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No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia

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We have prospectively assessed whether remifentanil-based anaesthesia is associated with clinically relevant acute opioid tolerance, expressed as greater postoperative pain scores or morphine consumption. Sixty patients undergoing elective gynaecological, non-laparoscopic, surgery were randomly assigned to receive remifentanil (group R, *n*=30) or sevoflurane (group S, *n*=30) based anaesthesia. Postoperative analgesia was provided with morphine through a patient-controlled infusion device. Mean (SD) remifentanil infusion rate in group R was 0.23 (0.10) μg kg^{-1} min^{-1} and mean inspired fraction of sevoflurane in group S was 1.75 (0.70)%. Mean (SD) cumulative morphine consumption during the first 24 postoperative hours was similar between groups: 28.0 (14.2) mg (group R) *vs* 28.6 (12.4) mg (group S). Pain scores, were also similar between groups during this period. These data do not support the development of acute opioid tolerance after remifentanil-based anaesthesia in this type of surgery.

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One of the main problems of remifentanil-based anaesthesia is the rapid disappearance of analgesia after cessation of its infusion. As a result, a preventive analgesic approach with intraoperative i.v. administration of longer acting opioids is frequently used.[1] Nonetheless, large doses of intraoperative morphine or fentanyl in major abdominal surgery under remifentanil-based anaesthesia have failed to provide entirely adequate analgesia.[2 3]

It has been demonstrated that development of acute opioid tolerance to the analgesic effect of opioids occurs in animals.[4–7] However, the occurrence of this phenomena in humans is controversial,[8 9] and even more its clinical relevance.[10 11] The objective of this study was to determine whether remifentanil-based anaesthesia is associated with clinically relevant acute opioid tolerance, expressed as greater postoperative pain scores or morphine consumption, when compared with sevoflurane-based anaesthesia.

Methods

With the approval of the School of Medicine Ethics Committee, we prospectively studied 60 un-premedicated women (ASA I–II, 20–60 yr) undergoing elective gynaecological, non-laparoscopic, surgery. Exclusion criteria included a history of chronic pain, drug abuse, psychiatric disease, obesity (body mass index >30), and the intake of any analgesic drug within 48 h before surgery.

In the operating room before induction of anaesthesia, patients were instructed on how to use the patient-controlled analgesia (PCA) device and the visual analogue scale (VAS) (0=no pain; 100=worst possible pain). The average of three consecutive (5-min interval) non-invasive arterial pressure (NIBP) measurements was considered as the basal value. After standard monitoring (ECG, pulse oximeter, NIBP), anaesthesia was induced with fentanyl 3 μg kg^{-1}, propofol 2 mg kg^{-1}, rocuronium 0.6 mg kg^{-1}, and 2% sevoflurane. The trachea was then intubated. Then, patients were assigned to one of two groups by a table of random numbers generated with the StatView statistical software package. Patients in group R (remifentanil-based anaesthesia) were initially maintained with 0.5% sevoflurane inspired fraction, 50% nitrous oxide in oxygen (4 litres min^{-1}) and remifentanil 0.25 μg kg^{-1} min^{-1}. Patients in group S (sevoflurane-based anaesthesia) were initially maintained with 2% sevoflurane inspired fraction and 50% nitrous oxide in oxygen (4 litres min^{-1}). Arterial pressure was measured every 2.5 min. Increments or decrements of 0.05–0.1 μg kg^{-1} min^{-1} of remifentanil (group R, *n*=30) and 0.5–1.0% sevoflurane (group S, *n*=30) were administered in order to maintain mean arterial pressure within 20% of basal values. All

patients were mechanically ventilated to maintain end tidal carbon dioxide 30–35 mm Hg. Rocuronium 5 mg bolus was given to maintain one or two responses of the adductor pollicis to train-of-four stimulation. Administration of atropine, ephedrine and i.v. fluid administration was left to the anaesthetist's discretion. Neostigmine 1–3 mg and atropine 0.5–1.5 mg were administered at the end of surgery to antagonize residual neuromuscular block, if required. The anaesthetist was not blinded to group assignment.

All patients were extubated in the operating room and transferred to the recovery unit, breathing room air. Postoperative pain was assessed and managed by the staff of the pain service of our hospital (blinded to group assignment). Dynamic pain VAS pain scores were assessed by asking patients to cough in the supine position at 0, 15, 30, 45, 60, 90, 120 min and 24 h after arrival in the recovery unit. Initially, morphine 3 mg bolus doses were given intravenously until VAS pain scores were <50 mm and then the PCA system was connected (bolus dose morphine 1 mg and droperidol 0.2 mg; 8 min lockout). The following postoperative complications were recorded: nausea and vomiting, sedation (evaluated with a four point rating scale: 0=fully awake; 1=somnolent, responsive to verbal commands; 2=somnolent, responsive to tactile stimulation; and 3=asleep, responsive to painful stimulation), hypoxaemia (pulse oximeter saturation <90%, breathing room air), and respiratory depression (ventilatory frequency <10 min^{-1}). Nausea and vomiting were treated with ondansetron 4 mg i.v. Hypoxaemia was treated with 35% oxygen administered by mask.

