Background: Remifentanil is commonly used to replace nitrous oxide in general anesthesia to avoid the side effects of the latter. However, there are reports that intraoperative remifentanil infusion can lead to acute opioid tolerance. In this study, the authors tried to determine the dose of remifentanil comparable in efficacy to 70% nitrous oxide and to evaluate its effect on postoperative pain and morphine consumption after colorectal surgery using isoflurane anesthesia.

Methods: Sixty adult patients undergoing open colorectal surgery were randomly assigned to receive either remifentanil or 70% nitrous oxide along with isoflurane anesthesia. After morphine analgesia titration in the postanesthesia care unit, patient-controlled analgesia was commenced. Morphine consumption and pain were scored at rest and during cough or movement for 24 h.

Results: The mean remifentanil infusion rate was 0.17 μg/kg·min⁻¹. The median visual analog pain score on arrival in the postanesthesia care unit was 1 (0–10) in the nitrous oxide group and 3 (0–9) in the remifentanil group (P < 0.05). Otherwise, there was no difference in pain scores at 5, 10, and 15 min and no difference in the total morphine consumption during the stay in the postanesthesia care unit. The two groups had similar total morphine consumption in the first 24 h and pain scores at rest and during movement. The incidence of postoperative nausea and vomiting was 10% in both groups. There was no difference in the sedation scores.

Conclusion: The substitution of 70% nitrous oxide with remifentanil at a mean infusion rate of 0.17 μg/kg·min⁻¹ for colorectal surgery did not affect postoperative opioid consumption.

NITROUS oxide, along with oxygen, is a commonly used carrier gas for volatile inhalational anesthetic agents. It has the advantage of providing analgesia and reducing the minimal anesthetic concentration of the anesthetic gases, and its low blood/gas solubility facilitates a relatively fast onset and offset. However, it is increasingly recognized to be associated with a number of undesirable effects, such as pollution, neurotoxicity, and megaloblastic anemia.1–3 Remifentanil, a potent, ultrashort-acting opioid analgesic that avoids these problems, is a potential replacement for nitrous oxide and is now commonly used as an analgesic agent during induction and maintenance of anesthesia.4 It can be given in very high doses during surgery without fear of postoperative respiratory depression.5,6 After surgery, it must be replaced by longer-acting opioids to provide postoperative analgesia.7–9 However, there have been reports suggesting that postoperative analgesic requirements in patients after remifentanil-based anesthesia are greater than expected.10–12

Acute opioid tolerance, manifest by increasing dose requirements to produce the same pharmacodynamic effect, could account for this phenomenon. There is evidence that high-dose infusion of a short-acting opioid in painful and long surgery may induce tolerance more rapidly than would be expected with a long-acting drug.13–19 This study was designed to investigate whether such tolerance is likely to occur when remifentanil is used as a substitute for 70% nitrous oxide in a typical intermediate-duration abdominal operation.

Materials and Methods

After approval from our institutional ethics review board (University of Hong Kong, Hong Kong SAR, China), we studied 60 adult patients undergoing open colorectal surgery in a large teaching hospital. Patients were excluded from the study if they had known allergy to remifentanil or morphine, had abnormal preoperative renal or hepatic function, regularly took analgesics or had a history of drug or alcohol abuse, were unable to have a body weight that was not within 20% of ideal, or had consumed any kind of opioid within the past 24 h, had a history of drug or alcohol abuse, were unable to use patient-controlled analgesia, were less than 18 yr old, or had a body weight that was not within 20% of ideal.

During the preoperative anesthetic assessment, patients were instructed on the use of patient-controlled analgesia, and the visual analog pain scale (VAS), with 0 signifying no pain and 10 being the most severe pain imaginable. No premedication was given before surgery.

During induction, patients breathed oxygen through a standard anesthetic breathing circuit. Anesthesia was induced with 2–3 mg/kg propofol and 1.5 μg/kg fentanyl. An atracurium bolus and infusion was used to induce and maintain neuromuscular block at a rate determined by the response to a peripheral nerve stimulator.

Patients were randomly assigned into one of two groups for maintenance of anesthesia. Randomization was based on computer-generated codes maintained in sequentially numbered, opaque envelopes. The enve-

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lopes were opened after induction of general anesthesia. The nitrous oxide group received isoflurane at an end-tidal concentration of 0.5–1.5% (according to clinical requirement), delivered with 70% nitrous oxide in oxygen. This was the current “normal standard of care” for these patients in this hospital. The remifentanil group also received isoflurane in the same way but delivered in an oxygen-air gas mixture. This group of patients also received an intravenous infusion of remifentanil at 0.05–0.5 μg·kg⁻¹·min⁻¹.

