lower over the whole study period after 2 and 5 μg/kg intrathecal morphine than after saline, but there was no difference between intrathecal doses. Pain scores while coughing and the incidence of side effects were similar in the three groups.

Conclusions: These data demonstrate that low-dose intrathecal morphine supplemented by PCA morphine provides better analgesia than PCA morphine alone after spinal fusion in children. The doses of 2 and 5 μg/kg seem to have similar effectiveness and side-effect profiles, whereas a reduction of intraoperative bleeding was observed in patients who received 5 μg/kg but not 2 μg/kg intrathecal morphine.

Patients undergoing major spinal surgery present a challenging postoperative pain management problem. They have large incisions and dissections extending over 8 or often 10 dermatomes. The potential for neurologic complication or sudden postoperative bleeding hinders the use of local anesthetics via the epidural route in the first 24 h after surgery. The epidural administration of liposoluble opioids has been proposed as an alternative to a standard analgesic regimen based on systemic morphine.1 However, other studies have yielded inconclusive results.2,3 Single-shot intrathecal morphine may be another alternative.

The renewed interest for intrathecal opioids comes from a large number of studies indicating that intrathecal morphine in low or very low doses may provide excellent postoperative analgesia with a low incidence of side effects, especially a low incidence of respiratory depression.4–10 The question of the effectiveness of low doses of intrathecal morphine has not been addressed in the context of spinal surgery in children.

This double-blind, randomized study was primarily designed to assess the postoperative analgesic effect of intrathecal morphine in doses of 2 and 5 μg/kg after spinal fusion in children. Cumulative patient-controlled analgesia (PCA) morphine consumption and postoperative pain scores were the main outcomes considered. Intraoperative blood loss, time to extubation, and side effects were also examined.

Methods

Following institutional approval (Comité Consultatif pour la protection des personnes dans la recherche biomédicale, Hôpital Saint-Antoine, Paris, France) and written informed consent had been obtained, 32 children with idiopathic scoliosis scheduled for spinal fusion with Cotrel Dubousset instrumentation were randomly allocated by a computer-generated list into three groups (intrathecal saline, 2 μg/kg intrathecal morphine, or 5 μg/kg intrathecal morphine). Exclusion criteria were American Society of Anesthesiologists physical status III or IV, inability to quantify pain on a visual analog scale, or presumed inability to use a PCA device for postoperative analgesia as assessed by the anesthesiologist during the preoperative visit. Whenever possible, an autologous transfusion program was instituted.

All patients were premedicated with 0.3 mg/kg midazolam orally 30 min before surgery. After induction of anesthesia with propofol, sufentanil, and atracurium, the trachea was intubated and children were turned in lateral position. A 4-ml solution containing 2 μg/kg preservative-free morphine, 5 μg/kg preservative-free morphine, or normal saline was injected in the subarachnoid space via a 25-gauge pencil-point spinal needle. The solution was prepared extemporaneously and aseptically by a blinded physician.

Perioperative monitoring included electrocardiogram, invasive arterial blood pressure, pulse oximetry, end-tidal carbon dioxide partial pressure, and somatosensory-evoked potentials. Anesthesia was maintained by a continuous infusion of propofol and sufentanil at the discretion of the attending physician with the goal of achieving moderate hypotension (mean arterial pressure between 50 and 60 mmHg). Weighting sponges and measuring blood collected in the cell saver assessed intraoperative blood loss. Hematocrit was repeatedly...
Table 1. Demographic and Intraoperative Data

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 10)</th>
<th>2 μg/kg Morphine (n = 10)</th>
<th>5 μg/kg Morphine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>15 ± 4</td>
<td>17 ± 3</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53 ± 14</td>
<td>53 ± 7</td>
<td>49 ± 10</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>244 ± 39</td>
<td>262 ± 57</td>
<td>214 ± 62</td>
</tr>
<tr>
<td>Total propofol used (mg/kg)</td>
<td>35 ± 9</td>
<td>49 ± 10</td>
<td>31 ± 14</td>
</tr>
<tr>
<td>Total sufentanil used (μg/kg)</td>
<td>4.2 ± 1.0</td>
<td>4.5 ± 2.1</td>
<td>3.1 ± 1.3</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml/kg)</td>
<td>41 ± 23</td>
<td>34 ± 19</td>
<td>14 ± 10*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* P < 0.05, 5 μg/kg morphine versus other groups.

measured, and bloodtransfusion was started when the hematocrit level dropped to 25%.

