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A Comparison of Four Intravenous Sedation Techniques and Bispectral Index Monitoring in Sinonasal Surgery

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SUMMARY

This study was performed to investigate the quality of different intravenous sedation techniques, and the correlation between the Bispectral Index (BIS) values and the Observer's Assessment of Alertness/Sedation (OAA/S) scores.

Eighty patients undergoing sinonasal surgery were randomly assigned to one of four groups. Group MF received midazolam and fentanyl, group PF received propofol and fentanyl, group MR received midazolam and remifentanil, and group PR received propofol and remifentanil.

Heart rate and mean arterial pressuure values were not different among the groups. SpO_2 decreased only after intravenous medication in groups MF and MR ($P<0.017$). Emesis was less common with propofol. A positive relationship existed between the BIS values and OAA/S scores during the operation in all groups and the strongest correlation was observed in group PR ($r=0.565$ and $P<0.001$).

In conclusion, these four intravenous sedation techniques did not change mean arterial pressure, heart rate or SpO_2 clinically and produced a similar level of light sedation. The BIS was useful for monitoring of sedation during sinonasal surgery under local anaesthesia with intravenous sedation.

Key Words: MONITORING: bispectral index. SURGERY: otorhinolaryngological.
ANAESTHETIC DRUGS: midazolam, propofol. OPIOIDS: fentanyl, remifentanil, conscious sedation

Sinonasal surgery is performed either under general anaesthesia or local anaesthesia with intravenous sedation[1-4]. Sedative hypnotics (benzodiazepines, propofol) and opioid combinations are frequently administered to provide patient comfort, sedation, anxiolysis, and supplemental analgesia during local anaesthesia. Although midazolam and fentanyl are widely used, their potent synergistic interaction can result in significant respiratory depression[5]. Propofol produces better sedation than midazolam, but both drugs have depressive effects on blood pressure and respiratory function. Remifentanil is a potent μ-agonist opioid with sedative effects and an ultra short half-life because of its metabolism by plasma and tissue esterases[6,7].

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The effects of anaesthetic drugs on the electroencephalogram (EEG) have been investigated recently to measure the depth of anaesthesia or sedation. Because of the difficulties associated with conventional EEG monitoring, computerized EEG-derived parameters (power bands; alpha, beta, delta, theta), frequency variables (95% Spectral Edge Frequency and Median Frequency) and phase-coupling, the Bispectral Index (BIS) has been used. The bispectral analysis of the EEG decomposes the signal into its component sine waves using a Fourier transformation. The BIS is a complex parameter, composed of a combination of time domain, frequency domain, and high order spectral subparameters[8-10]. The use of the BIS monitor in patients undergoing a procedure in the head region provides for a safe and cooperative environment without oversedation[11].

The purpose of this study was to compare the quality of sedation induced by different hypnotic and opioid combinations during sinonasal surgery. A secondary aim was to investigate the correlation between the Observer's Assessment of Alertness/Sedation (OAA/S) scale scores and their corresponding BIS values.

MATERIALS AND METHODS

Eighty patients undergoing sinonasal surgery were studied. All patients were of American Society of Anesthesiologists (ASA) physical status 1 and 2. Exclusion criteria were use of analgesics or sedatives within 24 hours of surgery, obesity, known pseudocholinesterase deficiency, neurologic and psychiatric disorders and concurrent use of cerebrally active medication. After obtaining Hospital Ethics Committee approval and written informed consent, patients were randomly assigned using a consecutive number sequence into one of four groups, to receive one of the sedative combinations.

The patients were fasted overnight and premedicated with intramuscular atropine (0.5 mg) and pethidine (1 mg/kg). Nasal cavities were sprayed with one or two puffs of xylometazoline (0.14 mg/puff) approximately one hour before surgery.

Cardiovascular monitoring was applied, including electrocardiography (ECG, leads II and V_5), pulse oximetry (SpO_2), and noninvasive blood pressure measurement (NIBP) using an automated blood pressure cuff (Datex Ohmeda, Cardiocap/5, Louisville, CO, U.S.A.). EEG signals were acquired by using standard BIS sensors applied to the frontotemporal area (Aspect Medical Systems, Natick, MA, U.S.A.). The BIS values were displayed by using an A-2000 BIS monitor (BIS algorithm version 3.4, Aspect Medical Systems, Leiden, The Netherlands).