All patients received 0.15 mg/kg morphine intravenously before skin incision. The dose of anesthetic drugs was adjusted when insufficient anesthesia was suspected. Insufficient anesthesia was suspected when a heart rate exceeding preinduction values by 15% and/or a systolic blood pressure exceeding baseline values by 20% for at least 1 min, presence of patient movement, coughing, tearing, or sweating was observed.

At skin closure, all anesthetic drugs were discontinued, and residual neuromuscular blockade was antagonized with 40–60 μg/kg intravenous neostigmine and 15–20 μg/kg intravenous atropine. The trachea was extubated when patients responded appropriately to verbal commands, the spontaneous respiratory rate exceeded 10 breaths/min, and there was full return of muscle strength according to peripheral nerve stimulation. Observation and management in the postanesthesia care unit (PACU) and subsequently the ward was conducted by nurses and acute pain team members who were not involved in the study and were unaware of the patients’ intraoperative randomization.

For the first 15 min after arrival in the PACU, pain was evaluated every 5 min by the PACU nurse using a behavioral score defined as follows: 0 = calm patient with no verbal or behavioral manifestation of pain; 1 = behavioral or verbal expression of pain; 2 = intense behavioral or verbal manifestation (crying, extreme agitation). Pain was also evaluated using a VAS (0 = no pain; 10 = worst imaginable pain).

Morphine titration commenced when the patient reported a VAS score greater than 3. Morphine boluses of 2 mg were given every 3 min until a VAS score of 3 or less was achieved. Fifteen minutes after arriving in the PACU, patients were connected to a patient-controlled analgesia device set to deliver 1 mg morphine as an intravenous bolus, with a lockout interval of 5 min and no background infusion or limits. This regimen of patient-controlled analgesia was continued when the patient was discharged back to the general ward.

### Measurement

We measured and compared patient demographic data, duration of surgery, isoflurane consumption, remifentanil consumption in the remifentanil group, opioid side effects (nausea and vomiting, pruritus, respiratory depression), behavioral score every 4 h, morphine consumption in the first hour and after 24 h, and VAS scores every 4 h at rest and during cough or movement. Isoflurane consumption was measured by calculating the area under the curve of end-tidal concentration over time.

### Data Analysis

Our acute pain database indicated a mean first 24-h morphine consumption of 30 mg for this type of surgery in healthy adults. To have an 80% chance of detecting a 20% increase in opioid consumption, by our calculations, at a level of P < 0.05, 30 patients were needed in each group.

Demographic data were assessed using unpaired t test, chi-square test, and Mann–Whitney U test. Remifentanil consumption, cumulative postoperative morphine consumption, VAS score for pain, and end-tidal isoflurane concentrations were analyzed with the Mann–Whitney U test. The time to first postoperative request for morphine was assessed by log-rank test.

Behavioral pain scores, postoperative pain, and sedation scores were analyzed with chi-square test or chi-square test with continuity correction as appropriate.

### Results

All 60 patients completed the study. There were no significant differences in the demographic data (table 1), isoflurane consumption values, or operation times. The mean remifentanil infusion rate (calculated from total dose of remifentanil, body weight, and duration of administration) was 0.17 μg·kg⁻¹·min⁻¹. There was no difference between the behavior scores in the first 15 min in the PACU (fig. 1). On arrival at the PACU, the behavioral score was 0 in 60% of the patients in the nitrous oxide group and 40% of the patients in the remifentanil group. The VAS score was 1 (0–3) in the nitrous oxide group and 3 (0–9) in the remifentanil group. After 15
min in the PACU, the behavioral score was 0 in 25% of the patients in both groups. The VAS score was 5 (0–10) in the nitrous oxide group and 5 (2–10) in the remifentanil group, which was not significantly different. There was no difference in the total morphine consumption during the stay in the PACU (fig. 2).

The two groups had similar total morphine consumption in the first 24 h and VAS scores at rest and during movement (figs. 3 and 4). The reported incidence of postoperative nausea and vomiting was 10% in both groups. There was no difference in the sedation scores.