Patient satisfaction with anaesthesia and pain management was assessed 24 h after surgery with a four point rating scale (1=very satisfied; 2=satisfied; 3=unsatisfied; 4=very unsatisfied).

Mean sevoflurane requirements for each patient were estimated from the vaporizer setting, which was recorded every 15 min. Mean remifentanil requirements were calculated by dividing the total amount of remifentanil infused (mg) by duration of anaesthesia (min) and weight (kg) for each patient.

The sample size was estimated to demonstrate a difference of at least 30% in morphine consumption (based on data of morphine consumption in this type of surgery obtained by the pain service of our hospital) with β=0.90 and α=0.05. The chi-squared and the unpaired Student's *t*-tests were used to study the homogeneity of general data. Two-way ANOVA was used to compare morphine consumption and VAS scores, and Mann–Whitney *U*-test to compare sedation and satisfaction. The level of statistical significance was set at $P<0.05$. All analyses were performed using the StatView statistical software package.

Results

All 60 patients completed the 24-h study. Patient characteristics and intraoperative data were similar in both groups (Table 1). Plasma creatinine concentrations were within normal limits in all patients. Seven well-controlled hypertensive patients were included in our study. Four patients in group S (two atenolol and two nifedipine) and three patients in group R (two enalapril and one atenolol). All these drugs were continued until the day of surgery. No patient required ephedrine and atropine only was used at the end of surgery after neostigmine administration for reversal of neuromuscular block. Mean (SD) remifentanil infusion rate in group R was 0.23 (0.1) $\mu g\ kg^{-1}\ min^{-1}$, and mean sevoflurane inspired fraction in group S was 1.75 (0.7)%. Before the PCA device was connected, morphine loading dose for group S was 11.9 (5.9) and for group R 13.7 (6.6) (NS). There were no differences between groups in pain scores (Fig. 1) and morphine consumption (Fig. 2) during the first 24 postoperative hours. In group R, 21 patients (70%) complained of nausea during the first 6 postoperative hours compared with 13 (43%) in group S ($P<0.05$). No

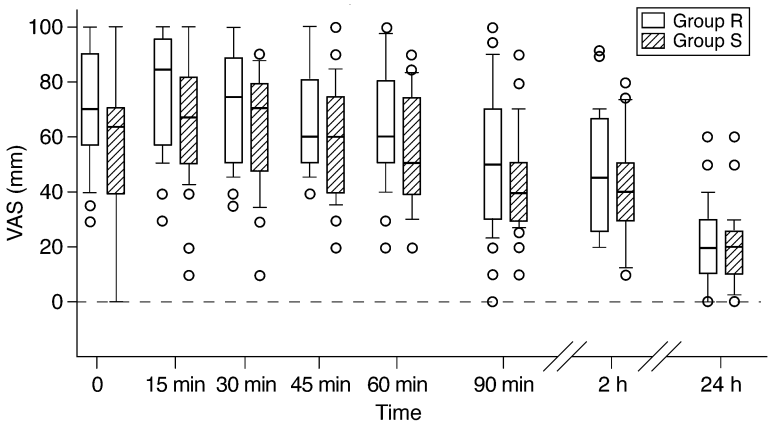

Fig 1 Box plots of the pain scores during the first 24 postoperative hours, for group R and S. The horizontal lines of each box represent the medians and quartiles. The top and bottom of the vertical lines specify the 90th and 10th percentile, respectively. Scores above and below the vertical lines are plotted with circles. No statistically significant difference was noted between groups (P=0.14). ANOVA for repeated measures was used.

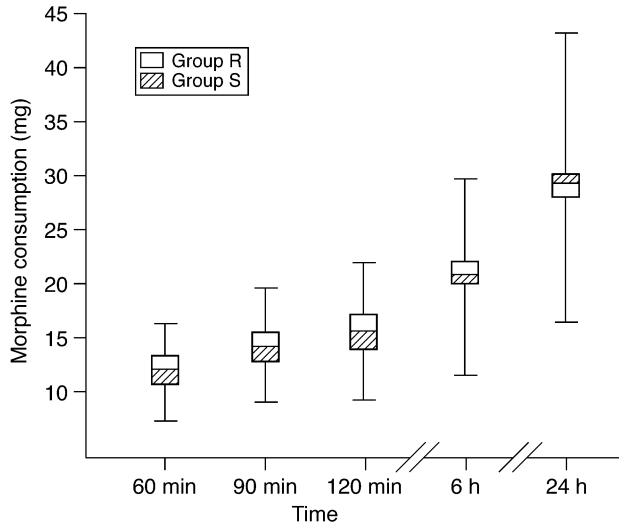

Fig 2 Cumulative morphine consumption in mg (mean (SD)), during the first 24 postoperative hours. No statistically significant difference was noted between groups (P=0.6). ANOVA for repeated measures was used. Group R=remifentanil-based anaesthesia, group S=sevoflurane-based anaesthesia.

