Reports Of Original Investigations

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

[Un prétraitement à la morphine n'empêche pas l'apparition d'hyperalgésie provoquée par le rémifentanil]

Conor McDonnell MD MB BCh BAO FCARSCI,* Christian Zaarour MD,* Rebecca Hull MBBS FRCA,* Priya Thalayasingam MBBS FANZCA,* Carolyne Pehora RN MN,* Janet Ahier RN BScN MN APN,† Mark W. Crawford MBBS FRCPC*

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 $\mu g \cdot kg^{-1}$ 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 $\mu g \cdot kg^{-1}$ 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 rémifentanil 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 rémifentanil 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 $\mu g \cdot kg^{-1}$ ou un volume équivalent de sérum physiologique avant le début d'une perfusion de rémifentanil. 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 sédation 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 sédation, les nausées ou les vomissements.*

Conclusion *: Le prétraitement avec 150 $\mu g \cdot kg^{-1}$ de morphine n'a pas diminué la consommation de morphine durant les 24 premières heures postopératoires chez des adolescents recevant une perfusion de rémifentanil pour une chirurgie corrective d'une scoliose idiopathique.*

CAN J ANESTH 2008 / 55: 12 / pp 813–818

From the Department of Anesthesia* and the Division of Orthopedic Surgery,† The Hospital For Sick Children, University of Toronto, Ontario, Canada.

Address correspondence to: Dr. Crawford, Department of Anesthesia, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Phone: 416-813-6466; Fax: 416-813-7543; E-mail: mark.crawford@sickkids.ca

Support was provided solely from departmental sources.

Clinicaltrialsfeeds.org – NCT00737997.

Accepted for publication August 21, 2008.

Revision accepted September 24, 2008.

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 μ-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.[3,4] 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.[4–10] 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.[11] 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.[3,10] 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 $mg \cdot kg^{-1}$ and glycopyrrolate 10 $\mu g \cdot kg^{-1}$, 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 $\mu g \cdot kg^{-1}$ 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 begun at a rate of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and subsequently titrated 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 ≥ 20% from baseline). An oxygen/air mixture was delivered at an inspired oxygen concentration of 30%. In keeping with standard practice 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 $\mu g \cdot kg^{-1}$ *iv* was administered 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 investigators, and the Acute Pain Service were unaware of group assignment until all recruitment and data collection 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 administered morphine 50 $\mu g \cdot kg^{-1}$ *iv* 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 $mg \cdot mL^{-1}$ 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 sedation 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 body weight (kg). Propofol and remifentanil consumption was calculated by dividing the total dose administered intraoperatively by the body weight and the duration of anesthesia (from induction until cessation 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 responsive 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 and/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 than one episode of nausea and/or vomiting resolving without treatment; 4 = more than one episode of nausea and/or vomiting requiring treatment with a first line anti-emetic; 5 = more than one episode of nausea and/or vomiting unresponsive to a first line anti-emetic. Placement of the surgical dressing was recorded as time zero. On arrival to the PACU, NRS pain scores and sedation, nausea, and vomiting scores were recorded every hour for four hours then every four hours for 48 hr. Dimenhydrinate 0.5 $mg \cdot kg^{-1}$ and ondansetron 0.1 $mg \cdot kg^{-1}$ were administered as first and second line anti-emetics, respectively.

Incidences of postoperative pruritus were also recorded. Diphenhydramine 0.5 $mg \cdot kg^{-1}$ was administered intravenously for pruritus, and acetaminophen 15 $mg \cdot kg^{-1}$ *po* was administered for pyrexia every four to six hours. The Acute Pain Service assessed each patient twice daily and the dose of morphine PCA was titrated to effect. For patients reporting NRS pain scores greater than 8 out of 10 in combination with morphine-related side effects, the service was instructed to switch PCA morphine to PCA hydromorphone in accordance with standard practice.

