Can Remifentanil Replace Nitrous Oxide During Anesthesia for Ambulatory Orthopedic Surgery with Desflurane and Fentanyl?

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BACKGROUND: The administration of nitrous oxide (N₂O) may be associated with side effects and toxicities. Remifentanil shares characteristics with N₂O, including MAC-reducing and antinociceptive effects and a rapid decrease in clinical effect when discontinued. We compared the outcome after ambulatory orthopedic surgery with desflurane and fentanyl supplemented with clinically equivalent doses of either N₂O or remifentanil.

METHODS: Seventy patients undergoing ambulatory orthopedic surgery were studied. Thirty-five received 66% N₂O and 35 received remifentanil 0.085 μg · kg⁻¹ · min⁻¹ in addition to desflurane, titrated to a bispectral index (BIS) value of 50, and a fentanyl infusion. The principle outcome measure was time to awakening to verbal stimulation. Secondary outcome measures included neuropsychological testing, time to orientation, hemodynamic values, pain and nausea visual analog scores, discharge times, and satisfaction scores. The average end-tidal desflurane concentration and fentanyl effect-site concentration were determined.

RESULTS: The median time (interquartile range) to awakening to verbal stimulation, 3.0 min (3.0–5.0 min) in the remifentanil group and 4.6 min (3.0–8.1 min) in the N₂O group was not significantly different. Median time to orientation was significantly faster in the remifentanil group: 6.0 min (5.0–8.5 min) compared with 8.0 min (5.0–12.8 min) for the N₂O group. There was no difference between groups in desflurane or fentanyl administration, neuropsychological testing, or any other outcome measure.

CONCLUSIONS: This study demonstrates that a remifentanil infusion of 0.085 μg · kg⁻¹ · min⁻¹ may be substituted for 66% N₂O during desflurane/fentanyl anesthesia without any clinically significant change in outcome.

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were time to orientation, performance on neurophysiologic (NP) tests during recovery, pain and nausea visual analog scale (VAS) scores, administration of medication to treat pain and nausea, time to discharge readiness, and satisfaction scores at time of discharge and at 1 day postoperatively.

**METHODS**

**Determination of Clinical Equivalency**

Lang et al. demonstrated that the whole blood concentration of remifentanil needed to decrease the MAC of isoflurane by 50% was 1.37 ng/mL, and MAC was decreased by 60% at 2 ng/mL, which is a similar degree of MAC reduction expected by 66% $N_2O$. We assumed a similar degree of desflurane MAC reduction and used STANPUMP (Steven Shafer, Palo Alto, CA; simulation mode) to model a remifentanil (Minto kinetics) bolus and infusion that would produce a stable whole blood concentration of 2 ng/mL in <5 min. This time course paralleled the increase in $N_2O$ seen with the gas flows planned for the study, 1 L/min $O_2$ and 2 L/min $N_2O$. It was determined that a bolus of remifentanil 0.7 µg/kg and infusion of 0.085 µg·kg$^{-1}$·min$^{-1}$ produced the desired blood concentration.

**Clinical Protocol**

After approval by the hospital IRB, 70 patients were recruited for the study and signed an informed consent. Inclusion criteria were age between 18 and 55 yr, orthopedic surgery of 1–2 h expected duration, and at 1 day postoperatively.

Seventy patients were randomized by envelope to either the $N_2O$ (NITROUS) or the remifentanil (REMI) groups. In the preoperative area, patients were familiarized with the pain and nausea VAS and a blinded research assistant administered the initial NP tests (Psychological Assessment Resources, Lutz FL), which included 10-s finger tap, digit-symbol substitution test, and color trail-making test Part A.