Table 1 Patients and surgical characteristics. *Values are mean (SD). H/T/O=hysterectomy, tumour resection, and other. There were no significant differences between groups

	Group R (n=30)	Group S (n=30)
Age (yr)*	45 (8)	44 (9)
Weight (kg)*	67 (12)	65 (13)
Height (cm)*	158 (7)	160 (7)
ASA (I/II)	(7/23)	(12/18)
Type of surgery (H/T/O)	(24/3/3)	(17/7/6)
Duration of surgery (min)*	98 (45)	96 (37)
Duration of anaesthesia (min)*	116 (34)	118 (40)

Table 2 Incidence of nausea and vomiting

	Group R (n/%)	Group S (n/%)	P value
0–6 h			
Nausea	21/70	13/43	0.037
Vomiting	6/20	6/20	
0–24 h			
Nausea	21/70	14/47	0.06
Vomiting	7/23	7/23	

differences were found with respect to nausea and vomiting during the period 0–24 h (Table 2). Seven (23%) patients in group S and eight (27%) in group R suffered hypoxaemia during the first 2 postoperative hours (NS) and all responded favourably to 35% oxygen. No patient had a ventilatory frequency <10 min^{-1}. No significant differences were found between groups with respect to sedation scores and level of satisfaction (Table 3).

Table 3 Patient satisfaction. There were no significant differences between groups

	Group R (n/%)	Group S (n/%)
Anaesthesia satisfaction		
Very satisfied	19/65	24/78
Satisfied	7/23	5/18
Unsatisfied	1/4	0/0
Very unsatisfied	2/8	1/4
Pain management satisfaction		
Very satisfied	22/73	23/75
Satisfied	7/23	6/21
Unsatisfied	1/4	1/4
Very unsatisfied	0/0	0/0

Discussion

These results show that remifentanil infusion during general anaesthesia in this type of surgery is not associated with clinically relevant evidence of acute opioid tolerance.

Some recent studies have suggested that acute opioid exposure to large doses of fentanyl[13] or remifentanil[10] during surgery can be associated with a clinically important tolerance effect to opioid analgesia, manifested by greater pain scores or opioid consumption during the postoperative period. Moreover, delayed hyperalgesia from opioid exposure has been proposed as another possible explanation for the apparently worse pain and greater opioid consumption.[10 14 15] Both acute opioid tolerance and delayed hyperalgesia seem to share some similar molecular mechanisms which involve the activation of excitatory glutamate receptors of the *N*-methyl-D-aspartate (NMDA) system in the central nervous system.[15 16] However, many other mechanisms and systems are probably involved in the development of opioid tolerance.[17]

Evidence is controversial in humans. Gustorff,[8] using electrical pain stimulation in a placebo-controlled volunteers study, did not find early tolerance during 3 h of 0.08 μg kg^{-1} min^{-1} remifentanil infusion. Nonetheless, Vinik and Kissin[9] showed in volunteers that the analgesic effect of remifentanil 0.1 μg kg^{-1} min^{-1} was maximum at 60–90 min and then progressively declined, reaching 25% of the peak value after 3 h of constant-rate infusion. The main weakness of this study was the lack of a control group to rule out a 'learning or customing' effect to painful stimulation. However, even though the study by Vinik and Kissin did not adequately reflect the complex perioperative clinical condition, anaesthesia duration might be a key factor influencing the development of acute opioid tolerance.[4] As a result, it could be that, in spite of the higher doses of remifentanil used in our study, longer anaesthesia might have led to the development of clinically significant acute opioid tolerance effect. This idea is reinforced by Guignard's study,[10] which showed, in patients who had received remifentanil-based anaesthesia for surgery averaging 4 h, their demand for morphine in the first 24 h was

nearly twice that of those who received desflurane-based anaesthesia.

Intensity of pain might be another factor that can influence the appearance of acute opioid tolerance. Using two animal models (upper and lower abdominal surgery), Ho and colleagues[18] explored the effect of postoperative pain on the prevention of acute tolerance to morphine antinociception in rats. They found that both types of surgery were associated with significant attenuation of acute opioid tolerance after i.v. infusion of morphine when compared with a control group. Similar results have been found in other animal models.[19] In our study, patients of both groups had high pain scores during the first 2 postoperative hours and this could have precluded the appearance of a clinically detectable opioid tolerance effect.

In animals, higher doses of morphine are more likely to produce acute opioid tolerance than lower doses.[4] Thus, the slightly higher remifentanil infusion rate in Guignard's study compared with ours cannot be ruled out as an additional explanation for the different results between both studies. With respect to postoperative complications and patient satisfaction, both anaesthesia regimens seem to be equally good. The higher rates of nausea observed in group R need to be confirmed because we do not have a record of fluid and neostigmine administration to be sure that both groups are comparable in this regard.

There is still a lot to learn with respect to the occurrence of acute tolerance, delayed hyperalgesia and pre-emptive opioid effect, their molecular mechanisms, their interactions and their clinical relevance in the perioperative period. However, based on our results we can conclude that remifentanil-based anaesthesia in this type of surgery is not associated with greater postoperative pain scores or morphine requirements when compared with sevoflurane-based anaesthesia. Clinical evidence of acute opioid tolerance is not supported by our results.

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