Intraoperative Infusion of 0.6–0.9 µg·kg⁻¹·min⁻¹ Remifentanil Induces Acute Tolerance in Young Children after Laparoscopic Ureteroneocystostomy

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ABSTRACT

Background: Intraoperative infusion of opioids has been associated with increased postoperative pain and analgesic requirements, but the development of tolerance in young children is less clear. This prospective, randomized, double-blinded study was designed to test the hypothesis that the intraoperative administration of remifentanil results in postoperative opioid tolerance in a dose-related manner in young children.

Methods: We enrolled 60 children (aged 1–5 yr) who were undergoing elective laparoscopic ureteroneocystostomy. Patients were randomized and received an intraoperative infusion of 0, 0.3, 0.6, or 0.9 µg·kg⁻¹·min⁻¹ remifentanil. Postoperative pain was managed by a parent/nurse-controlled analgesia pump using fentanyl. The primary outcome included the total fentanyl consumptions at 24 and 48 h postsurgery. Secondary outcomes were the postoperative pain scores and adverse effects.

Results: The children who received 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil required more postoperative fentanyl than the children who received saline or 0.3 µg·kg⁻¹·min⁻¹ remifentanil (all $P < 0.001$) for 24 h after surgery. The children who received 0.3–0.9 µg·kg⁻¹·min⁻¹ intraoperative remifentanil reported higher pain scores at 1 h after surgery than the children who received saline ($P = 0.002$, $P = 0.023$, and $P = 0.006$, respectively). No significant intergroup differences in recovery variables were observed, but vomiting was

What We Already Know about This Topic

- Remifentanil may produce hyperalgesia and increased pain after discontinuation in adults
- Although remifentanil has many advantages in young children, whether it causes hyperalgesia or increased pain or opioid requirements after discontinuation has not been examined

What This Article Tells Us That Is New

- In 60 children, aged 1–5 yr, intraoperative remifentanil 0.6–0.9 µg·kg⁻¹·min⁻¹ increased postoperative opioid analgesic requirements and 0.3–0.9 µg·kg⁻¹·min⁻¹ increased pain 1 h after surgery compared with intraoperative control

more frequent in the 0.9 µg·kg⁻¹·min⁻¹ remifentanil group than in the other groups ($P = 0.027$).

Conclusions: The intraoperative use of 0.3 µg·kg⁻¹·min⁻¹ remifentanil for approximately 3 h (range: 140–265 min) did not induce acute tolerance, but the administration of 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil to young children resulted in acute tolerance for 24 h after surgery in an apparently dose-related manner.

THE unique pharmacodynamic and pharmacokinetic characteristics of remifentanil have increased its dominant intraoperative role in children.[1,2] The context-sensitive halftime of remifentanil renders the offset for effect dose-independent, thus allowing prolonged infusion of large doses with little risk for delayed awakening or respiratory depression after surgery.[3,4] Similar to other potent opioids, however, intraoperative remifentanil may induce hyperalgesia and tolerance, manifesting as increased postoperative pain and analgesic requirements.[5–7] Opioid-induced hyperalgesia is a paradoxical pain sensitization of the nervous system whereby a patient receiving an opioid for the treatment of pain might actually have an increase in pain perception to noxious stimuli.[8] Tolerance is a pharmacologic concept defined as a progressive decrease in response to a drug and which can be overcome by increasing the dose of the drug. Although the difference between hyperalgesia and tolerance is difficult to tease out, opioid-induced hyperalgesia and tolerance may complicate the perioperative course of a patient who receives intraoperative opioid.

In young children, however, only a few studies have investigated the development of tolerance after the intraoperative infusion of remifentanil, and the results were anecdotal and

controversial. Furthermore, the precise dosage of remifentanil that is associated with tolerance in this population has not been determined. Although the intraoperative infusion of 0.25 µg·kg⁻¹·min⁻¹ remifentanil is associated with high postoperative pain–discomfort scores in 2- to 12-yr-old children,[9] the intraoperative infusion of 0.8 µg·kg⁻¹·min⁻¹ remifentanil is not associated with tolerance in infants aged 4–6 months.[10] These studies have important limitations, however, mostly steming from their structural weaknesses such as inappropriate study designs for the determination of tolerance.

This prospective, randomized, double-blinded study was designed to test the hypothesis that the intraoperative administration of remifentanil results in postoperative opioid tolerance in a dose-related manner in young children. Tolerance was evaluated by measuring postoperative pain scores and cumulative fentanyl consumption delivered by parent/nurse-controlled analgesia (PNCA) after laparoscopic ureteroneocystostomy.