After completion of surgery, all children were monitored for 24 h in the postanesthesia care unit (PACU). Immediately after extubation, they were instructed to use a PCA device whenever they felt in pain (intravenous morphine, 25 μg/kg bolus, lockout period 8 min, no background infusion). PACU nurses proceeded to titration with incremental doses of morphine (50 μg/kg) until pain relief. If satisfactory analgesia could not be maintained (visual analog scale < 40 mm, bolus/attempt < 0.7), PACU physicians were allowed to modify PCA settings. Analgesia was supplemented by intravenous propacetamol 30 mg/kg per 6 h, given systematically. The PACU nurses and physicians who collected the postoperative data were unaware of the group assignment.

The time to first PCA demand, the number of demands, and the cumulative dose of intravenous morphine delivered by the PCA pump were recorded. Children were asked to quantify their level of pain on a visual analog scale (0 = no pain, 100 = worst possible pain) at rest, every hour, and while coughing, four times hourly. Postoperative monitoring included hourly recording of sedation score (0 = awake, 1 = sleepy but easily arousable, 2 = very sleepy but still arousable with physical stimuli, 3 = difficult to awaken), respiratory rate, end-tidal carbon dioxide (through a nasal probe in spontaneously breathing patients), occurrence of nausea, vomiting, and pruritus, and appearance of paresthesias or inability to move the legs.

Statistical comparisons were performed on intent-to-treat basis. The sample size was determined on an expected difference of more than 15 mg in morphine consumption, with a standard deviation estimated at 10 mg from preliminary data, to achieve β = 0.8 with α = 0.05. The time to first PCA demand was compared by log rank test. Pain scores were analyzed by nonparametrical analysis of variance (Kruskal–Wallis test) because of their skewed distribution. Postoperative events were compared by chi-square analysis. Values are expressed as median and interquartile range or mean and SD, as appropriate.

Results

All patients underwent successful subarachnoid injection. Two patients were withdrawn from the study after major intra- or postoperative events that called for breaking their randomization code to check for the necessity of naloxone reversal. One patient belonged to the 2 μg/kg morphine group and the other to the saline group. The former presented sustained hypotension 2 h 30 min after skin incision, and somatosensory-evoked potentials could no longer be recorded. This resolved within 30 min after adequate fluid replacement. The latter had marked respiratory depression after surgery, 40 min after extubation of the trachea. He was reintubated, and ventilation was deemed necessary for the next 16 h.

Demographic and intraoperative data are given in table 1. The three groups did not differ in age, weight, and duration of surgery. During surgery, average mean arterial pressure was 53 ± 8, 54 ± 6, and 53 ± 6 mmHg in the saline, 2 μg/kg morphine, and 5 μg/kg morphine groups, respectively (fig. 1). The amounts of propofol and sufentanil used to achieve such level of moderate hypotension were slightly higher in the saline and 2 μg/kg morphine groups than in the 5 μg/kg morphine group, yet the difference was not statistically significant. Intraoperative blood loss was significantly lower in the morphine 5 μg/kg group than in the other groups. This was not accounted for by differences in the extent of surgery as the number of vertebral level fused (8 ± 2, 9 ± 4, and 7 ± 2 in the saline, 2 μg/kg morphine, and 5 μg/kg morphine groups, respectively) was not different between groups. Time from discontinuation of sufentanil infusion to extubation was 99 ± 42, 121 ± 70, and 101 ± 56 min in the saline, 2 μg/kg morphine, and 5 μg/kg morphine groups, respectively (no significant difference between groups).

