Effects of a loading dose of morphine before i.v. morphine titration for postoperative pain relief: a randomized, double-blind, placebo-control study

F. Aubrun1 *, J. Amour1, D. Rosenthal1, P. Coriat1 and B. Riou2

1Department of Anaesthesiology and Critical Care and 2Department of Emergency Medicine and Surgery, Centre hospitalo-universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris 6, Paris, France
*Corresponding author: Département d’Anesthésie-Réanimation, CHU Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75651 Paris Cedex 13, France. E-mail: frederic.aubrun@psl.ap-hop-paris.fr

Background. I.V. morphine titration (MT) allows adjustment of the dose needed for pain relief in the post-anaesthesia care unit (PACU). However, MT has limitations such as a delay to achieve pain relief. We thus assessed the effect of a fixed intraoperative loading dose of morphine administered before titration.

Methods. One hundred patients who were undergoing major orthopaedic surgery were included in a double-blind, randomized study comparing a loading dose of morphine (0.15 mg kg\(^{-1}\)) with placebo administered intraoperatively. MT was then administered in the PACU followed by patient-controlled analgesia (PCA) over 24 h. Data are expressed as mean (SD).

Results. The initial VAS (41 (36) vs 52 (35), NS) was not decreased in the morphine group. The VAS was lower in the morphine group in the PACU and PCA periods. The time to achieve effective pain relief was not decreased in the morphine group. The total dose of morphine administered in the PACU (including the loading dose) was significantly increased in the morphine group (+31% in mg kg\(^{-1}\), P<0.05). Morphine requirements during the PCA period were not different between groups. The incidence of sedation was increased and a severe episode of ventilatory depression occurred in the morphine group.

Conclusions. A loading dose of morphine administered at the end of surgery slightly decreased the VAS but did not reduce the time to pain relief or morphine consumption within the first 24 h. This slight improvement in analgesia was obtained at the expense of morphine-related adverse events.

Keywords: loading-dose, morphine titration; PACU; surgery, orthopaedic

Introduction
I.V. administration of opioids is usually recommended for acute pain relief in the immediate postoperative period\(^1\) and use of small i.v. boluses of morphine in the post-anaesthesia care unit (PACU) allows a rapid titration of the dose needed for adequate pain relief.\(^2\) \(^3\) \(^4\) However, i.v. morphine titration (MT) has a number of limitations.\(^4\) \(^6\) First, the mean value of the initial visual analogue pain score (VAS) in the PACU, before MT, is often high, above 70,\(^4\) \(^7\) which indicates severe pain.\(^3\) Second, complete pain relief may take a long time. Despite a short time interval between boluses during titration (5 min), the mean time to achieve complete pain relief is 15 min (range: 5–60 min).\(^4\) Third, during the pain relief process, the global relationship between VAS score and time appears to be not linear but sigmoid.\(^7\) Thus, during MT, the VAS score does not markedly change until the morphine dose approaches that dose ultimately needed to obtain pain relief. Lastly, the technique is time-consuming for the nurses.\(^7\)

Morphine has a slower onset of action than lipid soluble opioids and thus may require a loading dose to initiate an effect. With remifentanil-based anaesthesia, the rapid offset of remifentanil means that active postoperative pain management with i.v. 0.15 mg kg\(^{-1}\) morphine must
be achieved after major surgery before arrival in the PACU. However, very few authors have described or assessed the administration of a perioperative loading dose of morphine with a standard anaesthetic procedure including a long-acting opioid.

Therefore, the goal of our study was to test the hypothesis that a loading dose of morphine administered in the operating room before the end of surgery is associated (i) with a significant reduction in the time to achieve complete pain relief in the PACU, (ii) with a reduction in the dose required to alleviate immediate postoperative pain, thus achieving lower pain scores and better postoperative analgesia without an increase in morphine-related adverse effects.

Methods

This randomized, double-blind, placebo-controlled study was conducted between December 2003 and March 2005. The study protocol was approved by our institutional review board (Comité de Protection des Personnes se Prêtant à la Recherche Biomédicale Pitie-Salpétrière, Paris, France) and the trial was conducted according to standards of good clinical practice and the Helsinki Declaration. Written informed consent was obtained from all patients.