Materials and Methods

Subjects

This single-site study was conducted at Yonsei University Health System, Seoul, Korea, between June 2010 and February 2011. The study protocol was approved by the ethics committee of Clinical Trial Center, Yonsei University (Seoul, Korea), and the parents of all enrolled patients provided written informed consent. This prospective randomized double-blind trial enrolled 60 American Society of Anesthesiologists physical status I–II children, aged 1–5 yr, who were undergoing elective laparoscopic ureteroneocystostomy. Patients were excluded if they had a cardiopulmonary disease, genetic metabolic disorder, or a history of opioid use within 1 month before surgery.

Participants were recruited from the outpatient department for anesthesia preoperative evaluation. The preoperative interview included a medical history taking and physical examination. Parents were instructed in the principles of a PNCA device and their role in this study. Each participating parent was told to be at his/her child's bedside throughout the postoperative period to activate the PNCA device (AutoMed3200; AceMedical, Seoul, Korea). Parents were considered the "primary pain manager" and provided with written instructions about the operation of the PNCA, pediatric pain assessment, how to monitor PNCA-related adverse effects, and how to notify the anesthesiologist in the ward.

A ward physician, who was not involved in this trial, performed randomization and assignment. Using a computer-generated block randomization table,** patients were randomly assigned to cohorts that were then administered infusions of 0, 0.3, 0.6, or 0.9 µg·kg⁻¹·min⁻¹ remifentanil (n = 15 each). Drugs were prepared in unlabeled 50 ml syringes by a nurse anesthetist who did not participate in either the intraoperative management or the postoperative care. The unlabeled syringes were filled with normal saline or with 30, 60, or 90 µg/ml remifentanil, and the study drug was given during anesthesia at a fixed infusion rate.

Procedures

No premedication was administered. On arrival in the operating room, standard intraoperative monitors were applied to each child, including monitors of peripheral oxygen saturation, heart rate, and noninvasive mean arterial pressure, and their baseline values were recorded. Anesthesia was induced using thiopental sodium 5 mg/kg and fentanyl 1 µg/kg. Tracheal intubation was facilitated by administration of 0.5 mg/kg atracurium, and the patient's ventilation was controlled to maintain end-tidal carbon dioxide at 35 ± 5 mmHg. Anesthesia was maintained with 1–4 vol% sevoflurane in an oxygen–air mixture (FIO₂ 0.5), and the depth of anesthesia was adjusted by altering sevoflurane concentration to maintain a bispectral index (BIS A-1050 Monitor˚; Aspect Medical Systems, Newton, MA) of 40–60. The same urologist performed all surgical procedures so that surgical stimuli would be uniform. Intraoperative peripheral oxygen saturation, heart rate, blood pressure, minimum alveolar concentration-hour of sevoflurane, administered fluid, and duration of surgery were recorded.

At the end of surgery, all drugs were stopped without tapering. Neuromuscular blockade was reversed with intravenous glycopyrrolate 0.1 mg/kg followed by neostigmine 0.06 mg/kg. The trachea was extubated when the child was able to raise his eyebrows, open his eyes, and/or perform purposeful movements such as reaching for the endotracheal tube. After emerging from anesthesia, the PNCA pump was connected to an intravenous catheter by the attending anesthesiologist. After transfer to the postanesthetic care unit, parents were allowed to stay with their child during recovery, with all postoperative assessments performed by the blinded anesthesiologist. Postoperative pain control was maintained by a PNCA pump with fentanyl. The intravenous infusion tubing contained a one-way, back-check valve to prevent backflow and inadvertent dosing of the drug by gravity. The pump maintained a basal infusion rate of 0.2 µg·kg⁻¹·h⁻¹ fentanyl, thus allowing a bolus dose of 0.2 µg/kg fentanyl, and with a lockout time of 15 min for 48 h after surgery.

Both the blinded nurse in the postanesthetic care unit and the educated parent were allowed to administer bolus doses of analgesia to children thought to have pain greater than 4 on the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). The CHEOPS pain scale uses six items that were scored differently, *i.e.*, crying, facial expression, verbal expression, torso position, touching the wound with the hand, and leg movement. Its total score ranges from 0 to 10. It has been validated for use in children aged 1–7 yr.[11] Throughout the PNCA use, the child's vital signs

** http://www.random.org. Accessed September 3, 2012.

and adverse effects were closely monitored by the nurse and parent. If the child had any adverse effects, the PNCA device was temporarily stopped, and an anesthesiologist blinded to the study was immediately notified for appropriate management.