After surgery, morphine consumption began earlier in the saline group than in the 2 μg/kg and 5 μg/kg morphine groups. The time to first PCA demand was dose-dependently delayed by intrathecal morphine administration (P = 0.0009; see fig. 2). The point estimates for the 50th percentile of postextubation analgesic duration were 0.2 ± 0.1, 4.0 ± 1.3, and 9.0 ± 4.6 h in the saline,
2 μg/kg morphine, and 5 μg/kg morphine groups. PCA morphine consumption increased linearly over time in the three groups (fig. 3). As a consequence, cumulative postoperative morphine consumption differed significantly between groups \((P < 0.0001)\). The number of demands was also significantly different between groups \((67 \pm 24, 26 \pm 15, \text{ and } 20 \pm 17 \text{ in the saline, morphine } 2 \mu g/kg, \text{ and } 5 \mu g/kg \text{ groups, respectively})\). Yet the demand-to-bolus ratio was not significantly different \((0.60 \pm 0.23, 0.62 \pm 0.22, \text{ and } 0.71 \pm 0.16 \text{ in the saline, morphine } 2 \mu g/kg, \text{ and } 5 \mu g/kg \text{ groups, respectively})\).

Median pain scores at rest were in the 0–20-mm range during the first 24 h in the 2 and 5 μg/kg morphine groups (fig. 4). These values were significantly lower compared with the saline group at 2, 4, and 14 h after surgery \((P = 0.0003, 0.01, \text{ and } 0.03, \text{ respectively})\). In contrast, although there was a trend to lower scores for the first 6 h in the 5 μg/kg morphine group, pain scores while coughing were not significantly different between groups.

The cumulative number of adverse events (number of events recorded at 1-h sampling interval) in each group is presented in table 2. Except for the previously mentioned patient (who did not receive intrathecal morphine), respiratory adverse events requiring intervention were not encountered in this series of patients. End-tidal carbon dioxide partial pressure in excess of 55 mmHg, which can be considered as an index of mild respiratory depression, were observed six times in two patients who received saline, 10 times in four patients who received 2 μg/kg morphine and five times in two patients who received 5 μg/kg morphine. Recordings of respiratory rate fewer than 12 breaths/min were made 20 times in the saline group, 18 times in the 2 μg/kg morphine group, and 18 times in the 5 μg/kg group morphine, without any other symptom of opioid overdose. Nausea, vomiting, and pruritus also occurred with a similar frequency in the three groups. The need for treatment intervention was seldom experienced. Ondansetron was administered to two patients, metoclopramide to two patients, and nalbuphine to one patient.

Discussion

In this study, intrathecal morphine in doses of 2 and 5 μg/kg provided potent analgesia in the first 24 h after spinal fusion in children, as evidenced by low pain scores and low additional PCA morphine consumption. Several studies have already outlined the interest of intrathecal morphine for postoperative analgesia after spinal surgery\(^{11-15}\) or other major surgical procedures\(^{14,15}\) in children. Jones \textit{et al.}\(^{14}\) assessed the analgesic effect and complications of intrathecal morphine 20 and 30 μg/kg after open heart surgery. Although a long-lasting analgesia was observed (more than 22 h in 60% of the patients), nine of the 56 patients experienced significant respiratory depression requiring naloxone. In an-
other pioneer study, Dalens and Tanguy\textsuperscript{11} reported the successful management of postoperative pain with intrathecal morphine 25 $\mu$g/kg in a series of 20 cognitively impaired children who were scheduled for spinal fusion. More recently, Goodarzi\textsuperscript{13} has provided evidence that an intrathecal mixture of morphine and sufentanil (20 and 1 $\mu$g/kg, respectively) is superior to systemic opioids in an open study including 80 children operated on for idiopathic scoliosis. All these pediatric studies have considered doses of intrathecal morphine in excess of 20 $\mu$g/kg. It is now widely acknowledged that such high doses should be avoided because of their potential to induce unbearable side effects. Large surveys of pain occurring after cesarean section have led to the recommendation of a maximal dose of 0.2 mg in this setting.\textsuperscript{4,5,7} In other surgical procedures, doses between 0.3 mg (lower limb surgery) and 0.8 mg (thoracotomy) have been recommended and applied on large populations of patients with a low incidence of side effects.\textsuperscript{16} The effects of such low doses have not been assessed in the context of spinal surgery, nor in children.