Patients

Patients aged 18–70 yr, American Society of Anesthesiology status I–II, weighing between 50 and 100 kg and undergoing elective major orthopaedic surgery (with expected moderate to severe postoperative pain) were included in the study. Exclusion criteria were preoperative administration of morphine, allergy or contraindication to morphine (respiratory insufficiency, drug addiction), renal (serum creatinine >120 μmol litre⁻¹) or hepatic insufficiency (transaminases and/or alkaline phosphatases >3 times of upper normal value, and/or prothrombin time <60% of control), scheduled regional anaesthesia, age <18 or >70 yr, emergency surgery, pregnancy and breast-feeding. Patients with delirium or dementia, who did not understand the pain scales, or who were not French speaking were also excluded.

Study protocol

Patients were premedicated the day before and 1 h before surgery with hydroxyzine (50 or 100 mg). Anaesthesia was induced with propofol (2.5 mg kg⁻¹). Tracheal intubation was performed after muscle relaxation had been achieved with atracurium (0.5 mg kg⁻¹). Anaesthesia was maintained with i.v. boluses of sufentanil and isoflurane administered with oxygen and 50% nitrous oxide. Immediately before the end of surgery, a bolus of morphine (0.15 mg kg⁻¹) or the same volume of saline was i.v. administered in the morphine and placebo groups, respectively. Thirty minutes before the end of the operation, 50 mg of ketoprofen (Profenid, Laboratoire Sanofi-Aventis, Paris, France) were administered i.v. After satisfactory spontaneous ventilation and awakening, the trachea was extubated, and the patient was transferred to the PACU.

Postoperative pain management

During the preoperative visit, the visual analogue scale (VAS) (0–100, hand-held slide-rule type) was shown to the patients and their preoperative pain recorded.

All nurses in the PACU had been trained to assess pain using specific scales and to perform MT. They used the VAS, and a special form for data collection. When patients had difficulties in manipulating the VAS, nurses were allowed to use a numerical rating scale (from 0 to 100), as these two methods are equivalent.

A strict protocol has been implemented in our PACU after a previous study which determined the optimal regimen of MT. This protocol defined the dose of i.v. boluses of morphine, the interval between boluses, the VAS threshold required to administer morphine and the criteria to stop titration. After arrival of patients in the PACU, they were questioned, after tracheal extubation and the return of full consciousness, about the presence of pain (at least every 15 min before the onset of MT) and asked to rate pain intensity on a VAS scale. When the VAS was greater than 30, i.v. morphine was titrated every 5 min by 3 mg increments (2 mg in patients weighing ≤60 kg) and pain was assessed every 5 min until pain relief, defined as a VAS=0. When the patient was asleep, no attempt was made at arousal. In this situation the patient was considered as having adequate pain relief and was assigned a score of 0. When pain was too severe to obtain a VAS (patient refusal), it was scored 100. Clinical monitoring included ventilatory frequency measurements, pulse oximetry (SpO₂), sedation according to the Ramsay score, arterial blood pressure and heart rate. MT was stopped if the patient had a ventilatory frequency lower than 12 bpm or a SpO₂ lower than 95% or both, and/or experienced a serious adverse event related to morphine administration (allergy with cutaneous rash or hypotension or both, vomiting, severe pruritus). In the case of severe ventilatory depression (ventilatory frequency <10 bpm), naloxone (i.v. bolus of 0.04 mg) was administered until the ventilatory frequency was greater than 12 min⁻¹. As previously reported, severe postoperative pain was defined as an initial VAS=70.

Immediately after MT, patients were provided with a patient-controlled analgesia (PCA) morphine pump (9300 pump, Sims-Graceby, Vitry-sur-Seine, France) over 24 h. Patients received morphine 1 mg ml⁻¹, with a 1 ml bolus, 7 min lockout interval, and no limitation in the dose delivered per hour. Heart rate, arterial blood pressure, ventilatory frequency, sedation, VAS pain scores, the total administered dose of morphine and number of demands per patient were evaluated every hour during the first 4 h and then every 4 h until 24 h. Sedation was assessed using the Ramsay sedation scale.
At the end of the study, patients were asked to rank their global satisfaction considering pain management using a satisfaction VAS (0: absolutely not satisfied; 100: perfectly satisfied).