The depth of sedation was assessed clinically by using the responsiveness component of the modified OAA/S scale. Sedation scores of 3, 4, and 5 are classified as conscious, and sedation scores of 0, 1, 2 are considered to be unresponsive and unconscious (Table 1)[12].

After obtaining baseline data including heart rate (HR), mean arterial pressure (MAP), SpO_2, BIS values and sedation scores, further readings were recorded at five-minute intervals during the operation.

The patients in group 1 (G-MF, n=20) received intravenous midazolam (0.07 mg/kg) and fentanyl (1 μg/kg). Patients in group 2 (G-PF, n=20) received propofol by infusion (2 mg/kg/h) and intravenous fentanyl (1 μg/kg). Patients in group 3 (G-MR, n=20) received intravenous midazolam (0.07 mg/kg) and remifentanil infusion (0.05 μg/kg/min). Patients in group 4 (G-PR, n=20) received propofol by infusion (2 mg/kg/h) and remifentanil by infusion (0.05 μg/kg/min). Sedation doses were chosen for each agent[13].

TABLE 1

Responsiveness scores of the modified Observer's Assessment of Alertness/Sedation Scale

Response	Score level
Responds readily to name spoken in normal tone	5 (alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

After intravenous medication, local anaesthesia was applied by soaking cotton pledgets in a total of 6 ml pantocaine (amethocaine) (4%, 4 ml) and adrenaline (1:1000, 2 ml) solution. Some of the typical mucosal points on the middle turbinate, lateral nasal wall and, if necessary, the sphenopalatine neurovascular bundle, were injected with 1-1.5 ml of lignocaine (1%) and adrenaline (1:200,000) solution. When septoplasty or submucosal resection was planned, infiltration anaesthesia was applied under the nasal septal mucosa.

All assessments were performed by the same research anaesthetist who was blind to the BIS value and to the combination in order to minimize interobserver variability. During the procedure, no additional opioid medication was administered. Doses of midazolam and propofol were administered by the same research anaesthetist according to the OAA/S scores, aiming for a level of 4 (3 to 5) for maintenance. For additional doses, the observer was not blind to the hypnotic agent. BIS scores were recorded by the second anaesthesist.

Adverse effects such as nausea, vomiting, hypotension (mean arterial pressure, MAP <60 mmHg), bradycardia (heart rate, HR <60 beats/min with hypotension), hypertension (MAP >110 mmHg) and low saturation levels (SpO_2 <90%) were recorded. Hypotension was treated by Trendelenberg positioning and fluid infusion. If fluid therapy was ineffective a vasopressor (intravenous ephedrine 5-10 mg) was given. Respiratory depression was addressed by asking the patient to breathe deeply—supplemental oxygen was not used routinely in order to see the effects of combinations on oxygen saturation, but was administered if the SpO_2 was below 90%.

The data were analysed with SPSS 8.0 for Windows statistical program. Results were expressed as mean and standard deviation (SD) for continuous variables.

The OAA/S values of the groups were compared using the Kruskal-Wallis test, the other parameters (age, weight, duration of surgery, HR, MAP, SpO_2, BIS) were compared with ANOVA and P<0.01 was considered statistically significant. Bonferroni adjusted Student's t-test was used to evaluate differences in the BIS and SpO_2 among the groups.

Differences in the OAA/S scores of the groups were looked for using the Bonferroni adjusted Mann-Whitney U test, with statistical significance set at $P<0.017$. The OAA/S values within the groups were analysed repeatedly using the Friedman test, and for the other parameters repeated measures ANOVA was used (with $P<0.01$ considered significant). Pairwise comparison of the significant variations in the OAA/S was performed using the Wilcoxon Signed Ranks test. Paired samples tests were used to compare significant variations in other parameters between groups (two-tailed). A value of $P<0.0036$ was used for statistical significance with Bonferroni adjustment. The relationship between sedation score and the BIS value at each assessment point was found using Pearson correlation analysis.