Postoperative adverse effects, including shivering, sedation, desaturation, vomiting, and pruritus, were assessed and treated appropriately. Parents were instructed to pay attention and to watch for episodes of abrupt lower abdominal cramps with the sensation of voiding in their children. When bladder spasms were suspected, 0.5 mg/kg ketorolac was administered as a treatment. Postoperative sedation was evaluated using the eight-point modified Ramsay Sedation Scale,[12] and oversedation was defined as greater than 4. Postoperative desaturation (oxygen saturation <90%) was routinely monitored by the attending parents and the ward nurses using continuous pulse oximetry, which was used to evaluate all children during the first 48 h of PNCA use. Supplemental oxygen and rescue naloxone were administered as needed for desaturation. If a child seemed to be oversedated or desaturated, the basal infusion rate was reduced by half. Children who vomited at least once were administered ondansetron 0.1 mg/kg IV, and those with pruritus were administered pheniramine 1 mg/kg IV.

The primary outcomes included the total amount of fentanyl administered *via* PNCA at 24 and 48 h postsurgery. Secondary outcome variables included the postoperative CHEOPS pain scores at 1, 3, 6, 12, 24, and 48 h and the incidence of adverse effects.

Statistical Analysis

Sample sizes were calculated as described previously,[13] in that the mean total dose of fentanyl-based PNCA during the first postoperative 24 h was 18.1 ± 4.6 µg/kg. Assigning 15 patients to each of the 4 groups allowed an α of 0.05 and a power of 0.9 for a 30% intergroup difference in the reference value.

All data were presented as mean ± SD. Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL).

A normality test was performed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Intergroup differences in patient demographics and intraoperative variables were analyzed using ANOVA with the Duncan *post hoc* test. Intergroup differences in the total amount of fentanyl administered over the 0–24 and 24–48 h periods were analyzed using repeated measures ANOVA. To compare all pairwise groups, significance levels by multiple tests were used the Bonferroni correction ($P < 0.05/12$). Intergroup differences in the postoperative CHEOPS pain scores between group S and the other groups were analyzed using repeated measures ANOVA. Incidences of postoperative side effects among groups were compared using the Fisher exact test. All statistical tests were two-tailed, and P value less than 0.05 was considered statistically significant (except multiple comparisons).

Results

A total of 60 children were enrolled, and none were excluded or dropped out during the course of the trial. As a result, each group comprised 15 patients. The four groups were comparable in mean age, height, weight, duration of surgery, and total intraoperative fluid administered (table 1). Intraoperative minimum alveolar concentration-hour of sevoflurane in the 0.6 and 0.9 µg·kg^{-1}·min^{-1} groups were lower than in the 0 µg·kg^{-1}·min^{-1} (saline) group and were lower in the 0.9 than in the 0.3 µg·kg^{-1}·min^{-1} group ($P < 0.05$). Intraoperative heart rate and systolic and diastolic blood pressures were similar in the four groups (fig. 1).

PNCA was successfully administered to all children in the postanesthetic care unit and the ward. All parents stayed with their children at the bedside, and there were no technical problems related to the use of the PNCA device. Fentanyl consumption *via* PNCA differed significantly among the 4 groups at 0–24 and 24–48 h postsurgery (table 2). There was a significant interaction between group and time for the amount of fentanyl consumption *via* PNCA ($P < 0.001$). We observed a dose-dependent relationship between the amount of intraoperatively administered remifentanil and the postoperative 0–24 h requirement of fentanyl. During the

Table 1. Demographics and Intraoperative Data

Variables	Group S (n = 15)	Group 0.3 (n = 15)	Group 0.6 (n = 15)	Group 0.9 (n = 15)
Age, month	32.9 ± 14.3	29.8 ± 14.2	32.3 ± 12.3	32.6 ± 15.7
Weight, kg	18.4 ± 6.9	15.0 ± 5.4	14.5 ± 3.4	15.2 ± 4.1
Height, cm	104.2 ± 16.3	95.7 ± 15.3	94.1 ± 14.4	96.9 ± 15.1
Operation duration, min	182.1 ± 32.5	166.9 ± 20.2	179.6 ± 37.0	170.1 ± 29.3
Administered fluid, ml	261.4 ± 80.8	263.0 ± 67.0	253.8 ± 98.9	264.0 ± 65.3
MAC, h	9.9 ± 2.1	8.1 ± 1.1	6.3 ± 2.1*	5.8 ± 2.1*†

Data are mean ± SD.