**Adverse effects**

The occurrence of the following adverse effects was recorded during the PACU and PCA periods: nausea and vomiting, respiratory depression (ventilatory frequency lower than 12 bpm or $\text{SpO}_2$ lower than 95% or both with 3 litre min$^{-1}$ oxygen), urinary retention requiring urine drainage, itching and sedation (Ramsay scale 2). Nausea, vomiting, pruritus, urinary retention and respiratory depression were considered as morphine-related adverse effects. Sedation was not considered as a morphine-related adverse event, as previously reported.4–7

**Randomization and blinding**

Randomization was performed using a random number table and was equilibrated every 10 patients. Opaque sealed envelopes of randomization were opened by a nurse not involved in the care of the patient just before the end of anaesthesia. This nurse prepared the solution of morphine or placebo (saline) in a separate room and provided the blinded solution to the anesthesiologist who attended the patients.

**End points**

The main end point was the time to achieve pain relief in the PACU. The secondary efficacy end-points were the number of patients with postoperative severe pain, the number of patients who required MT, the duration of stay in the PACU period, the consumption of morphine during the PACU and PCA periods, the number of demands for morphine and the number of boluses received during the PCA period, the total dose administered over 24 h, the VAS during the PACU and PCA periods, the consumption of morphine during the PACU and PCA periods, the number of patients who required MT, the duration of stay in the PACU period, the incidence of patients with postoperative severe pain, the number of patients with severe pain, the number of patients with severe pain, and the duration of surgery.

<table>
<thead>
<tr>
<th>Placebo group (n=50)</th>
<th>Morphine group (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Men</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Women</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 (13)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 (10)</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>24.2 (3.5)</td>
</tr>
<tr>
<td>BMI &gt;30 kg m$^{-2}$</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>II</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Preoperative VAS</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Preoperative analgesic</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Preoperative NSAID</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Spine surgery</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Premedication</td>
<td>48 (94%)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>115 (100–130)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>190 (180–200)</td>
</tr>
<tr>
<td>Propofol dose (mg)</td>
<td>199 (49)</td>
</tr>
<tr>
<td>Sufentanil dose (µg)</td>
<td>44 (13)</td>
</tr>
</tbody>
</table>

and the Fisher’s exact method was used to compare two proportions. All comparisons were two-tailed and a $P$-value of <0.05 was required to rule out the null hypothesis. Statistical analysis was performed using a computer and NCSS 2004 software (Statistical Solutions Ltd).

**Results**

A total of 100 patients consented to participate and were randomly assigned to one of the two study groups. No patient dropped out and thus, 100 patients were included for analysis, 50 in the morphine group and 50 in the placebo group. The groups were well balanced with regard to patient characteristics, ASA status, preoperative pain and analgesics administered type of surgery, anaesthetic doses, and durations of anaesthesia and surgery (Table 1). There were no significant differences between groups in the time between induction and administration of morphine/placebo [142 (47) vs 143 (49) min, NS] and time between administration of morphine/placebo and tracheal extubation [59 (26) vs 63 (45) min, NS].

The initial pain VAS (defined as the VAS before MT) [41 (36) vs 52 (35), NS] and the number of patients with severe pain (30% vs 42%, NS) were not significantly decreased in the morphine group. Nevertheless, the VAS was significantly lower in the morphine group in the PACU period (Fig. 1A). The time to obtain pain relief was not significantly decreased in the morphine group [16 (19) vs 22 (20) min, NS].
Although there was a non-significant trend towards a decrease in the number of patients requiring titration and a significant decrease in the dose of morphine required during titration in the morphine group, the total dose of morphine administered during the PACU period (including the loading dose) was significantly increased in the morphine group (+64% in mg and +31% in mg kg$^{-1}$) (Table 2). There was no significant difference among groups in the duration of stay in the PACU [150 (95% CI 135–180) min in the morphine group vs 160 (95% CI 140–180) min in the placebo group, NS]. Morphine requirements during the PCA period and the total dose of morphine administered within the first 24 h were not significantly different between groups (Table 2), but the VAS was lower in the morphine group (Fig. 1B). The number of requests [32 (95% CI 7–41) vs 21 (95% CI 13–29), NS] and the number of boluses administered [22 (95% CI 13–29) vs 21 (95% CI 13–29), NS] during PCA were not significantly different in the two groups.

