Pre-treatment with morphine does not prevent the development of remifentanil-induced hyperalgesia

**Purpose:** Remifentanil, an ultra short-acting opioid commonly used to supplement general anesthesia, is associated with the development of hyperalgesia that manifests clinically as an increase in postoperative analgesic requirement. This study involving adolescents undergoing scoliosis surgery evaluated whether pre-treatment with morphine prior to commencing remifentanil infusion would decrease the initial 24-hr morphine consumption and pain scores.

**Methods:** Forty ASA I–II pediatric patients undergoing surgical correction of idiopathic scoliosis were recruited in a prospective, randomized, double-blind fashion to receive 150 μg·kg⁻¹ morphine or an equal volume saline prior to commencing remifentanil by infusion. The primary outcome was the initial 24-hr postoperative morphine consumption. Numeric rating scale (NRS) pain scores at rest and on coughing were recorded, as were scores for nausea, vomiting, and sedation and incidences of pruritus.

**Results:** The groups were demographically similar. No differences were observed between groups vis-à-vis the initial 24-hr morphine consumption, NRS pain scores, sedation, nausea, or vomiting.

**Conclusion:** Pre-treatment with 150 μg·kg⁻¹ morphine did not decrease the initial 24-hr morphine consumption in adolescents who received remifentanil by infusion for surgical correction of idiopathic scoliosis.

**Objectif:** Le remifentanil est un opioïde à action extra-courte couramment utilisé comme adjuvant à une anesthésie générale. Il est associé à l’apparition d’hyperalgésie, laquelle prend la forme clinique d’une augmentation des besoins analgésiques postopératoires. Cette étude portait sur des adolescents subissant une chirurgie de correction de scoliose. Son objectif était de déterminer si un prétraitement à la morphine avant la perfusion de remifentanil diminuerait la consommation de morphine et l’intensité de la douleur dans les 24 premières heures suivant l’opération.

**Méthode:** Quarante adolescents ASA I–II subissant une chirurgie corrective pour une scoliose idiopathique ont été recrutés de façon prospective, randomisée et à double insu, à recevoir de la morphine 150 μg·kg⁻¹ ou un volume équivalent de sérum physiologique avant le début d’une perfusion de remifentanil. La consommation de morphine durant les 24 premières heures postopératoires était l’objectif primaire. Les scores de douleur sur l’échelle d’évaluation numérique (EEN) au repos et en toussant ont été notés, de même que les scores concernant les nausées, les vomissements, la séduction et l’apparition de prurit.

**Résultats:** Les groupes étaient semblables d’un point de vue démographique. Aucune différence n’a été observée entre les groupes quant à la consommation de morphine des 24 premières heures, les scores de douleur EEN, la séduction, les nausées ou les vomissements.

**Conclusion:** Le prétraitement avec 150 μg·kg⁻¹ de morphine n’a pas diminué la consommation de morphine durant les 24 premières heures postopératoires chez des adolescents recevant une perfusion de remifentanil pour une chirurgie corrective d’une scoliose idiopathique.
The challenges of major scoliosis surgery include the need to provide profound intraoperative analgesia while simultaneously facilitating neurophysiological monitoring of spinal cord motor-evoked potentials.\(^1\) Intraoperative infusion of the ultra short-acting synthetic \(\mu\)-opioid agonist, remifentanil,\(^2\) allows the anesthesiologist to meet these challenges. Hyperalgesia and/or acute tolerance, manifesting clinically as increased postoperative analgesic requirements, can develop rapidly when potent opioids such as remifentanil are delivered by infusion.\(^3\) After infusion of high-dose remifentanil for surgical procedures such as scoliosis repair that comprise long operative times and extensive surgical trauma, clinically significant hyperalgesia develops. One trial demonstrated that the initial 24-hr postoperative morphine consumption increased by 30% in adolescents who had received remifentanil by infusion for scoliosis repair compared with those who received intermittent morphine alone.\(^3\) Various strategies to attenuate the development of remifentanil-induced hyperalgesia have been studied.\(^4^\)-\(^1^0\) The majority of these studies have focused on the role of the N-methyl-D-aspartic acid antagonist, ketamine, and have failed to demonstrate a reduction in postoperative pain or analgesic consumption.

