Intraoperative Remifentanil Infusion Does Not Increase Postoperative Opioid Consumption Compared with 70% Nitrous Oxide


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 postanaesthesia 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⁻¹ · min⁻¹. The median visual analog pain score on arrival in the postanaesthesia 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 postanaesthesia 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⁻¹ · minute⁻¹ for colorectal surgery did not affect postoperative opioid consumption.
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 · 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

### Table 1. Patient Demographic and Operative Data

<table>
<thead>
<tr>
<th></th>
<th>Nitrous Oxide Group (n = 30)</th>
<th>Remifentanil Group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62.1 (12.4)</td>
<td>58 (16.1)</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>12:18</td>
<td>15:15</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>55.6 (10.7)</td>
<td>55.8 (12.6)</td>
</tr>
<tr>
<td>ASA, I/II/III</td>
<td>6/24/0</td>
<td>14/15/1</td>
</tr>
<tr>
<td>Duration of anesthesia, min</td>
<td>167 (97–327)</td>
<td>162.5 (52–448)</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>155 (60–288)</td>
<td>133 (21–297)</td>
</tr>
<tr>
<td>Area under the curve of isoflurane usage, %·min</td>
<td>76 (28.2–170.4)</td>
<td>58.9 (13.7–204.5)</td>
</tr>
<tr>
<td>Type of surgery, anterior posterior resection/low anterior resection/ colectomy</td>
<td>10/11/9</td>
<td>10/7/13</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), median (range), or numbers (percent). No significant differences \( P > 0.05 \).

ASA = American Society of Anesthesiologists (physical status).
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.

**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.

**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.
Tolerance to remifentanil has been demonstrated after a 60- to 90-min infusion in volunteers and was found to be related to the dose used. Guignard et al. showed a 60- to 90-min infusion in volunteers and was found to be related to the dose used. Guignard et al. showed that the dose was as effective as 70% nitrous oxide intraoperatively. There was 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 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) 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


Fig. 4. Total morphine consumption in the first 24 h. Data are presented as median [range]. N\textsubscript{2}O = nitrous oxide; PACU = postanesthesia care unit.
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11. Fletcher D, Pinaud M, Scherpereel P, Clyti N, Chauvin M: The efficacy of intravenous 0.15 versus 0.25mg/kg intraoperative morphine for immediate post-operative analgesia after remifentanil-based anaesthesia for major surgery. Anesth Analg 2000; 90:666–71