**Discussion**

Nitrous oxide has been used clinically in anesthesia for more than 150 yr. Although it is a relatively weak anesthetic, it can reduce the minimum alveolar concentration (MAC) of volatile anesthetic agents. It is also an effective analgesic. This effect may be related to its anti-N-methyl-D-aspartate receptor properties. Many anesthesiologists have stopped using nitrous oxide in their daily practice because of concern about its ad-

![Fig. 1. Time course of the distribution of the behavioral pain scores in the first 15 min in the postanesthesia care unit (PACU). N₂O = nitrous oxide.](Image)

![Fig. 2. Box plots of the pain scores during the first 15 min in the postanesthesia care unit (PACU). The top and bottom lines of the box show the 25th and 75th percentiles, respectively. The solid slides inside the box indicate the medians (some of the medians are equal to the 25th or 75th percentiles, so the two lines overlap). The whisker caps show the 10th and 90th percentiles (some 25th percentiles equal the 10th percentiles and some 75th percentiles equal the 90th percentiles, so the whisker caps have been omitted). The circles are the observations outside the 10th or the 90th percentiles. N₂O = nitrous oxide; VAS = visual analog scale.](Image)

![Fig. 3. Box plots of pain during the first 24 h, at rest (top) and during movement (bottom). N₂O = nitrous oxide; VAS = visual analog scale.](Image)
verse effects. 20,27,28 In colorectal surgery, it may also cause bowel distention. 29 The anti-N-methyl-D-aspartate receptor activity of nitrous oxide can cause a neurotoxic vacuole reaction in neurons of the posterior cingulated/ retrosplenial cortex. 27 These neurotoxic effects, including the cell death reaction, depend on the duration of exposure, and the clinical significance has been controversial, but since the introduction of short-acting opioids such as remifentanil, there is less justification for its continued use. 20

However, there are reports that intraoperative remifentanil infusion can lead to acute opioid tolerance. Both animal and human studies support the possibility of rapid development of tolerance to short-acting opioids such as alfentanil. 13–19,30 Opioids with a short duration of action tend to be associated with a faster development of tolerance. 13,17 Given the pharmacokinetic properties of remifentanil, rapid development of opioid tolerance would be expected.

Tolerance to remifentanil has been demonstrated after a 60- to 90-min infusion in volunteers 40 and was found to be related to the dose used. Guignard et al. showed a higher pain score and increased postoperative morphine consumption in patients having 0.3 μg · kg⁻¹ · min⁻¹ remifentanil infusion in a 4-h major abdominal operation compared with 0.1 μg · kg⁻¹ · min⁻¹. 19 A 0.3-μg · kg⁻¹ · min⁻¹ remifentanil infusion rate is a reasonably high dose because it reduces the MAC of isoflurane by approximately 80%. 30 Another study, using a dose of 0.23 μg · kg⁻¹ · min⁻¹ for surgery and lasting around 100 min, did not show any difference in pain scores or postoperative morphine consumption from a placebo group. 34 Dose is also a significant factor determining the development of acute tolerance. 19,32 Recently, it was shown that remifentanil at a computer-controlled, pharmacokinetic-based target concentration of 3.1 ± 1.2 ng/ml can cause withdrawal hyperalgesia in volunteers when capsaicin is used to induce mechanical hyperalgesia and allodynia. 35 However, in another volunteer study, there was no tolerance to a 3-h, 0.08-μg · kg⁻¹ · min⁻¹ remifentanil infusion, using electrical potential as the pain stimulus. 34

Duration of opioid infusion is another crucial factor determining the development of acute tolerance. Vinik and Kissin 18 showed a declining analgesic effect with a constant 0.1-μg · kg⁻¹ · min⁻¹ remifentanil infusion. The analgesic effect reached its maximum at 60–90 min, and only a quarter of the original efficacy was left at the end of the third hour of infusion. The development of tolerance was also dose related in this study because with the same 3-h infusion time, a higher infusion rate was associated with more acute tolerance.

In this study, we substituted 70% nitrous oxide with a remifentanil infusion for the maintenance of intermediate duration anesthesia. An overall average 0.17-μg · kg⁻¹ · min⁻¹ remifentanil infusion was used for surgery with a mean duration of 170 min. We found that this dose was as effective as 70% nitrous oxide in a short duration phase and no difference in postoperative morphine consumption or pain scores, either in the early recovery phase or during the subsequent 24 h.

In clinical practice, opioid tolerance will be manifest by higher pain scores and greater morphine consumption. We did not demonstrate the presence of acute opioid tolerance with our use of remifentanil in this study. The contrast with the findings of Guignard et al. is possibly a result of the higher remifentanil infusion rate used in that study for a longer duration.

We conclude that a mean remifentanil infusion rate of 0.17 μg · kg⁻¹ · min⁻¹ is as effective as 70% nitrous oxide for attenuating intraoperative pain in colorectal surgery. This infusion rate of remifentanil did not lead to the development of acute opioid tolerance postoperatively.

References


intravenous anaesthesia with remifentanil and propofol. *Anesthesiology* 1997; 87:235–43