A combination of opioid agonists or opioid rotation has demonstrated some success in decreasing or preventing opioid-induced hyperalgesia.\(^1^1\) Theoretically, the use of a pure opioid agonist with different receptor binding characteristics and a longer duration of action than remifentanil may be beneficial when trying to prevent opioid-induced hyperalgesia. It has previously been postulated that administering a longer-lasting opioid such as morphine, before commencing remifentanil infusion, might attenuate the development of hyperalgesia.\(^2^1^0\) It is a common but untested clinical practice to administer morphine by bolus prior to initiating remifentanil by infusion. However, in the absence of published data on pre-treatment with morphine, no statement can be made as to the clinical efficacy of this practice in this setting.

We hypothesized that remifentanil-induced hyperalgesia may be attenuated by the administration of morphine prior to initiation of remifentanil by infusion. To test this hypothesis, we evaluated the initial 24-hr morphine consumption and pain scores in adolescents who received either a bolus of intravenous morphine or a placebo before initiation of remifentanil by infusion for scoliosis surgery.

**Methods**

With approval by the Research Ethics Board at the Hospital for Sick Children, Toronto, 40 unpremedicated ASA physical status I-II children aged 11–18 yr, scheduled to undergo posterior instrumentation for correction of idiopathic scoliosis during the period from December 2006 to December 2007, were recruited to this prospective, randomized, double-blind study. The study was registered in a public registry (clinicaltrials.gov, NCT00737997) prior to commencing recruitment. Written consent was obtained from parents, guardians, or the adolescents themselves, as was verbal assent from the children, as appropriate. Exclusion criteria comprised opioid use within three months before surgery, the inability to self-administer morphine using a patient-controlled analgesia (PCA) device, elective postoperative ventilation, obesity (>130% of ideal body weight), known sensitivity to any study medication, and refusal to participate.

Using a table of random numbers, patients were randomly assigned to either a morphine group or a control group. Group assignments were kept in sealed, opaque, sequentially numbered envelopes that were opened after gaining consent and assent. At this point, an unblinded anesthesiologist who was not involved in the study opened the envelopes and prepared the study medication. Preoperatively, a medical history and physical examination were performed and the patients were instructed in the use of a PCA device and a numeric rating scale (NRS) for assessment of postoperative pain intensity (0 = no pain and 10 = worst pain imaginable).