* $P < 0.05$ compared to group S. † $P < 0.05$ compared to group 0.3.

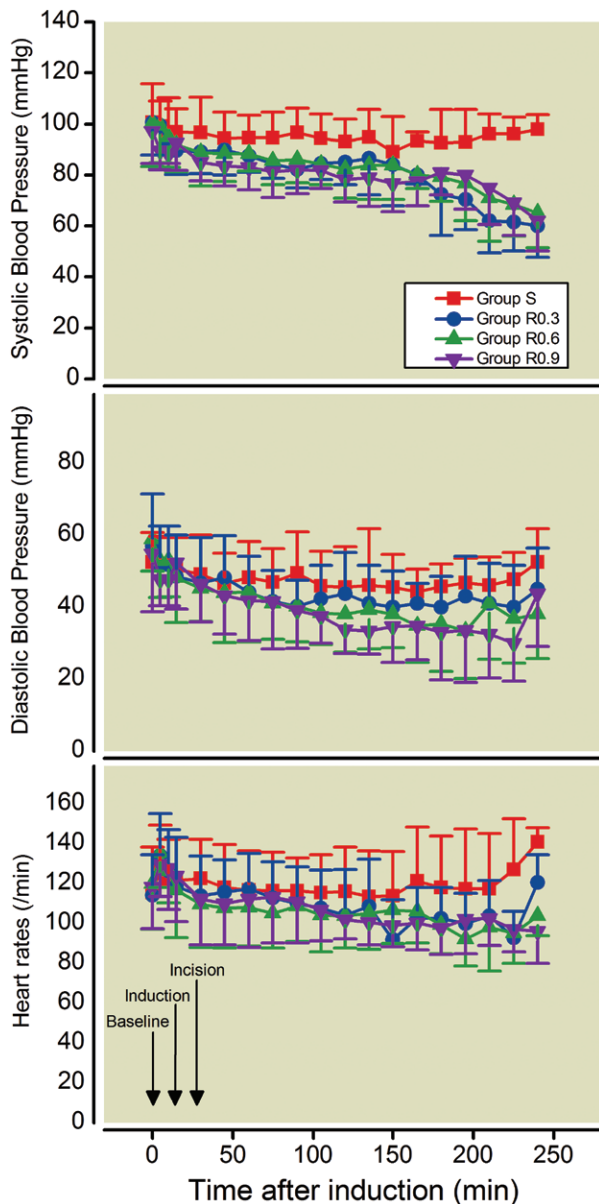MAC = minimum alveolar concentration.

Fig. 1. Baseline and intraoperative heart rate and blood pressure in the four groups of patients.

0–24 h postsurgery period, the children who intraoperatively received 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil required more fentanyl *via* PNCA than children who received saline and 0.3 µg·kg⁻¹·min⁻¹ remifentanil (all $P < 0.001$), and the children who received 0.9 µg·kg⁻¹·min⁻¹ remifentanil required more fentanyl than children who received 0.6 µg·kg⁻¹·min⁻¹ remifentanil ($P < 0.001$). During the 24–48 h postoperative period, however, the dose-dependent relationship between the amount of intraoperative remifentanil administered and the postoperative requirement for fentanyl was less clear; fentanyl requirements were higher in children who received 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil than the control group, but statistical significance was only shown in children who received 0.6 µg·kg⁻¹·min⁻¹ remifentanil ($P < 0.001$).

CHEOPS pain scores at 1 h after surgery were lower in children receiving saline than in the 0.3, 0.6, and 0.9 groups ($P = 0.002$, $P = 0.023$, and $P = 0.006$, respectively) (fig. 2).

In the postanesthetic care unit, more children in the 0.9 µg·kg⁻¹·min⁻¹ (6 of 15, 40%) group vomited and received antiemetic treatment than in the other groups ($P = 0.027$) (table 3). There were no significant intergroup differences in other recovery variables, including shivering, oversedation, agitation, pruritus, and discharge time.