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 idiopathic scoliosis was 1.65 $mg \cdot kg^{-1}$ ± 0.41 $mg \cdot kg^{-1}$.[3] To demonstrate a 25% difference in 24-hr morphine consumption (0.41 $mg \cdot kg^{-1}$), we estimated that 18 patients per group were required for a two-tailed α of 0.05 and a ß 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 morphine 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.

Results

Treatment groups were similar with respect to age, weight, gender, thoracic Cobb angle, number of vertebral levels instrumented, and duration of anesthesia (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 protocol 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-

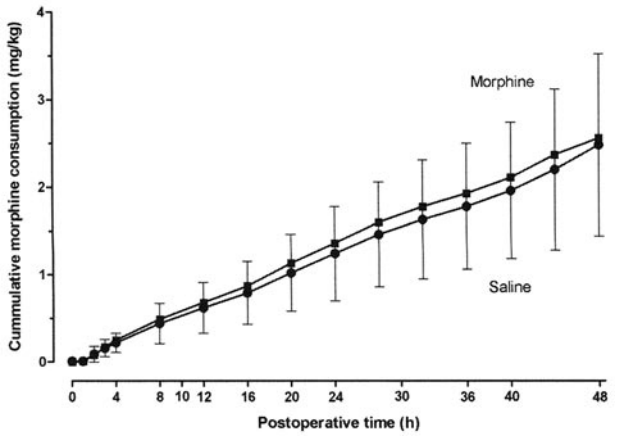

FIGURE 1 Cumulative postoperative morphine consumption in the initial 48 hr after surgery for correction of idiopathic scoliosis in adolescents who received morphine or saline before infusion of remifentanil. Postoperative morphine consumption did not differ between groups.

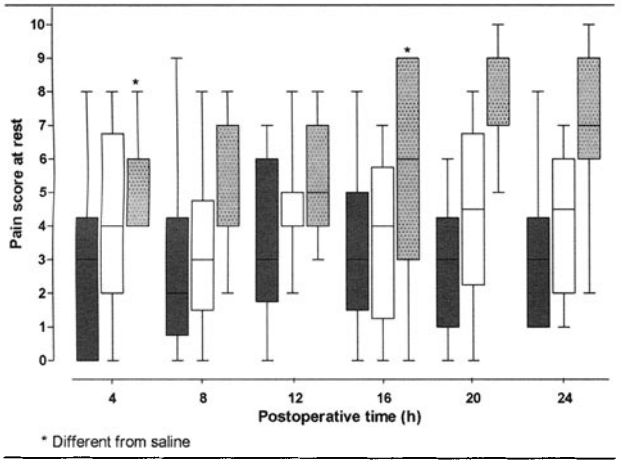

FIGURE 2 Box and whisker plot showing numeric rating scale (NRS) pain scores at rest in the first 48 hr after surgery. Differences between groups were not statistically significant. Values are median, interquartile range, and range.

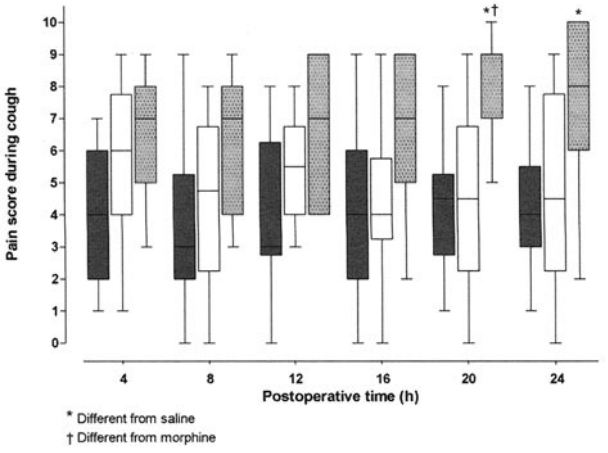

FIGURE 3 Box and whisker plot showing numeric rating scale (NRS) pain scores during requested cough in the first 48 hr after surgery. Differences between groups were not statistically significant. Values are median, interquartile range, and range.