On arrival to the operating room, standard intraoperative monitors (electrocardiogram, pulse oximeter, and non-invasive blood pressure) were applied to each patient, and baseline values were recorded. Seventy percent nitrous oxide in oxygen was administered via facemask, and a peripheral intravenous catheter was inserted. After administering 100% oxygen, anesthesia was induced using propofol 4 mg·kg\(^{-1}\) and glycopyrrolate 10 μg·kg\(^{-1}\), and tracheal intubation was performed without the use of neuromuscular blocking agents. Ventilation was controlled to maintain normocarbia. Immediately after induction of anesthesia, patients recruited to the morphine group received morphine at a dose of 150 μg·kg\(^{-1}\) diluted in normal saline to a volume of 10 mL; whereas those recruited to the control group received an equal volume of saline alone. A second intravenous catheter and a radial artery catheter were inserted and each patient’s bladder was catheterized in accordance with standard practice. To facilitate intraoperative motor-evoked potential monitoring, no neuromuscular blocking agents, nitrous oxide, or inhaled anesthetic agents were administered after surgical incision. Following induction of
anesthesia, propofol was infused at a rate of 100–150 
\(\mu g \cdot kg^{-1} \cdot min^{-1}\). In addition, remifentanil infusion was 
going at a rate of 0.2 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) and subsequently 
tritated in increments of 0.05 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) according 
to hemodynamic response (i.e., a change in heart rate 
or blood pressure of \(\geq 20\%\) from baseline). An oxygen/air mixture was delivered at an inspired oxygen 
concentration of 30%. In keeping with standard prac-
tice for this institution, controlled hypotension was 
not induced so as to avoid exacerbation of any spinal 
cord ischemia resulting from surgical distraction. A 
bolus dose of morphine 100 \(\mu g \cdot kg^{-1}\) was adminis-
tered approximately 30 min before the end of surgery, 
and remifentanil infusion was discontinued in both 
groups at skin closure. The study was blinded in that 
the operating room anesthesiologist, the study inves-
tigators, and the Acute Pain Service were unaware of 
group assignment until all recruitment and data col-
exion were complete. After tracheal extubation, the 
patients were transferred to the postanesthetic care unit 
(PACU) where an anesthesiologist or nurse, blinded 
to group assignment, assessed pain control and admin-
istered morphine 50 \(\mu g \cdot kg^{-1}\) at five-minute intervals 
until the patient was comfortable, i.e., absence of any 
verbal or behavioural expression of pain. At this point, 
PCA was initiated using an intravenous syringe pump 
(3300; Graseby, Herts, UK) containing 1 mg.mL\(^{-1}\) 
morphine in a volume of 50 mL. The pump was set 
to deliver morphine by bolus of 20 \(\mu g \cdot kg^{-1}\) with a six-
minute interval lockout and a continuous background 
infusion of 10 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\).

Secondary outcomes, including pain scores at rest 
and while coughing, and nausea, vomiting, and seda-
tion scores, were recorded every hour for four hours 
and then every four hours for 48 hr. Twenty-four and 
48-hr morphine consumption was calculated as the 
sum of all morphine administered in the PACU and 
on the ward during the respective interval divided by the 
boby weight (kg). Propofol and remifentanil con-
sumption was calculated by dividing the total dose 
administered intraoperatively by the body weight and 
the duration of anesthesia (from induction until cessa-
tion of infusion).

Sedation was rated on a numeric scale of 1 to 5: 1 = 
completely awake; 2 = awake but drowsy; 3 = asleep but 
responsive to verbal commands; 4 = asleep but respon-
sive to tactile stimuli; and 5 = asleep and unresponsive 
to any stimuli. Nausea and vomiting were rated on a 
numeric scale of 0 to 5: 0 = no episodes of nausea or 
vomiting; 1 = one episode of nausea or vomiting 
which resolved without treatment; 2 = one episode of 
nausea and/or vomiting requiring treatment with a 
first line anti-emetic (i.e., dimenhydrinate); 3 = more 

Results

Treatment groups were similar with respect to age, 
weight, gender, thoracic Cobb angle, number of ver-
tebal levels instrumented, and duration of anesthe-
sia (Table). Forty-five patients were screened prior to 
enrolment, and 40 of these were recruited. One data 
set was misplaced, and two patients were lost to pro-
tocol violations leaving 37 data sets for analysis, 18 in 
the morphine group and 19 in the saline group.

Figure 1 summarizes the cumulative morphine con-

Statistical analysis

The primary outcome was the initial 24-hr morphine 
consumption. The sample size estimation was based 
on a study from this institution demonstrating that the 
initial 24-hr morphine consumption after surgery for 
iidopathic scoliosis was 1.65 mg.kg\(^{-1}\) \(\pm\) 0.41 mg.kg\(^{-1}\).\(^3\) 
To demonstrate a 25% difference in 24-hr morphine 
consumption (0.41 mg.kg\(^{-1}\)), we estimated that 18 
patients per group were required for a two-tailed \(\alpha\) 
of 0.05 and a \(B\) of 0.2 (power = 80%). Forty patients 
were recruited to accommodate any potential protocol 
violations or dropouts. Two-way repeated measures 
analysis of variance was used for comparison of mor-
phine consumption. The Mann-Whitney rank sum test 
was used for between-group comparison of NRS pain 
scores, and Fisher’s exact test was used for comparison 
of nominal data. All comparison tests were two-tailed, 
and a significance level of 0.05 was used.