In the operating room, routine clinical monitors were applied including a BIS XP™ sensor (Aspect Medical System, Newton MA, version 3.23, 15 s smoothing) applied according to the manufacturer’s specifications. Midazolam 0.05 mg/kg was given for anxiolysis, and beginning 5 min later, three heart rate and arterial blood pressure measurements were obtained during the subsequent 3 min. These were averaged and served as baseline hemodynamic measurements. After administration of oxygen, general anesthesia was induced with propofol 1.5 mg/kg and fentanyl 1.5 µg/kg. A laryngeal mask airway (LMA) was inserted without neuromuscular blockade and a fentanyl infusion of 0.75 µg·kg$^{-1}$·h$^{-1}$ was started.

An unblinded anesthesiologist then began the study medication. For those in the NITROUS group, the flow meters were set to oxygen 1 L/min, $N_2O$ 2 L/min and were covered, and the patient received a sham saline bolus and infusion. For patients in the REMI group flow meters were set to oxygen 1 L/min, air 2 L/min and were covered, and the patient received a remifentanil bolus 0.7 µg/kg, followed by infusion of 0.085 µg·kg$^{-1}$·min$^{-1}$. The MAC calculation displayed on the Datex S/5 monitor (Datex-Ohmeda, Helsinki, Finland) was also covered for all patients. Desflurane 4% was begun and ventilation was controlled to maintain an end-tidal carbon dioxide of 32 mm Hg. Regional anesthetics were not used.

During the procedure, a second, blinded anesthesiologist made the decisions about clinical care based on the following variables: desflurane was adjusted to maintain a BIS value of 50; a fentanyl bolus 0.2 µg/kg was administered as often as every 2 min for heart rate or arterial blood pressure more than 20% above baseline, tearing, sweating, or patient movement. During surgery, the heart rate, BIS values, and end-tidal desflurane concentration were recorded by a computer, every second using RUGLOOP (written by Michel Straus and Tom DeSmet, University of Ghent, Belgium, more information at http://www.anesthesia-uzgent.be); arterial blood pressure was determined every minute. The area under the end-tidal desflurane concentration curve was determined from induction to drug discontinuation. BIS and hemodynamic data were averaged each minute using LABGRAB (also written by Michel Straus and Tom DeSmet) and determined from skin incision until drug discontinuation. For each patient, the percent change in average hemodynamic data from baseline to the surgical period was calculated.

At the conclusion of the surgery, the surgeon injected 30 mL 0.25% bupivacaine intraarticularly, the first anesthesiologist discontinued the desflurane, fentanyl, and study drugs simultaneously and administered ketorolac 60 mg IV. No attempt was made to titrate or decrease the anesthetic dosing during skin closure. The second, blinded anesthesiologist determined time to eye opening to verbal stimulation, LMA removal, and orientation to date and place. Verbal stimulation was achieved by loudly calling the patient’s name every 20 s and the LMA was removed when the patient followed commands and had a respiratory rate of at least 8 breaths per minute. In the postanesthesia care unit (PACU) at 20, 40, and 60 min after awakening, 100-mm VAS pain and nausea scores were recorded and a blinded research assistant repeated the NP tests. Medication administered for nausea and pain was recorded. Pain was treated with fentanyl 25 µg every 5 min, until VAS pain was below 30 mm, and nausea was treated with ondansetron 4 mg. Time spent in Stage 1 (acute postoperative care) and Stage 2 (subacute care, preparation for discharge) PACU were determined, and discharge from each unit was based on the usual clinical criteria. At the time of discharge...
patient discharge from the hospital, a series of satisfaction questions was administered and the questions were repeated by telephone 24 h later.

The fentanyl infusions and all fentanyl boluses, including the induction dose, were simulated post hoc using STANPUMP in simulation mode (Shafer kinetics). For each patient, the area under the concentration–time curve was determined from induction to drug discontinuation.

**Statistical Analysis**

Parametric data were analyzed by unpaired t-testing; nonparametric data were compared with Mann–Whitney rank-sum analysis. Awakening and orientation time were compared by Kaplan–Meier survival analysis. NP data were analyzed by Kruskal–Wallis repeated measures ANOVA. The proportion of patients between groups was compared by χ² analysis. A P value of 0.05 was considered significant. SigmaStat version 3.0 (Systat, Port Richmond, CA) was used for statistical analysis.