The major finding of the present study is that intrathecal morphine in doses of 2 or 5 $\mu$g/kg, supplemented by PCA morphine, provided better analgesia than PCA morphine alone in the first 24 h after scoliosis surgery. We deliberately choose to combine spinal and systemic opioids administration because, in the context of major spinal surgery, severe pain is expected to last more than 4 or 5 days, and there is no way to cover the entire period with a single-shot intrathecal injection. There is ample experimental evidence that intrathecal and systemic opioids act synergistically\textsuperscript{17} (see also Yaksh\textsuperscript{18} for review). Such interactions are so potent that, in the past, clinicians have advocated against their intentional use.\textsuperscript{19} The present study provides evidence that it is possible to take advantage of the synergy between spinal and systemic opioids under close monitoring in PACU. Indeed, the fact that PCA morphine was made available immediately in the postoperative period allowed for a smooth transi-
In this study, the doses of 2 and 5 μg/kg seemed to offer the same quality of analgesia and the same side-effect profile. This result is not surprising when compared with the results of dose-finding studies conducted in adults. For pain occurring after cesarean section, it was recently suggested that doses as low as 0.075 mg may be as effective as 0.2 mg.8 In this study, pairwise comparisons revealed no significant differences between eight doses in the 0.025–0.5-mg range. Only a model of linear regression from a threshold value revealed the dose–effect relation. In the context of total hip or knee replacement, doses of intrathecal morphine of 0.1 or 0.3 mg seem to represent the best compromise between analgesic effectiveness and incidence of side effects.9,10

For analgesia after spinal surgery without instrumentation, doses of 0.25 and 0.5 mg, but not 0.125 mg, were found to provide better quality of analgesia compared with controls.20 Thus, available evidence suggests that beyond a threshold, the dose of intrathecal morphine affects more the duration than the quality of analgesia per se. It should be mentioned that our study failed to demonstrate the superiority of intrathecal morphine over parenteral morphine to relieve pain evoked by cough. This finding is in agreement with several experimental evidences that suggest that neuraxial opioids may have differential effects on different pain qualities. Such a view is further supported by the results of studies that have assessed the effect of neuraxial opioids administered by the epidural route on dynamically evoked pain.2,21,22 Although some studies have reported that large dose of intrathecal morphine can provide significant pain relief during mobilization,11,23 we believe that the administration of local anesthetics in addition to opioids remains the only way to gain strong analgesia on cough or movement.

The lower intraoperative bleeding in children who received the dose of 5 μg/kg intrathecal morphine compared with the two other groups is an unexpected finding. Perioperative blood loss was not considered as a main outcome variable in the design of the study. Data were only recorded to provide information about treatment group comparability. The blood pressure data show that children in this group tended to have lower values of mean arterial pressure at the second hour during surgery, but the difference did not reach statistical significance. Although non statistically significant either, there was a tendency for lower sufentanil and propofol requirements in children of this group to achieve similar level of hypotension, the latter being in fact defined by the lowest value compatible with somatosensory-evoked potential recording rather than by an absolute value. Although the physiologic mechanisms by which intrathecal opioid may induce hypotension are unclear, the present finding of decreased intraoperative blood loss associated with intrathecal morphine is in agreement with several clinical reports.11,13 Dalens and Tanguy11 reported decreased intraoperative blood pressure and blood loss in children treated with 25 μg/kg intrathecal morphine compared with that encountered in their usual practice. In the study of Goodarzi,13 children of the intrathecal morphine group experienced blood loss of 27 ± 43% of their blood volume versus 53 ± 43% in children of the control group who received “normotensive standard anesthesia technique.” In the present study, the finding of lower intraoperative blood loss in the 5 μg/kg group is an argument in favor of the dose of 5 μg/kg over the dose of 2 μg/kg, but the relation between blood loss and intrathecal morphine requires further investigations.

In conclusion, intrathecal morphine in low doses provides analgesia of better quality than PCA morphine after spinal fusion in children. The present data suggest that the dose of 5 μg/kg may be a better choice than 2 μg/kg, because it is associated with a reduction of intraoperative bleeding, even though the benefits in terms of quality of analgesia are not patent. In this dose range, the median duration of analgesia is 9.0 ± 4.6 h. This is less than the 24-h interval that is required for close neurologic monitoring. Thus, the critical time of overlap between intrathecal and parenteral morphine can be safely monitored in the PACU without delaying the return of patients to the surgical ward.

Table 2. Postoperative Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Saline</th>
<th>2 μg/kg Morphine</th>
<th>5 μg/kg Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal carbon dioxide &gt; 55 mmHg</td>
<td>6</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory rate &lt; 12 breaths/min</td>
<td>20</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Sedation score &gt; 2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Values are total number of events recorded in each group, at 1-h sampling interval over the 18-h observation period (minimum, 0; maximum, 18 × 10 − 180). There are no statistically significant differences between groups.