Although there was a non-significant trend towards an increase in urinary retention, the incidence of morphine-related adverse effects were not significantly different between groups during the PACU and the PCA periods (Table 3). Nevertheless, a severe ventilatory depression (ventilatory frequency <10 bpm, and level 4 of the Ramsay score) occurred in one patient from the morphine group requiring ventilation and naloxone administration. The incidence of sedation was significantly increased in the morphine group in the PACU (Table 3). Patients’ satisfaction (using VAS 0–100) was not different in both groups [77 (26) mm in morphine group vs 73 (27) mm in placebo group, NS].

**Discussion**

In the present study, we observed that intraoperative morphine loading (0.15 mg kg$^{-1}$) slightly decreased the postoperative pain scales but did not significantly reduce the time to achieve pain relief in the PACU or the morphine consumption over 24 h. However, intraoperative morphine loading resulted in an increase in the incidence of morphine-related adverse effects.
I.V. MT is an efficient technique to obtain pain relief in most patients in the postoperative period. However, some problems persist. Some of these problems are linked to the technique of titration itself. The initial VAS scores are often high and there is a delay between the arrival into the PACU and the start of MT.\(^4\ ^7\ ^7\ ^17\) Even if the mean dose for pain relief is about 10 mg,\(^4\ ^7\ ^7\ ^17\ ^18\) it has been demonstrated that some patients need more than 5 or 10 boluses, thus taking a long time to achieve pain relief.\(^4\ ^7\ ^7\ ^17\ ^18\) Lastly, the VAS remains high during the titration procedure until the last bolus, as previously demonstrated.\(^7\) Other problems are linked to morphine and its adverse effects and the goal of many studies has been to investigate the use of non-opioid analgesics to reduce the dose of morphine and thus the incidence of morphine-induced adverse effects. Some drugs such as ketamine or nefopam reduce the dose of morphine titrated and the risk of morphine analgesia failure, but may also induce adverse effects.\(^19\) Perioperative acetaminophen does not always reduce the dose of morphine given in the PACU and the incidence of morphine-related adverse effects.\(^20\ ^22\) Provision of analgesia using non-opioid drugs, together with a long-acting opioid is a valuable technique for improving analgesia in the PACU, and may enable a reduction in the dose of titrated morphine. An effective transition for the immediate postoperative management of postoperative pain in patients undergoing moderate to severe predictable pain may be the administration of a fixed dose of morphine 20–30 min before the end of surgery performed with remifentanil.\(^8\ ^9\ ^22\ ^23\)

Very few studies have assessed the benefit of a loading dose of morphine in the intraoperative period while using sufentanil as an opioid during the surgical procedure. In a randomized study, Pico and colleagues\(^24\) evaluated the effects of perioperative administration of titrated morphine on the quality of postoperative pain control. During skin closure while patients were spontaneously breathing via the orotracheal tube, one group received morphine boluses of 3 mg every 5 or 10 min. The titration was continued until the ventilatory frequency decreased with a lowest ventilatory frequency of 12 bpm. This group of patients was compared with a control group without perioperative MT. In this study, perioperative administration of morphine reduced the time needed to achieve adequate postoperative analgesia.\(^24\) The titrated dose of morphine was comparable with the fixed dose of morphine (0.15 mg kg\(^{-1}\)) used in our study [10.3 (1.3) mg vs 10.4 (2.0) mg, NS]. In contrast, the morphine dose administered in the PACU was significantly reduced (7.25 vs 15.4 mg, \(P<0.001\)) in the study from Pico and colleagues,\(^24\) whereas the administration of a loading dose of morphine at the end of surgical procedure resulted in an increase in the cumulative dose of titrated morphine in the PACU and over the first 24 h in our study.\(^24\) What are the possible explanations of these results? First, a dose of 0.15 mg kg\(^{-1}\) of morphine administered during surgery may have been too high for some patients with moderate pain, even if this dose did not delay the extubation time. Second, while both groups received a comparable perioperative dose of sufentanil, the loading dose of morphine may have enhanced subsequent hyperalgesia and tolerance. Rapid development of acute opioid tolerance is well established in animals and humans after various opioids.\(^25\ ^26\ ^27\) Even if most studies about the concept of abnormal pain sensitivity concern remifentanil or short-acting synthetic narcotics such as fentanyl or alfentanil, we can argue that morphine can induce hyperalgesia even after a single shot.\(^28\ ^30\) Our study was concerned only with implications for postoperative pain management during the immediate postoperative period with a higher dose of i.v. morphine required for acute pain relief, and did not consider subacute pain management. It is worth noting that the PCA dose and the total dose of morphine over 24 h were not significantly different between the two groups.