**Power Analysis**

The study was powered to detect a difference in time of 2 min to awakening between the groups. Using a group standard deviation, from pilot data, of 4 min with an [alpha] of 0.05 and a power of 0.8, we determined that 32 patients per group were required. We chose to enroll 35 per group to allow for dropouts or technical problems.

**RESULTS**

Thirty-five patients were enrolled in each group. One patient in the REMI group was excluded because the remifentanil syringe became disconnected from the IV line sometime during the case. There was no difference in patient demographics between the groups, as displayed in Table 1. Hemodynamic differences between the groups are displayed in Table 2. The baseline resting heart rate and systolic blood pressure were greater in the REMI group than in the NITROUS group. During surgery, there were no differences between the groups but there was a larger decrease in heart rate between baseline and surgery in the REMI group than measured in the NITROUS group.

Data regarding the surgery and anesthesia dosing are presented in Table 3. Case time, desflurane usage (area under the concentration–time curve), and fentanyl usage (total delivery, infusion rate [baseline infusion plus boluses] in μg·kg⁻¹·min⁻¹), median number of boluses per hour, or area under the concentration–time curve were not significantly different. Seven patients in the REMI group and six in the NITROUS group required no

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**Table 1.** Demographics

<table>
<thead>
<tr>
<th></th>
<th>REMI (n = 34)</th>
<th>NITROUS (n = 35)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>34.6 ± 9.9</td>
<td>33.0 ± 8.8</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>26.4 (3.2)</td>
<td>25.8 (2.7)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>173 (9)</td>
<td>175 (10)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>80 (15)</td>
<td>78 (13)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Gender (M:F)</strong></td>
<td>23:11</td>
<td>25:10</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Surgeries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACL reconstruction</td>
<td>15</td>
<td>17</td>
<td>N.S.</td>
</tr>
<tr>
<td>Shoulder arthroscopy</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ORIF ankle</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ORIF wrist</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ORIF patella</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ankle arthroscopy</td>
<td>1</td>
<td>2</td>
<td></td>
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</tbody>
</table>

Mean (so). BMI = body mass index; ACL= anterior cruciate ligament; ORIF= open reduction, internal fixation.

**Table 2.** Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>REMI (n = 34)</th>
<th>NITROUS (n = 35)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>77.5 (12.7)</td>
<td>69.9 (9.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Surgery</td>
<td>61.8 (10.0)</td>
<td>60.9 (9.3)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−21% (−26% to −12%)</td>
<td>−17% (−21% to −2%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>129.6 (12.5)</td>
<td>123.1 (10.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>Surgery</td>
<td>121.6 (16.3)</td>
<td>120.8 (16.2)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−8% (−14% to 3%)</td>
<td>−3% (−11% to 7%)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75.5 (8.4)</td>
<td>75.3 (9.5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Surgery</td>
<td>71.5 (11.4)</td>
<td>72.7 (9.9)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−4% (−16% to 3%)</td>
<td>−4% (−14% to 6%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Baseline and surgery values are mean (so). Change from baseline is median (25th percentile–75th percentile).
The scatter plot of average desflurane and average calculated effect-site fentanyl concentration is displayed in Figure 1. The intraoperative BIS values from incision until drug discontinuation (mean ± SD) were also similar: 47.8 ± 3.6 and 48.3 ± 2.8 (N.S.), for the REMI and NITROUS groups, respectively.