Discussion

We have shown here that the intraoperative infusion of 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil for approximately 3 h (range: 140–265 min) increased fentanyl consumption in young children undergoing laparoscopic ureteroneocystostomy for 24 h after surgery in a dose-dependent manner. These findings support the hypothesis that intraoperative use of 0.6 and 0.9 µg·kg⁻¹·min⁻¹ remifentanil is significantly associated with the postoperative development of opioid-induced acute tolerance in the pediatric population. A lower dose of 0.3 µg·kg⁻¹·min⁻¹ of remifentanil was not associated with acute tolerance. This randomized controlled trial is the first to determine the intraoperatively infused dose of remifentanil that induces acute tolerance in young children.

Remifentanil may be considered an ideal opioid, despite many drawbacks to its usage in pediatric patients, including its "off-label" use, the lack of comprehensive randomized clinical trials, and concerns about adverse effects because of its high potency. Its unique pharmacologic profile, including high potency, rapid onset/offset, and lack of accumulation even after prolonged infusions, makes remifentanil a highly predictable, attractive choice for anesthetic challenges in a wide variety of pediatric procedures.[1,14] However, there are concerns about the postoperative risks of opioid-induced hyperalgesia and acute tolerance, despite conflicting results in clinical trials.[9,10,15,16] For example, acute tolerance was demonstrated after intraoperative infusion of 0.28 µg·kg⁻¹·min⁻¹ remifentanil in 12- to 17-yr-old adolescents undergoing scoliosis surgery.[15] In that study, the cumulative morphine consumption for 24 h after surgery was significantly greater (30%) in the remifentanil (1.65 ± 0.41 mg/kg) than in the intermittent morphine (1.27 ± 0.32 mg/kg) group. In our study, the fentanyl consumption during 0–24 h after surgery in children who received 0.3 µg·kg⁻¹·min⁻¹ remifentanil was 20% higher than in those who received saline (11.1 ± 1.9 *vs.* 9.4 ± 1.6 µg/kg), but this difference did not reach statistical significance. However, we found that higher doses (0.6–0.9 µg·kg⁻¹·min⁻¹) of remifentanil had a greater effect on the fentanyl consumption. For example, the cumulative fentanyl consumption at 24 h was 89% higher in children who received 0.9 µg·kg⁻¹·min⁻¹ remifentanil than in those who received no remifentanil. Another randomized double-blinded study in children aged 2–12 yr undergoing adenotonsillectomy as outpatients found that infusion

Table 2. Postoperative Fentanyl Consumption *via* PNCA

Variables	Group S	Group 0.3	Group 0.6	Group 0.9
Fentanyl 0–24 h, µg/kg	9.4 ± 1.6 (8.5–10.3)	11.1 ± 1.9 (10.0–12.1)	14.3 ± 2.5*† (12.9–15.7)	17.8 ± 3.6*†‡ (15.8–19.8)
P value compared to				
Group 0.3	0.040			
Group 0.6	<0.001	<0.001		
Group 0.9	<0.001	<0.001	<0.001	
Fentanyl 24–48 h, µg/kg	6.8 ± 1.5 (5.6–8.0)	7.8 ± 2.2 (6.6–9.0)	10.3 ± 2.7* (9.1–11.5)	9.2 ± 2.1 (8.0–10.4)
P value compared to				
Group 0.3	0.257			
Group 0.6	<0.001	0.004		
Group 0.9	0.007	0.109	0.198	

Data are mean ± SD (95% CI).

* $P < 0.05/12$ compared to group S. † $P < 0.05/12$ compared to group 0.3. ‡ $P < 0.05/12$ compared to group 0.6.

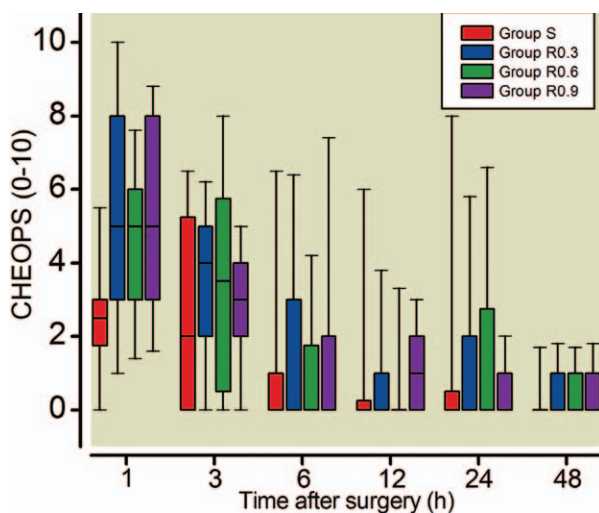PCNA = parent/nurse-controlled analgesia.