TABLE 2

Patient characteristics, operation types and operation times

	G-MF (n=20)	G-PF (n=20)	G-MR (n=20)	G-PR (n=20)
Male/Female (n)	13/7	15/5	10/10	13/7
Age (years)	30.5 (9.7)	29.7 (9.1)	29.9 (9.3)	31.1 (9.5)
Weight (kg)	71.4 (13.2)	73.6 (10.6)	66.2 (12.8)	69.2 (11.8)
FESS/S/FESS+S	10/9/1	9/10/1	7/11/2	6/11/3
Duration of surgery (min)	44.8 (15.2)	56.0 (21.2)	51.3 (19.5)	51.5 (16.2)

Mean (SD)
FESS: functional endoscopic sinus surgery/S: septoplasty
G-MF: group received midazolam and fentanyl
G-PF: group received propofol and fentanyl
G-MR: group received midazolam and remifentanil
G-PR: group received propofol and remifentanil

RESULTS

The demographic data of the patients, surgery types and duration of surgery did not significantly differ among the groups (Table 2).

There was no significant difference in HR and MAP values among the groups, and there were only clinically unimportant significant differences within the groups (Figures 1 and 2).

SpO_2 values after administration of sedation in group MF and group MR were lower than those in group PF and group PR ($P<0.01$) (Figure 3).

The BIS values of the patients who received midazolam decreased more than those of the propofol groups. The differences between group MR and group PF, group MR and group PR were significant ($P<0.01$). The OAA/S scores did not change significantly.

A positive relationship was found in all groups between the BIS values and the OAA/S scores during the operation (group MF; r=0.334 and $P<0.001$,

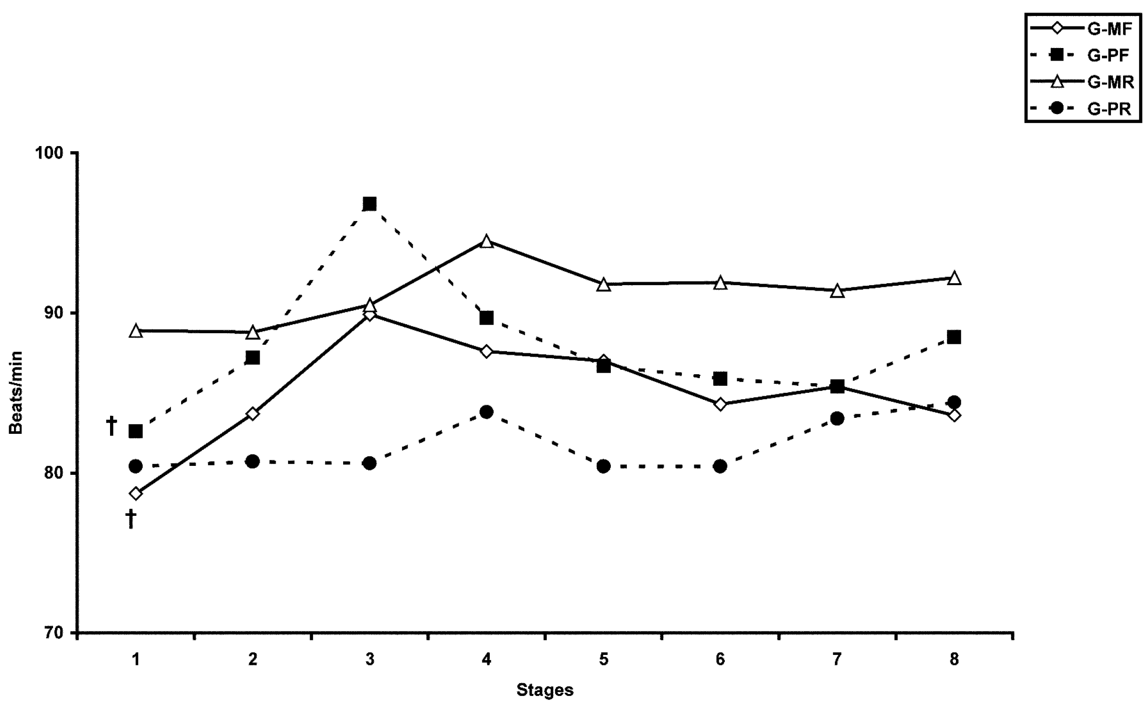

FIGURE 1: Heart Rate (beats/min). Stages: Preoperative (baseline) (1), after intravenous sedation induced (2), after local anaesthesia (3), at the beginning of the operation (4), during the operation (5, 6, 7) and at the end of the operation (8).
†: $P<0.004$ significant difference within the group.