The median (interquartile range) time to eye opening on verbal command was 3.0 min (3.0–5.0 min) in the REMI group and 4.6 min (3.0–8.1 min) in the NITROUS group; the difference was not statistically significant. One patient in the REMI group took 19 min to awaken, 10 min longer than the patient with the next longest time. When this patient was excluded as an outlier, the awakening time in the REMI group was significantly faster ($P = 0.021$). The median (interquartile range) to orientation was 6.0 min (5.0–8.5 min) in the REMI group 8.0 min (5.0–12.8 min) in the NITROUS group, a statistically significant difference ($P = 0.034$). The survival curve of those not oriented is displayed in Figure 2.

Results of the NP tests are shown in Figure 3. At no time point was there a significant difference between the two groups. For each test, performance was better 60 min after eye opening compared with 20 min. In the NITROUS group, the 40-min performance was significantly better than the 20-min performance in the digit symbol substitution test, and the 60-min scores were significantly better than the 40-min scores on the color trail-making test.

There were no differences between the groups for the VAS pain and nausea scores at 20, 40, or 60 min as shown in Table 4. The percentage of patients treated for nausea (26% in the REMI group and 40% in the NITROUS group) was not statistically different, nor was the percentage of patients treated for pain (63% in the REMI group and 54% in the NITROUS group). Time to discharge eligibility from Stage 1 and Stage 2 PACU was also not statistically different. Stage 1 was 100 ± 43 min and 88 ± 34 min, and Stage 2 was 103 ± 43 min and 102 ± 49 min for the REMI and NITROUS groups, respectively.

VAS satisfaction scores at time of discharge are shown in Table 4. There was no significant difference between the groups. There was also no difference in satisfaction scores obtained from the next day follow-up phone call (data not shown).
DISCUSSION

This study demonstrates that, during ambulatory orthopedic surgery with a desflurane–fentanyl general anesthetic, an infusion of remifentanil 0.085 μg·kg⁻¹·min⁻¹ compared with 66% N₂O resulted in faster time to orientation with no differences in other recovery measurements, including NP testing.

N₂O use is associated with unwanted side effects, which include distention of gas-filled cavities and postoperative nausea and vomiting.¹⁰ The greater potential consequence of N₂O exposure is inhibition of the enzyme methionine synthetase.⁹ The clinical implications of this inhibition are not entirely clear but have been associated with hematological and neurological toxicity,¹¹–¹⁴ as well and possible effects on the fertility of operating room personnel.¹⁵ N₂O use has also been associated with increased myocardial ischemia after carotid endarterectomy, probably related to the N₂O-induced increase of homocysteine.¹⁶ In contrast, N₂O has been shown to have N-methyl-D-aspartate receptor antagonist properties in rats and could potentially benefit the prevention of tolerance to opioids.¹⁷ Ultimately, each practitioner has to decide how he or she interprets the relative risks and benefits of N₂O use.

Practitioners, who choose to eliminate N₂O from their practice, need to reconfigure their anesthetic technique to replace its contribution to the anesthetic state. One strategy is to increase the delivery of the primary anesthetic. Arellano et al.¹⁸ reported that elimination of N₂O in a propofol–fentanyl anesthetic resulted in an increase in propofol administration of 15% in patients undergoing termination of pregnancy and 25% in gynecological laparoscopy patients with no change in discharge times. When using a volatile anesthetic, one may replace N₂O by increasing volatile anesthetic delivery. With more soluble anesthetics, such as isoflurane, such an increase would lead to prolonged emergence. With less soluble anesthetics, such as desflurane or sevoflurane, the time for patients’ brain concentration to decrease below MAC-awake would not be significantly prolonged. However, there are important recovery milestones, such