Fig. 2. Postoperative pain scores Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) at 1, 3, 6, 12, and 24 h after surgery in the four groups of patients. Data are presented as box plots with 10th and 90th percentiles (*whiskers*), interquartile ranges (*boxes*), and medians (*solid line*). The pain scores assessed at 1 h after surgery were lower in the saline-infused group than the other groups ($P = 0.002$, $P = 0.023$, and $P = 0.006$, respectively), whereas the subsequent scores were similar between the four groups.

of 0.25 µg·kg⁻¹·min⁻¹ remifentanil showed higher pain–discomfort score 5–20 min after surgery than did a bolus of 2 µg/kg fentanyl, suggesting postoperative hyperalgesia in the former group.[9] In that study, however, pain scores were measured only for 60 min after surgery in the postanesthetic care unit, and postoperative analgesic rescue did not differ between the two groups.

Other studies have yielded conflicting results. The comparison of sevoflurane/fentanyl and propofol/remifentanil in infants aged 4–6 months undergoing cleft-lip and palate repair found that morphine consumption in the two groups was similar, despite the higher infusion rate (0.8 µg·kg⁻¹·min⁻¹) in the remifentanil group.[10] These results, however,

may have been affected by the administration of fentanyl 4 µg/kg in the remifentanil group just before the end of surgery. Furthermore, there might have been a possible contribution of intraoperative concurrent propofol infusion in the remifentanil group in their study.[15] A comparison of isoflurane plus a remifentanil infusion starting at 0.25 µg·kg⁻¹·min⁻¹ or a sufentanil bolus found that postoperative visual analog scale pain scores were lower in the remifentanil than in the sufentanil group, with no evidence of increased morphine consumption in the remifentanil group.[16] In that study, acute postoperative hyperalgesia in the remifentanil group might be prevented by an intraoperative bolus of morphine 100 µg/kg about 30 min before the end of surgery. In our trial, all children received fentanyl *via* PNCA for postoperative pain control instead of a bolus injection of long-acting opioid such as morphine or hydromorphone, because fentanyl dose does not have any significant adverse effects on the cardiovascular system and its metabolites do not include active forms. By omitting a long-acting analgesic, some children may awaken in pain due to the ultrashort duration of action of remifentanil. However, PNCA is able to respond quickly and efficiently to postoperative pain and, unlike the bolus administration of opioids, can precisely estimate the analgesic requirement for each child without masking a remifentanil-induced acute tolerance.

The reason for discrepancies regarding the acute tolerance of remifentanil in previously reported studies may be due to the structural weaknesses of the study protocols. In most clinical studies, the dose and duration of infused remifentanil were insufficient or surgical procedures did not cause sufficient postoperative pain to demonstrate a difference in analgesic consumption. Results from an animal model indicated that strong surgical pain may be associated with significant attenuation of acute tolerance of morphine antinociception compared with a control group,[17] suggesting that a high intensity of postoperative pain may interfere with the development of opioid tolerance. Intravesical ureteroneocystostomy is a commonly performed urologic

Table 3. Postoperative Data

Variables	Group S (n = 15)	Group 0.3 (n = 15)	Group 0.6 (n = 15)	Group 0.9 (n = 15)	P Value
Bladder spasms	4 (26.7%)	3 (20%)	3 (20%)	4 (26.7%)	NS
Vomiting	0 (0%)	2 (13.3%)	2 (13.3%)	6 (40.0%)	0.027
Sedation	0 (0%)	0 (0%)	1 (6.7%)	1 (6.7%)	NS
Shivering	0 (0%)	0 (0%)	1 (6.7%)	1 (6.7%)	NS
Pruritus	1 (6.7%)	0 (0%)	1 (6.7%)	2 (13.3%)	NS
PACU time, min	42.1 ± 22.8	32.0 ± 15.8	29.9 ± 18.7	33.1 ± 15.1	NS

Data are number of patients (%) or mean ± SD.

NS = not significant; PACU = postanesthetic care unit.

procedure in children with vesicoureteral reflux. The goal of this procedure is to detach and reimplant the ureters within the submucosal tunnel, preventing reflux *via* a flap-valve mechanism. After this operation, many children suffer from moderate-to-severe intermittent pain, including pain at the surgical incision and bladder spasms. The clinical impact of our results may be due to the intensity and characteristics of postoperative pain and well-controlled pain management using PNCA. Additional studies are warranted to investigate the relationships between the development of tolerance and pain intensity.