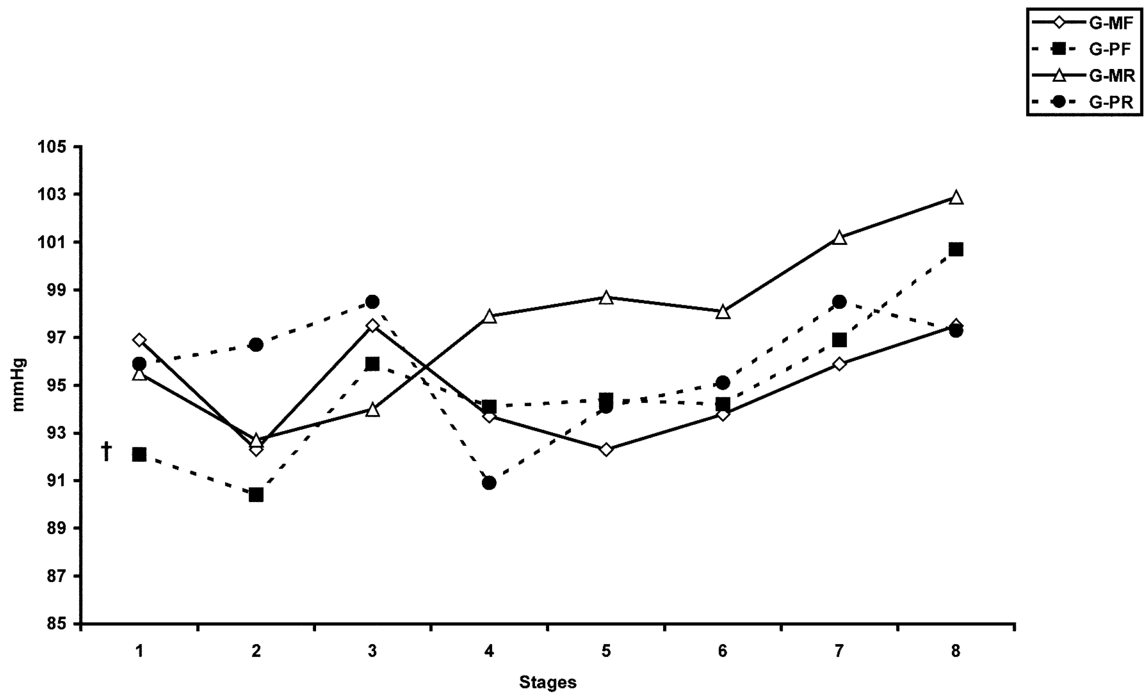

FIGURE 2: Mean Arterial Pressure (mmHg). Stages: Preoperative (baseline) (1), after intravenous sedation induced (2), after local anaesthesia (3), at the beginning of the operation (4), during the operation (5, 6, 7) and at the end of the operation (8).
†: $P<0.004$ significant difference within the group.