The authors thank Liliane Boudet, M.D., Hélène Goldenberg, M.D., Marie-Paule Scemama, M.D., and Sylvie Schrayer, M.D., Staff Anesthesiologists, Service

Anesthesiology, V 94, No 3, Mar 2001
d’Anesthésie-Réanimation, Centre Hospitalier Universitaire Armand Trousseau—
for, Paris, France, for their contributions.

References

1. Joshi GP, McCarroll SM, O’Rourke K: Postoperative analgesia after lumbar
laminectomy: Epidural fentanyl infusion versus patient-controlled intravenous
Postoperative pain control after lumbar spine fusion. Patient-controlled analgesia
control following spinal surgery: Paucity of evidence and need for studies.
P, Makar A, Moore J, Davis H, Lee J: Mini-dose intrathecal morphine for the relief
of post cesarean section pain: Safety, efficacy, and ventilatory response to carbon
5. Milner AR, Bogod DG, Harwood RJ: Intrathecal administration of morphine
for elective Caesarean section. A comparison between 0.1 mg and 0.2 mg.
Anaesthesia 1996; 51:871–3
6. Bailey PL, Rhondeau S, Schafer PG, Lu JK, Timmins BS, Foster W, Pace NL,
Stanley TIE: Dose-response pharmacology of intrathecal morphine in human
volunteers. ANESTHESIOLOGY 1993; 79:49–59
7. Minzer AR, Bogod DG, Harwood RJ: Intrathecal morphine for elective Caesarean
section: A comparison between 0.1 mg and 0.2 mg. Anaesthesia 1996; 51:871–3
8. Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose response relation-
ship of intrathecal morphine for postoperative analgesia. ANESTHESIOLOGY 1999;
90:457–44
tion of the dose of intrathecal morphine in total hip surgery: A dose-finding study.
Anesth Analg 1999; 88:822–6
10. Cole P, Czaske DA, Wheatley RG: Efficacy and respiratory effects of low-
dose spinal morphine for postoperative analgesia following knee arthro-
Spine 1998; 13:494–8
12. Kreckel SW, Helikson MA, Kittle D, Eggers GW Jr: Intrathecal morphine
(STM) for postoperative pain control in children: A comparison with nalbuphine
13. Goodarzi M: The advantages of intrathecal opioids for spinal fusion in
children. Paediatr Anaesth 1998; 8:131–4
14. Jones SEF, Beasley JM, Macfarlane DWR, Davis JM, Hall-Davies G: Intrathe-
56:137–40
15. Tobias JD, Deshpande JK, Wetzel RC, Facker J, Maxwell LG, Solca M:
Phila 1990; 29:44–8
16. Gwirtz KH, Young NY, Byers ES, Alley C, Levin K, Walker SG, Stoelting RK:
The safety and efficacy of intrathecal opioid analgesia for acute postoperative
pain: Seven years’ experience with 5969 surgical patients at Indiana University
17. Yeung J, Rudy TA: Multiplicative interaction between narcotic agonisms
expressed at spinal and supraspinal sites of antinociceptive action as revealed by
concurrent intrathecal and intracerebroventricular injections of morphine.
J Pharmacol Exp Ther 1980; 215:633–42
18. Yaksh TL: Pharmacology and mechanisms of opioid analgesic activity,
Anesthesia. Biologic Foundations. Edited by Yaksh TL, Lynch CL, Zapol WM,
921–35
LM: Development of an anesthesiology-based postoperative pain management
service. ANESTHESIOLOGY 1988; 68:100–6
20. Ross DA, Drasner K, Weinstein PR, Flaherty JF, Barbaro NM: Use of
intrathecally administered morphine in the treatment of postoperative pain after
lumbar spinal surgery: A prospective, double-blind, placebo-controlled study.
Neurosurgery 1991; 28:700–4
analgetic effects of low-dose epidural morphine and morphine-bupivacaine at
rest and during mobilization after major abdominal surgery. Anesth Analg 1992;
75:362–5
morphine for postoperative pain relief following lumbar spine surgery. J Neuro-
surg 1985; 63:413–6

Anesthesiology, V 94, No 3, Mar 2001