The proposed mechanism underlying the development of hyperalgesia and acute tolerance involves activation of the dorsal horn *N*-methyl-D-aspartate system,[18,19] inactivation of μ-opioid receptors,[20] spinal dynorphin release,[21] and up-regulation of the cyclic adenosine monophosphate pathway.[22] Although the exact mechanism underlying the development of acute tolerance is unclear, there is little reason to think that the mechanism involved would differ much between the adult and pediatric populations. In adults, a remifentanil dose of 0.3 μg·kg^{-1}·min^{-1} induces tolerance when infused for longer periods (a mean period of 4.9 h was tested in the study).[5] In our results, although the mean consumption of fentanyl in group 0.3 over a 24-h period was approximately 20% greater than that in control, the difference was not statistically significant. This outcome could be the result of a type 2 statistical error, given the small size of only 15 patients per group. Furthermore, the dose-dependent difference during 24–48 h period after surgery was less clear than the difference during 0–24 h; fentanyl consumption was approximately 40% greater in the 0.6 and 0.9 groups than the control, but only the results of the 0.6 group were statistically significant. Therefore, additional studies are required to investigate whether prolonged intraoperative infusion of remifentanil at 0.3 μg·kg^{-1}·min^{-1} causes acute tolerance and whether acute tolerance lasts for 24 h or 48 h.

Large doses of remifentanil have been reported to cause significant bradycardia and hypotensive episodes. A bolus dose of 5 μg/kg remifentanil may cause severe hypotension in anesthetized children,[14] and high doses of remifentanil,

either by induction boluses or starting at an infusion rate of greater than 0.5 μg·kg^{-1}·min^{-1}, caused bradycardia and hypotension, findings not observed after infusion of 0.25 μg·kg^{-1}·min^{-1} remifentanil.[23] None of our patients experienced severe bradycardia or hypotension requiring intraoperative treatment, despite receiving relatively higher infused doses of remifentanil, a finding that may have been due to the absence of a loading dose. This finding is in agreement with those of a previous study,[10] which found that intraoperative heart rate was significantly lower in patients administered propofol/remifentanil than in those administered sevoflurane, with no patient treated for hemodynamic depression with atropine, phenylephrine, or ephedrine even when administered high infused doses of remifentanil (0.8 μg·kg^{-1}·min^{-1}). Furthermore, sevoflurane has a positive chronotropic effect, offering some protection against bradycardia.[24]

PNCA is considered a safe and efficacious modality for postoperative pain control in infants and young children.[13,25,26] Although PNCA has become common practice in our institution and none of our patients showed PNCA-associated respiratory compromise, there are still concerns regarding the risk of overdose and the potential for respiratory compromise. Particular attention should be paid to each child's coexisting medical problems and the use of additional sedatives, both of which may decrease the safety margin of the PNCA technique.[13]

There are several limitations and some methodologic issues in this study. First, we acknowledge that the differences in minimum alveolar concentration-hour at higher doses of remifentanil could have affected the results; the higher pain scores recorded at 1 h after surgery in the remifentanil group could have been due to fewer minimum alveolar concentration-hour and increased alertness compared with the saline group. However, it is generally accepted that subanesthetic concentrations of inhalation anesthetics have no hypoalgesic or hyperalgesic effects.[27–29] It is thus unlikely that residual sevoflurane confounded our results. Further studies are needed to investigate the relationship between inhaled anesthesia and the development of acute opioid tolerance. In

addition, due to concerns identified during peer review, the plan of analysis was amended to ensure control for multiple analyses of the primary outcome. Thus, these data were analyzed using a different approach than originally planned.

In summary, an approximately 3-h infusion of 0.3 μg·kg⁻¹·min⁻¹ remifentanil during ureteroneocystomy does not induce tolerance, but the use of 0.6 or 0.9 μg·kg⁻¹·min⁻¹ remifentanil can cause postoperative acute tolerance in young children for 24 h after surgery in an apparently dose-related manner.