TABLE Patient characteristics and intraoperative outcomes

	Morphine (n =18)	*Saline (n =19)*
Age (yr)	14.8 ± 1.7	14.5 ± 1.9
Weight (kg)	54.2 ± 8.8	51.3 ± 8.4
Male: Female	4:14	3:16
Thoracic Cobb angle (degrees)	63 (45-74)	62 (41-81)
Length of instrumentation (vertebral levels)	10 (8-14)	10 (7-12)
Anesthesia duration (min)	415 ± 83	391 ± 97
Propofol infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	127 ± 18	126 ± 16
Remifentanil infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.27 ± 0.10	0.30 ± 0.06

Values are mean ± SD, ratio, or median (range). Patient demographics and extent of surgery were comparable in the two groups.

sumption in the first 48 hr after surgery. There was no statistical difference for cumulative postoperative morphine consumption at any time point between the two groups. The cumulative initial 24-hr morphine consumption in the saline group was 1.24 ± 0.54 $mg \cdot kg^{-1}$ compared with 1.36 ± 0.47 $mg \cdot kg^{-1}$ 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

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 ($P = 0.003$ *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 ± 53 $\mu g \cdot kg^{-1}$ morphine intraoperatively consumed significantly less PCA morphine compared with those receiving intraoperative remifentanil infusion. Therefore, we selected 250 $\mu g \cdot kg^{-1}$ as the total morphine dose in the study group and divided that into a pre-remifentanil dose (150 $\mu g \cdot kg^{-1}$) and a post-remifentanil dose (100 $\mu g \cdot kg^{-1}$).

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 $\mu g \cdot kg^{-1}$ 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 $\mu g \cdot kg^{-1}$ does not attenuate remifentanil-induced hyperalgesia in this surgical population.

References

1 *Gibson PR.* Anaesthesia for correction of scoliosis in children. Anaesth Intensive Care 2004; 32: 548–59.

2 *Thompson JP, Rowbotham DJ.* Remifentanil - an opioid for the 21st century. Br J Anaesth 1996; 76: 341–3.

3 *Crawford MW, Hickey C, Zaarour C, Howard A, Naser B.* Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. Anesth Analg 2006; 102: 1662–7.

4 *Guignard B, Bossard AE, Coste C, et al.* Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000; 93: 409–17.

5 *Joly V, Richebe P, Guignard B, et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005; 103: 147–55.

6 *Van Elstraete AC, Lebrun T, Sandefo I, Polin B.* Ketamine does not decrease postoperative pain after remifentanil-based anaesthesia for tonsillectomy in adults. Acta Anaesthesiol Scand 2004; 48: 756–60.

7 *Ganne O, Abisseror M, Menault P, et al.* Low-dose ketamine failed to spare morphine after a remifentanil-based anaesthesia for ear, nose and throat surgery. Eur J Anaesthesiol 2005; 22: 426–30.

8 *Engelhardt T, Zaarour C, Naser B, DeRuiter J, Crawford MW.* Effects of intraoperative ketamine on remifentanil-induced opioid tolerance after scoliosis surgery. Anesthesiology 2006; 105: A592 (abstract).

9 *Batra YK, Shamsah M, Al-Khasti MJ, Rawdhan HJ, Al-Qattan AR, Belani KG.* Intraoperative small-dose ketamine does not reduce pain or analgesic consumption during perioperative opioid analgesia in children after tonsillectomy. Int J Clin Pharmacol Ther 2007; 45: 155–60.

10 *Lenz H, Raeder J, Hoymork SC.* Administration of fentanyl before remifentanil-based anaesthesia has no influence on post-operative pain or analgesic consumption. Acta Anaesthesiol Scand 2008; 52: 149–54.

11 *Koppert W.* Opioid induced hyperalgesia – Pathophysiology and clinical relevance. Acute Pain 2007; 9: 21–34.

12 *Dunbar PJ, Chapman CR, Buckley P, Gavrin JR.* Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. Pain 1196; 68: 265–70.