Table 4. Pain, Nausea, and Satisfaction Visual Analog Scores

<table>
<thead>
<tr>
<th></th>
<th>REMI (n = 34)</th>
<th>N₂O (n = 35)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>0 (0–22)</td>
<td>4 (0–24)</td>
<td>N.S.</td>
</tr>
<tr>
<td>40 min</td>
<td>7 (0–28)</td>
<td>4 (0–26)</td>
<td>N.S.</td>
</tr>
<tr>
<td>60 min</td>
<td>3 (0–31)</td>
<td>5 (0–27)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>40 (15–36)</td>
<td>40 (17–58)</td>
<td>N.S.</td>
</tr>
<tr>
<td>40 min</td>
<td>40 (24–57)</td>
<td>42 (23–56)</td>
<td>N.S.</td>
</tr>
<tr>
<td>60 min</td>
<td>28 (7–55)</td>
<td>32 (23–50)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pain satisfaction</td>
<td>80 (51–100)</td>
<td>89 (72–100)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Nausea satisfaction</td>
<td>95 (70–100)</td>
<td>93 (49–100)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Drug satisfaction</td>
<td>100 (97–100)</td>
<td>100 (84–100)</td>
<td>N.S.</td>
</tr>
<tr>
<td>QOR satisfaction</td>
<td>99 (86–100)</td>
<td>92 (71–100)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td>100 (98–100)</td>
<td>98 (94–100)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Median (25th–75th percentile) score on 100 mm scale.

QOR = quality of recovery score.
as ability to swallow, that require a lower drug concentration. McKay et al.,19 for example, demonstrated that patients who received desflurane were significantly more successful at swallowing liquids upon awakening compared with those who received sevoflurane, an effect most likely due to the lower solubility of desflurane. Eger and Shafer20 calculated that the time required for a 92%-95% decrement of volatile anesthetic level was prolonged with increasing length of exposure even with modern, less soluble drugs. It stands to reason that some recovery milestones may be delayed with the increased volatile anesthetic concentration that a non-N₂O containing anesthetic would require, even when low solubility anesthetics are used.

Another strategy is to replace the N₂O with remifentanil. Lee et al.21 demonstrated that a remifentanil infusion of 0.17 μg·kg⁻¹·min⁻¹ could replace 70% N₂O in patients receiving isoflurane undergoing colorectal surgery. In the current study, we used a lower remifentanil infusion, 0.085 μg·kg⁻¹·min⁻¹ and a fentanyl infusion plus bolus design. In the study by Lee et al., all patients received 0.15 mg/kg morphine sulfate before skin incision, and remifentanil infusion was adjusted for criteria similar to those used in the current study for fentanyl bolus administration. The difference in the MAC-reducing ability of the “background” opioid probably accounts for the difference in remifentanil administration between the studies.

Several comments should be made about our study design. First, the study was designed to deliver to both groups an equivalent “depth of anesthesia,” which can be conceptualized as separate, but related, “depth of hypnosis” and “depth of antinociception.” In our study, desflurane was the primary hypnotic drug, and although N₂O and opioids can produce hypnosis, their primary role in the anesthetic was their antinociceptive properties. We attempted to obtain an equivalent depth of hypnosis by titrating the desflurane concentration to the BIS monitor (see below), and an equivalent depth of antinociception was attempted by treating autonomic or somatic signs of nociception with small fentanyl boluses. Second, the clinical equivalency between remifentanil and N₂O was determined using their ability to reduce MAC. By extrapolating data from the interaction of isoflurane and remifentanil in reducing MAC, an infusion rate was determined with pharmacokinetic modeling. There are confidence intervals associated with each step, and there is a possibility of cumulative error, which could have lead to drug delivery that was less clinically equivalent than intended. The specific interaction of desflurane and remifentanil has not been described. Albertin et al.22 recently described the reduction in desflurane MAC-BAR by remifentanil in the presence of 60% N₂O. They found a 57% reduction with a remifentanil target-controlled infusion of 1 ng/mL and a 68% reduction at 3 ng/mL, data that were neither available during study design nor directly applicable because of the presence of N₂O. It should be noted that the average anesthetic in each group, represented in Figure 1, was indistinguishable, supporting that the method used to determine clinical equivalency during study design was valid.