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Figure 1 summarizes the cumulative morphine con-
Cumulative postoperative morphine consumption did not differ between groups. The cumulative initial 24-hr morphine consumption in the saline group was 1.24 ± 0.54 mg·kg⁻¹ compared with 1.36 ± 0.47 mg·kg⁻¹ in the morphine group.

Regarding NRS pain scores, no significant difference was demonstrated between groups during the first 48 hr after surgery, either at rest (Figure 2) or on coughing (Figure 3). Differences in sedation scores and nausea and vomiting scores were not statistically significant.

Seven patients needed conversion from PCA morphine to PCA hydromorphone at 20–24 hr after surgery. All seven were from the morphine group (P = 0.003 vs control group). Five of the seven patients had described significant pain unresponsive to treatment (increasing the background infusion and bolus dose), five had described significant pruritus unresponsive to treatment (administration of first and second line anti-pruritics within a four-hour period), and one had described significant nausea and vomiting (unresponsive to administration of two anti-emetics within a four-hour time period). There were no respiratory, cardiovascular, or neurological complications.

**Discussion**

In the current study, administration of morphine prior to initiation of remifentanil infusion did not decrease postoperative morphine requirement. Intraoperative

**TABLE**

<table>
<thead>
<tr>
<th></th>
<th>Morphine (n=18)</th>
<th>Saline (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>14.8 ± 1.7</td>
<td>14.5 ± 1.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.2 ± 8.8</td>
<td>51.3 ± 8.4</td>
</tr>
<tr>
<td>Male: Female</td>
<td>4:14</td>
<td>3:16</td>
</tr>
<tr>
<td>Thoracic Cobb angle</td>
<td>63 (45-74)</td>
<td>62 (41-81)</td>
</tr>
<tr>
<td>(degrees)</td>
<td>10 (8-14)</td>
<td>10 (7-12)</td>
</tr>
<tr>
<td>Length of instrumentation</td>
<td>127 ± 18</td>
<td>126 ± 16</td>
</tr>
<tr>
<td>(vertebral levels)</td>
<td>0.27 ± 0.10</td>
<td>0.30 ± 0.06</td>
</tr>
<tr>
<td>Anesthesia duration (min)</td>
<td>415 ± 83</td>
<td>391 ± 97</td>
</tr>
<tr>
<td>Propofol infusion rate (µg·kg⁻¹·min⁻¹)</td>
<td>127 ± 18</td>
<td>126 ± 16</td>
</tr>
<tr>
<td>Remifentanil infusion rate (µg·kg⁻¹·min⁻¹)</td>
<td>0.27 ± 0.10</td>
<td>0.30 ± 0.06</td>
</tr>
</tbody>
</table>

Values are mean ± SD, ratio, or median (range). Patient demographics and extent of surgery were comparable in the two groups.
infusion of remifentanil was associated with the development of hyperalgesia manifesting clinically as an increase in postoperative morphine consumption.\(^3\)\(^4\) The increase in postoperative morphine consumption was variable, ranging from 30% to 100% for comparable durations of remifentanil infusion.\(^3\)\(^4\) One explanation offered for the observed differences in postoperative opioid consumption between these studies was that morphine administered at induction of anesthesia may have had a preemptive analgesic effect, thereby attenuating the development of remifentanil-induced acute opioid tolerance. In accordance with this notion, some clinicians currently administer a longer acting opioid before commencing remifentanil infusion. The results of the current study suggest that this practice does not attenuate remifentanil-induced hyperalgesia. This finding is in agreement with a recent study investigating the administration of fentanyl before infusion of remifentanil for orthopedic surgery.\(^10\)