Previous studies have demonstrated that perioperative administration of a 0.1 mg kg\(^{-1}\) morphine bolus did not modify the awakening concentration of isoflurane or sevoflurane.\(^31\ ^32\) Also, no significant delay in extubation has been observed in these studies. We confirmed these findings, although the dose administered (0.15 mg kg\(^{-1}\)) was greater than the doses used in previous studies. The time between administration of morphine/placebo and tracheal extubation were not significantly different between the two groups.

Pico and colleagues\(^24\) have suggested that administration of perioperative morphine could reduce the incidence of severe morphine-related adverse effects but the present study could not confirm this. The incidence of morphine-related adverse effects were not significantly different between groups during the PACU and the PCA periods except one patient of severe respiratory depression occurring during the PCA period in the morphine group. Nevertheless, the power of our study is limited by the relatively small sample size for the study of postoperative adverse effects. However, the higher morphine dose used in the PACU in the morphine group could explain the higher incidence of sedation in the PACU. In a previous study, we observed dissociated effects of morphine on the course of sedation and analgesia with sedation occurring first, followed by analgesia.\(^33\) Sedation cannot be arbitrarily attributed to the occurrence of an adequate level of analgesia. Among patients in whom MT was discontinued because of sedation, 25% still exhibited a level of VAS above 50.\(^33\) Moreover, sedation has been shown to be associated with the frequent need of rescue analgesia after (and despite) i.v. MT.\(^14\) In the same way, Dahan and colleagues\(^34\) studied the influence of i.v. morphine on breathing and analgesia in healthy volunteers. These authors demonstrated that, despite the lack of efficient analgesia, moderate to severe respiratory depression remains possible.\(^34\) These results strengthen our view that MT should be stopped as soon as the patient is asleep as this situation may be also considered as a predictor of respiratory depression.
Some remarks must be included concerning the limitations of our study. First, the use of VAS assumes that pain is a unidimensional experience. Although intensity is a very important dimension of pain, it is clear that pain refers to a variety of sensations that cannot be categorized under a single linguistic label which varies only in intensity. Nevertheless, it should be pointed out that VAS has been widely accepted because of its ease of administration, its minimal intrusiveness and its conceptual simplicity. Second, we did not specifically assess the effect of a loading dose of morphine after major surgery with very severe predictable postoperative pain. However, postoperative pain is such a subjective phenomenon that we cannot precisely predict postoperative morphine consumption even after very painful surgery. Third, the power of our study was not sufficient to detect an increase in morphine-related adverse events. Nevertheless, the unfavourable trends we observed in our study concerning the usual adverse events together with the rarest but also most severe of the adverse effects, strongly suggest that the concept of a loading dose of morphine before titration may be dangerous. Moreover, the significant increase in sedation may be considered as a danger signal. Our study highly suggests that any new proposed protocol including a loading dose must be able to demonstrate primarily its safety concerning morphine-related adverse effects. Fourth, our patients received NSAIDs that are known to decrease significantly morphine-related adverse effects. Thus, our results may not apply to patients treated with opioids only. Fifth, the type of surgery was heterogeneous and we cannot rule out the possible role of other variables that could have affected the outcome, although the study was randomized. Sixth, the initial VAS was not very high in our study and thus the postoperative pain should not be considered as severe. Lastly, our study was performed in the perioperative setting and thus our results may not apply to other clinical conditions such as emergency medicine. Nevertheless, in emergency conditions, concerns about safety are uppermost because of the difficulties in monitoring patients in the PACU.

In conclusion, although a loading dose before i.v. MT slightly decreased the postoperative pain scores, we did not observe any significant reduction in the time to pain relief in the PACU and in morphine consumption over the postoperative period. Moreover, this slight improvement in analgesia was obtained at the expense of morphine-related adverse events, leading to concerns about safety.

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