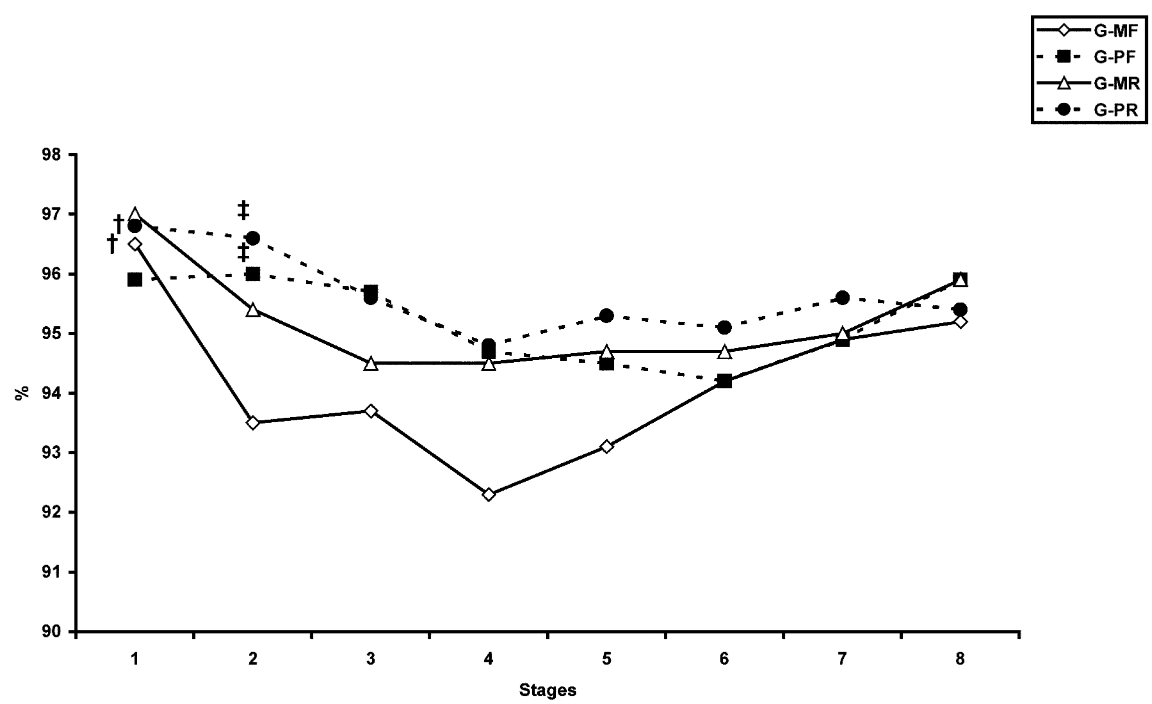

FIGURE 3: Oxygen Saturation (%). Stages: Preoperative (baseline) (1), after intravenous sedation induced (2), after local anaesthesia (3), at the beginning of the operation (4), during the operation (5, 6, 7) and at the end of the operation (8).
†: $P<0.004$ significant difference within the group
‡: $P<0.02$ when compared with the values of G-MF and G-MR

group PF; r=0.423 and $P<0.001$, group MR; r=0.310 and $P<0.001$, group PR; r=0.565 and $P<0.001$). The strongest correlation was found in group PR (Figures 4-7).

Five patients in group MF, one patient in group PF, and four patients in group MR complained of nausea and received antiemetic therapy. Vomiting did not occur. Hypotension was more frequent in group PF and three patients in this group were treated with ephedrine. Bradycardia was observed in only one patient (group MF). Hypertension was seen in four patients in group MF (three of the four had received antihypertensive medication), in three patients in group PF, in two patients in group MR, and in four patients in group PR (two of the four had received antihypertensive medication). Supplemental oxygen was applied to 12 patients in group MF, four in group PF, two in group MR, and six in group PR. No muscular rigidity or pruritus occurred.

DISCUSSION

In sinonasal surgery, local anaesthesia with sedation may result in shorter total operative times, shorter recovery times, and less frequent nausea, vomiting, and epistaxis than general anaesthesia[4]. In this study, we compared different combinations of hypnotics and opioids commonly used for sedation during sinonasal surgery.

The ideal opioid for sinonasal surgery under monitored anaesthesia care must provide rapid onset of effect, allow rapid titration of anaesthetic depth with haemodynamic stability, lead to rapid recovery times and produce few drug side-effects. Remifentanil has appropiate pharmacokinetic properties, and is an effective adjunct to regional and local anaesthesia[14,15].

Sedation is characteristic of potent μ-opioids and the sedation dose of remifentanil was estimated as 0.043 μg/kg/min[6]. Continous infusion is an appropriate method for titration of sedation during monitored anaesthesia care and respiratory depression is directly associated with bolus administration of remifentanil[5,14]. In our study, we used remifentanil by infusion (0.05 μg/kg/min) with midazolam or propofol.

Jellish and colleagues[7] provided intravenous anaesthesia with propofol/remifentanil or propofol/fentanyl combinations for otologic procedures and found that remifentanil-based anaesthesia produced better haemodynamic stability. Lower MAP values with remifentanil may be beneficial in reducing bleeding in the surgical field. The study by Balakrishnan and colleagues[16] demonstrated that the frequencies of adverse event rates for fentanyl and remifentanil were similar. In the study by Loop and Priebe[15], the combination of propofol and remifentanil, used for induction during otorhinolaryngeal surgery was associated with a higher incidence of hypotension and bradycardia, but a lower incidence of nausea. Except for minor changes in HR and MAP we did not find any clinically important difference