Contrary to the notion that morphine pre-treatment would attenuate remifentanil-induced hyperalgesia, the current study suggests that there is a trend for patients receiving morphine pre-treatment to consume more opioid after surgery and to have greater pain scores compared with controls. In addition, the need for opioid rotation was significantly greater in the morphine group \((P = 0.003 \text{ vs control group})\). Patients receiving fentanyl pre-treatment prior to remifentanil infusion also demonstrated a trend towards increased NRS pain scores from four to 24 hr after surgery.\(^10\) In both studies, the increase in postoperative opioid consumption was relatively small and of questionable clinical significance. We estimate that approximately 300 patients per group would be required for 80% power to reject the null hypothesis. Nevertheless, the clinical practice of administering a longer acting opioid prior to commencing remifentanil infusion may be associated with an increase in postoperative opioid-related side effects, postoperative pain, and opioid consumption.

In the current study, mean initial 24-hr morphine consumption is less than that observed in our previous study.\(^3\) There were no differences between this study and the previous one in terms of age, gender, thoracic Cobb angle, number of vertebral levels instrumented, or rate of remifentanil infusion. However, in the current study, the mean duration of anesthesia was approximately one hour shorter. Therefore, the development of remifentanil-induced hyperalgesia may be time- and dose-dependent, and the shorter surgical time demonstrated in the current study may have decreased the initial 24-hr morphine consumption beyond that seen in the previous study.\(^3\)

The purpose of the current study was to examine whether early administration of morphine would attenuate the development of postoperative remifentanil-induced hyperalgesia. The total dose of morphine in our study group was based on data from our previous study demonstrating that adolescents who received \(237 \pm 53 \mu\text{g.kg}^{-1}\) morphine intraoperatively consumed significantly less PCA morphine compared with those receiving intraoperative remifentanil infusion. Therefore, we selected 250 \(\mu\text{g.kg}^{-1}\) as the total morphine dose in the study group and divided that into a pre-remifentanil dose \((150 \mu\text{g.kg}^{-1})\) and a post-remifentanil dose \((100 \mu\text{g.kg}^{-1})\).

We titrated remifentanil infusion according to hemodynamic response in the current study. Pre-treatment with morphine did not appear to have any impact on intraoperative analgesic requirements, as remifentanil consumption in both groups was similar. However, we did not investigate the dose-dependent nature of this finding, and the current study was not powered for this purpose.

An interesting observation in the current study was that all seven patients who needed conversion from morphine PCA to hydromorphone PCA were from the morphine group. All were converted at approximately the same time-point (20–24 hr after surgery, not coinciding with Acute Pain Service ward rounds). In order to calculate cumulative morphine consumption, we converted the hydromorphone consumption of these seven patients to the equivalent dose of morphine using an equivalence ratio of morphine to hydromorphone of 3:1.\(^12\) This may be seen as a limitation of the current study; however, exclusion of the data from these seven patients has no impact on the finding that there was no difference in morphine consumption between groups from time zero to 20 hr after surgery.

The balance between the desirable effects of remifentanil anesthesia to facilitate neurological monitoring and the potential for the development of hyperalgesia is best judged in light of type of surgery, critical requirements for neurological monitoring, and expected degree of postoperative pain. Future research may choose to investigate the impact of duration of surgery on the development of remifentanil-induced hyperalgesia. Given the observation that all patients needing conversion to hydromorphone PCA were from the morphine group, it may also be prudent to further examine whether morphine bolus prior to initiating the remifentanil infusion actually increases postoperative morphine consumption and morphine-related side effects in some patients. The results of the current study may not be applicable to other patient...
populations, including children with secondary scoliosis who often have comorbid conditions that would have excluded them from participation.

In summary, to achieve comparable analgesia after surgery for idiopathic scoliosis, adolescents who received morphine 150 µg·kg⁻¹ prior to initiation of remifentanil infusion consumed no less morphine in the first 24 hr after surgery than adolescents who received placebo. This suggests that prior administration of morphine 150 µg·kg⁻¹ does not attenuate remifentanil-induced hyperalgesia in this surgical population.

References