The study was designed to result in a variation in fentanyl delivery. The baseline fentanyl administration (bolus 1.5 μg/kg and infusion 0.75 μg·kg⁻¹·h⁻¹) was designed to result in a plasma fentanyl concentration of approximately 1 ng/mL, which would be adequate for only a percentage of the population when desflurane was titrated to a BIS of 50. Indeed, the number of patients who required no additional fentanyl bolus in each group was similar and were approximately 18% of the study population; the majority of the patients required additional fentanyl boluses to maintain an acceptable anesthetic state. The calculated average fentanyl plasma concentration (1.6 ng/mL) delivered in this study would be expected to decrease volatile anesthetic MAC by approximately 50%23. The average desflurane AUC of 2.8% and 2.6% for the REMI and NITROUS groups, respectively, is in concert with this expected degree of MAC reduction. With the addition of 0.6 MAC-reducing equivalents from the remifentanil or N₂O, the average patient received an overall anesthetic of approximately 1.6 MAC, which is approximately MAC-BAR.24 There was variation in both fentanyl and desflurane dosing required to maintain an adequate anesthetic state among patients (Fig. 1). This degree of population variation is not different from that seen in other studies of opioid/volatile anesthetic interaction.25

Although they have clinical similarities, N₂O and remifentanil are not identical; they have different sites of action in the central nervous system and different interactions with volatile anesthetics. Remifentanil exerts its effects on the μ-opioid receptor, primarily those located in the dorsal horn of the spinal cord, periaqueductal gray, and locus coeruleus. N₂O has been reported to have several sites of action. In the rat model, N₂O releases norepinephrine in the spinal cord, which causes analgesia through activation of α-1 adrenergic receptors.26 Spinal γ-aminobutyric acid receptors27 and brainstem opioid and γ-aminobutyric acid receptors28 may also be involved in analgesic effects. The interaction of N₂O and volatile anesthetics is best described as additive.29,30 The interaction of opioids and volatile anesthetics, however, is synergistic.27 The study design assumes that the desflurane–fentanyl–N₂O interaction25 is similar to desflurane–fentanyl–remifentanil interaction. The latter has not been specifically described, nor, in fact, has the interaction of fentanyl and remifentanil. The lack of data about these interactions does not prevent them from being used clinically in combination. Our purpose in study design was not to determine the nature of these interactions, but rather to simply determine whether replacing N₂O with remifentanil in an otherwise standard anesthetic would result in a similar or improved outcome.

Desflurane was administered by titrating to the BIS monitor. N₂O and opioids have different effects on the
electroencephalogram, which may result in unintended differences in desflurane administration. Although the effect of the drug combinations used in this study on the BIS have not been specifically characterized, it has been demonstrated that neither opioid nor N₂O, when given individually, significantly changes the BIS value. Both N₂O and opioid, however, shift the relationship of BIS value to responsiveness to stimulation to the right. That is, in the presence of N₂O or opioid, the BIS value increases in 50% of a population that responds to a particular stimulus.

We did not find a significant difference in the primary end-point, time to eye opening. The study was powered to detect a difference of 2 min between the groups; the actual median difference in time was 1.6 min. Excluding the outlier in the REMI group would have led to a significant difference, however. The statistically significantly faster time to orientation is interesting, but may lack clinical relevance, as we could demonstrate no difference in NP testing. Nor did the difference in time to orientation lead to significant differences in discharge time or patient satisfaction.

The study demonstrates that the clinical outcome after an infusion of remifentanil 0.085 μg·kg⁻¹·min⁻¹ compares favorably with 66% N₂O in a desflurane/fentanyl anesthetic during ambulatory orthopedic surgery. Patients receiving remifentanil were oriented more rapidly with no difference in any recovery or satisfaction measurement; however, the study was not designed nor powered to consider these as primary outcome measures. Substituting remifentanil for N₂O may be an effective strategy for those who want to achieve similar rapid recovery profiles as that of N₂O, while avoiding the potential toxicities of the latter.

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