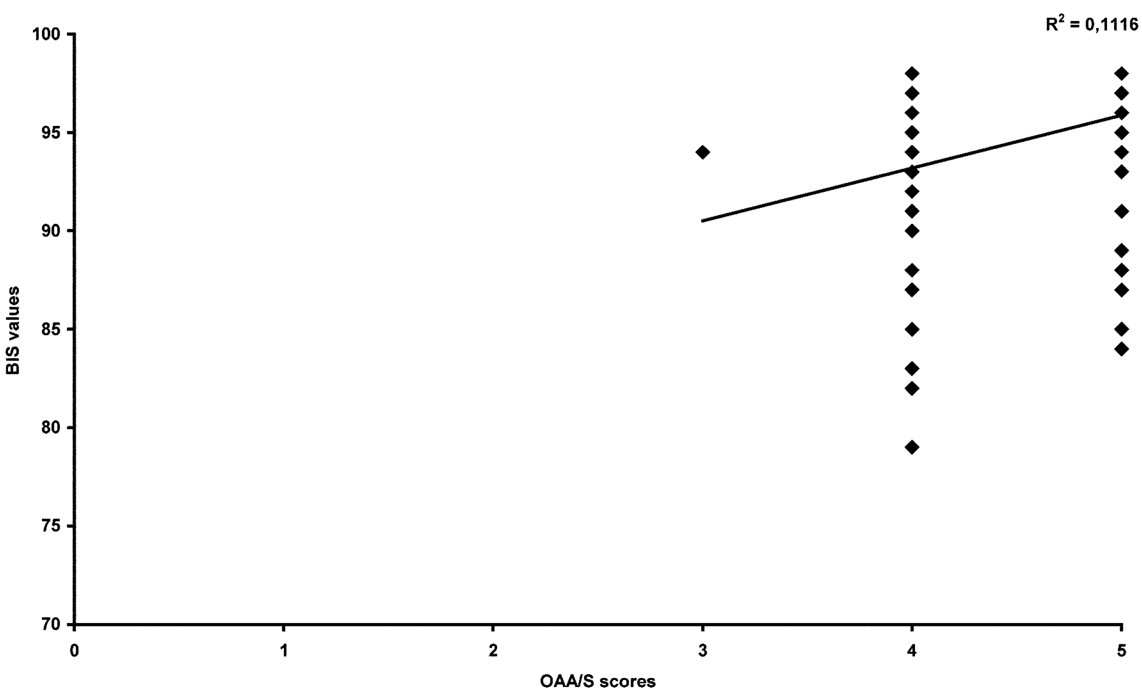

FIGURE 4: Scattergram of the relation between BIS values and OAA/S scores in group MF.