References

1. Marsh DF, Hodkinson B: Remifentanil in paediatric anaesthetic practice. Anaesthesia 2009; 64:301–8

2. Sammartino M, Garra R, Sbaraglia F, De Riso M, Continolo N: Remifentanil in children. Paediatr Anaesth 2010; 20:246–55

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

4. Servin FS: Remifentanil: An update. Curr Opin Anaesthesiol 2003; 16:367–72

5. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D, Chauvin M: Acute opioid tolerance: Intraoperative remifentanil increases postoperative pain and morphine requirement. ANESTHESIOLOGY 2000; 93:409–17

6. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M: Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106:49–57

7. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M: Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. ANESTHESIOLOGY 2005; 103:147–55

8. Chu LF, Angst MS, Clark D: Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. Clin J Pain 2008; 24:479–96

9. Davis PJ, Finkel JC, Orr RJ, Fazi L, Mulroy JJ, Woelfel SK, Hannallah RS, Lynn AM, Kurth CD, Moro M, Henson LG, Goodman DK, Decker MD: A randomized, double-blinded study of remifentanil versus fentanyl for tonsillectomy and adenoidectomy surgery in pediatric ambulatory surgical patients. Anesth Analg 2000; 90:863–71

10. Steinmetz J, Holm-Knudsen R, Sørensen MK, Eriksen K, Rasmussen LS: Hemodynamic differences between propofol-remifentanil and sevoflurane anesthesia for repair of cleft lip and palate in infants. Paediatr Anaesth 2007; 17:32–7

11. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A: Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. Paediatr Anaesth 2007; 17:720–33

12. Agrawal D, Feldman HA, Krauss B, Waltzman ML: Bispectral index monitoring quantifies depth of sedation during emergency department procedural sedation and analgesia in children. Ann Emerg Med 2004; 43:247–55

13. Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK: Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. ANESTHESIOLOGY 2010; 113:672–7

14. Ross AK, Davis PJ, Dear Gd GL, Ginsberg B, McGowan FX, Stiller RD, Henson LG, Huffman C, Muir KT: Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg 2001; 93:1393–401

15. 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

16. Roulleau P, Gall O, Desjeux L, Dagher C, Murat I: Remifentanil infusion for cleft palate surgery in young infants. Paediatr Anaesth 2003; 13:701–7

17. Ho ST, Wang JJ, Liaw WJ, Lee HK, Lee SC: Surgical pain attenuates acute morphine tolerance in rats. Br J Anaesth 1999; 82:112–6

18. Jordan B, Devi LA: Molecular mechanisms of opioid receptor signal transduction. Br J Anaesth 1998; 81:12–9

19. Kissin I, Bright CA, Bradley EL Jr: Acute tolerance to continuously infused alfentanil: The role of cholecystokinin and N-methyl-D-aspartate-nitric oxide systems. Anesth Analg 2000; 91:110–6

20. Trafton JA, Abbadie C, Marek K, Basbaum AI: Postsynaptic signaling via the [mu]-opioid receptor: Responses of dorsal horn neurons to exogenous opioids and noxious stimulation. J Neurosci 2000; 20:8578–84

21. Gardell LR, Wang R, Burgess SE, Ossipov MH, Vanderah TW, Malan TP Jr, Lai J, Porreca F: Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. J Neurosci 2002; 22:6747–55

22. Borgland SL: Acute opioid receptor desensitization and tolerance: Is there a link? Clin Exp Pharmacol Physiol 2001; 28:147–54

23. Wee LH, Moriarty A, Cranston A, Bagshaw O: Remifentanil infusion for major abdominal surgery in small infants. Paediatr Anaesth 1999; 9:415–8

24. Piat V, Dubois MC, Johanet S, Murat I: Induction and recovery characteristics and hemodynamic responses to sevoflurane and halothane in children. Anesth Analg 1994; 79:840–4

25. Monitto CL, Greenberg RS, Kost-Byerly S, Wetzel R, Billett C, Lebet RM, Yaster M: The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. Anesth Analg 2000; 91:573–9

26. Choi SH, Lee WK, Lee SJ, Bai SJ, Lee SH, Park BY, Min KT: Parent-controlled analgesia in children undergoing cleft palate repair. J Korean Med Sci 2008; 23:122–5

27. Galinkin JL, Janiszewski D, Young CJ, Klafta JM, Klock PA, Coalson DW, Apfelbaum JL, Zacny JP: Subjective, psychomotor, cognitive, and analgesic effects of subanesthetic concentrations of sevoflurane and nitrous oxide. ANESTHESIOLOGY 1997; 87:1082–8

28. Petersen-Felix S, Arendt-Nielsen L, Bak P, Roth D, Fischer M, Bjerring P, Zbinden AM: Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. Br J Anaesth 1995; 75:55–60

29. Tomi K, Mashimo T, Tashiro C, Yagi M, Pak M, Nishimura S, Nishimura M, Yoshiya I: Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. Br J Anaesth 1993; 70:684–6