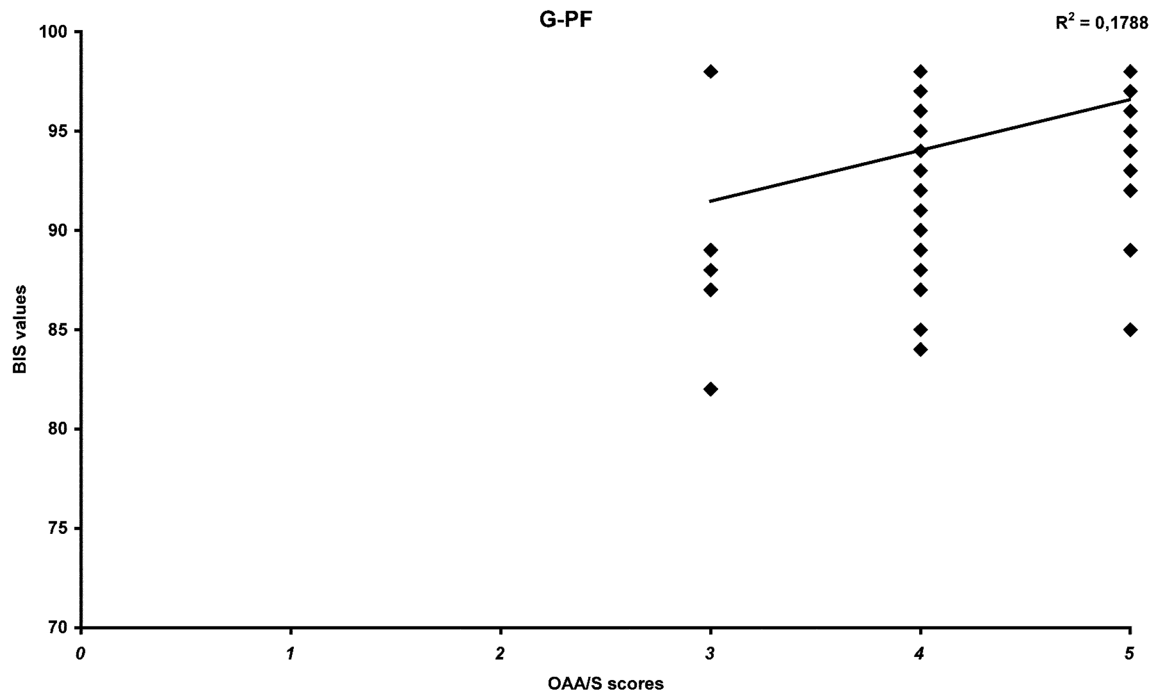

FIGURE 5: Scattergram of the relation between BIS values and OAA/S scores in group PF.

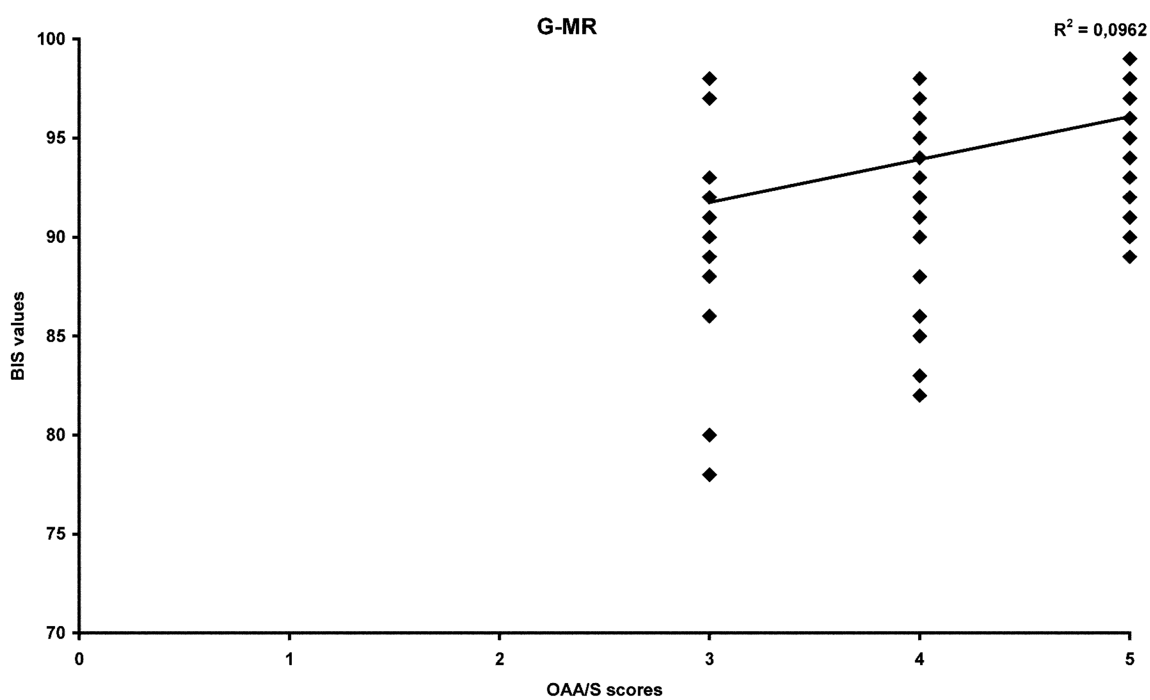

FIGURE 6: Scattergram of the relation between BIS values and OAA/S scores in group MR.

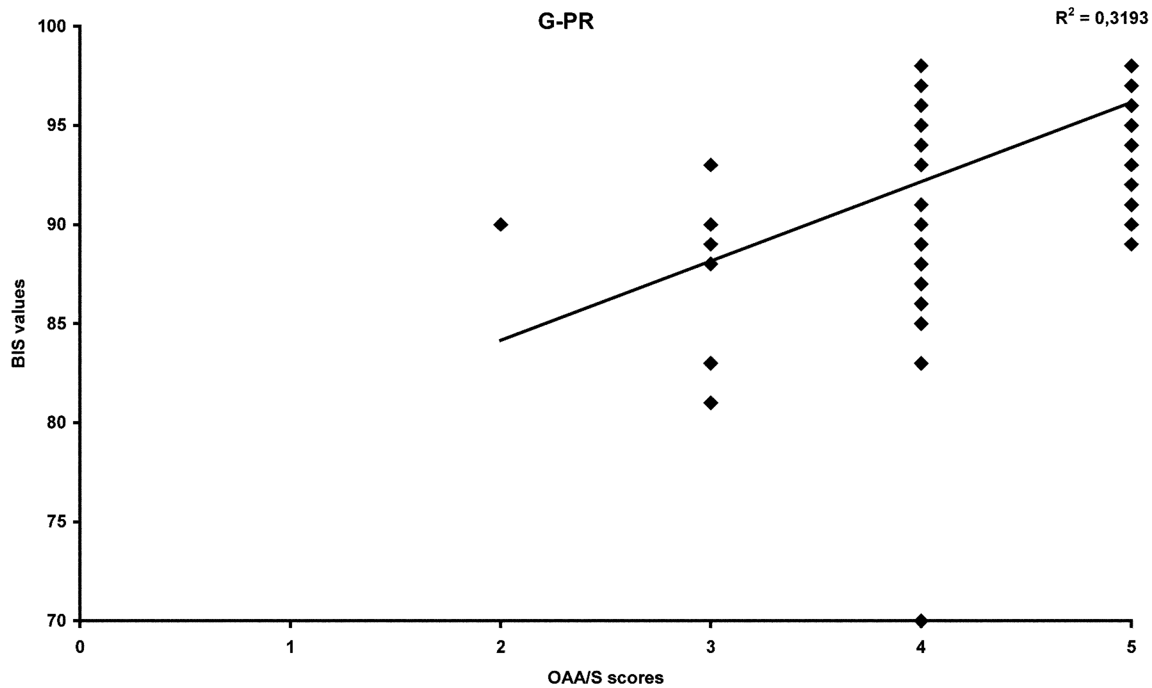

FIGURE 7: Scattergram of the relation between BIS values and OAA/S scores in group PR.

between the four drug combinations. As noted by others[4,15], emetic symptoms were less frequent among patients who received propofol.

The BIS is a numeric index ranging from 0 to 100, with awake patients scoring in the mid to upper nineties and conscious sedation associated with a fall in BIS to the eighties[17]. The clinical evaluation of depth of sedation requires frequent stimulation during the operation, and may disturb both the patient and the surgeon[18]. The BIS monitor specifically measures the state of hypnosis, not the level of analgesia. Safe sedation, in which the airway and protective reflexes remain intact, combines the effects of hypnosis and analgesia, the latter being augmented by local anaesthesia. The BIS may be helpful in recognizing oversedation in case of inadequate analgesia[11]. Hypnotics affect the EEG by an action on the cerebral cortex, whilst opioids exert their analgesic action in part by inhibition of subcortical structures. At analgesic concentrations, opioids produce minimal sedation, so BIS values should not be affected by opioids at analgesic concentrations[19]. Similarly, in an earlier study[20], fentanyl blunted haemodynamic responses to intubation without changing the BIS. Barr and co-workers[21] showed that the BIS did not reflect accurately the hypnotic effects of fentanyl. In addition, it was reported that the BIS did not reflect the increased hypnotic effect of addition of an analgesic concentration of μ-opioid to propofol[22]. In contrast, Strachan and Edwards[23] showed that increasing doses of remifentanil caused a greater reduction in the BIS and that opioids reduced the BIS when combined with propofol. We found a decrease in the BIS after anaesthetic medication in all patients, but this decrease was only significant for the midazolam and fentanyl group. Nevertheless, all combinations produced similar clinical levels of light sedation.

In the studies reporting the correlation between the BIS and propofol- or midazolam-induced sedation level, the BIS was found to be a better predictor of depth of sedation with propofol[21] than with midazolam[24]. The BIS exhibited a strong correlation with the OAA/S scores during propofol-induced sedation[18]. Our results are in agreement with these studies. We observed a positive relationship between the BIS values and the OAA/S scores during the operation in all groups, with the strongest correlation among patients receiving propofol and remifentanil.

In conclusion, these four drug combinations did not cause clinically important changes in haemodynamic and respiratory parameters (MAP, HR, SpO_2) and produced satisfactory light sedation for sinonasal surgery. Although all of the combinations appeared safe, a combination including propofol may be preferable because of the lesser emetic effect. The BIS may be a valuable tool for assessing the depth of sedation in sinonasal surgery, where it may be difficult to determine the level of sedation clinically.

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