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CLINICAL RESEARCH

Effects of remifentanil on awakening of propofol sedated patients submitted to upper gastrointestinal endoscopy: a randomized clinical trial

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Sedation;
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Abstract

Background and objectives: Sedation for endoscopic procedures aims to provide high quality sedation, lower risks, short recovery time, superior recovery quality and absence of side effects, seeking high patient level of satisfaction. The goal of the study was to assess administration of remifentanil combined with propofol regarding the effects of the drug association during sedation and recovery for patients submitted to upper gastrointestinal diagnostic endoscopy.

Method: One hundred and five patients were assessed, randomly divided into three groups of 35 patients. The Control Group was sedated with propofol alone. Study Group 1 was sedated with a fixed dose of 0.2 $\mu g.kg^{-1}$ remifentanil combined with propofol. Study Group 2 was sedated with 0.3 $\mu g.kg^{-1}$ remifentanil combined with propofol. We assessed the quality of sedation, hemodynamic parameters, incidence of significant hypoxemia, time for spontaneous eye opening, post-anesthetic recovery time, quality of post-anesthetic recovery, presence of side effects and patient satisfaction.

Results: Study Group 1 showed better quality of sedation. The groups in which remifentanil was administered combined with propofol showed shorter eye-opening time and shorter post-anesthetic recovery time compared to the control group. The three groups presented hemodynamic changes at some of the moments assessed. The incidence of significant hypoxemia, the quality of post-anesthetic recovery, the incidence of side effects and patient satisfaction were similar in the three groups.

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Conclusions: The combination of propofol with remifentanil at a dose of 0.2 $\mu g.kg^{-1}$ was effective in improving the quality of sedation, and at doses of 0.2 $\mu g.kg^{-1}$ and 0.3 $\mu g.kg^{-1}$ reduced the time to spontaneous eye opening and post-anesthetic recovery in comparison to sedation with propofol administered alone.

PALAVRAS-CHAVE
Sedação;
Endoscopia digestiva alta diagnósticos;
Propofol;
Remifentanil;
Recuperação anestésica

Efeitos do remifentanil sobre despertar de pacientes sedados com propofol para endoscopia digestiva alta: estudo clínico randomizado

Resumo

Justificativa e objetivos: A sedação para procedimentos endoscópicos pretende fornecer boa qualidade de sono, menores riscos, tempo de recuperação mais curto, qualidade de recuperação superior e ausência de efeitos colaterais, buscando um elevado nível de satisfação dos pacientes. O objetivo deste estudo foi avaliar a influência da associação do remifentanil ao propofol e seus efeitos durante a sedação e a recuperação em exames de endoscopia digestiva alta diagnóstica.

Método: Foram avaliados 105 pacientes, divididos aleatoriamente em três grupos de 35 pacientes. O Grupo Controle foi sedado apenas com o uso de propofol, o Grupo de Estudo 1 foi sedado com uso de remifentanil em dose fixa de 0,2 $\mu g.kg^{-1}$ associado ao propofol. E o Grupo de Estudo 2 foi sedado com o uso de remifentanil em dose fixa de 0,3 $\mu g.kg^{-1}$ associado ao propofol. Foram avaliados qualidade da sedação, comportamento hemodinâmico, incidência de hipoxemia significativa, tempo para abertura ocular espontânea, tempo de recuperação pós-anestésica, qualidade da recuperação pós-anestésica, presença de efeitos colaterais e satisfação do paciente.

Resultado: O Grupo de Estudo 1 apresentou melhor qualidade de sedação. Os grupos em que se associou o remifentanil apresentaram tempo para abertura ocular e tempo de recuperação anestésica mais curtos em relação ao grupo controle. Os três grupos apresentaram alterações hemodinâmicas em algum dos momentos avaliados. A incidência de hipoxemia significativa, a qualidade da recuperação pós-anestésica, a incidência de efeitos colaterais e a satisfação dos pacientes foram similares nos três grupos.

Conclusão: Conclui-se que a associação do remifentanil na dose de 0,2 $\mu g.kg^{-1}$ mostrou-se efetivo na melhora da qualidade da sedação, e nas doses 0,2 $\mu g.kg^{-1}$ e de 0,3 $\mu g.kg^{-1}$, reduziu o tempo de abertura ocular espontânea e o tempo de recuperação pós-anestésica dos pacientes em relação a sedação apenas com propofol.

Introduction

Over the past few years, we have witnessed a change in the use of sophisticated endoscopic equipment and devices, as well as in sedation techniques.[1] As a consequence, endoscopic and therapeutic procedures have become better tolerated and accepted by patients and endoscopists in most centers around the world. Gastrointestinal (GI) endoscopy is an uncomfortable procedure, with a potential feeling of gagging, retching and choking.[2]

Sedation relieves patient anxiety and discomfort and has become routine for patients undergoing colonoscopy and upper GI endoscopy.[3,4] In developed countries such as Switzerland,[5] Canada,[6] Italy,[7] and the United States,[8] even low-risk endoscopic procedures are routinely performed with some form of sedation.[9]

The introduction of new sedative drugs together with the goal to increase satisfaction and efficiency has changed the practice of sedation for endoscopy.[8] Numerous drugs are available to successfully provide moderate and deep sedation, and other drugs are in the clinical stage of development.[1] Moderate sedation using midazolam associated with an opioid represents the standard or traditional sedation regimen; nonetheless propofol has been used in many countries. It has been suggested that adhesion to propofol use will increase among endoscopists and it will become the preferred sedative agent in the near future. Satisfaction with sedation is greater among endoscopists using propofol than those using the traditional sedation regimen.[8]

As all anesthetic drugs can show side effects, their desirable and undesirable properties should be pondered. The incidence of nausea, from the point of view of the patient, is the main anesthetic outcome to be avoided,[10] and from the perspective of the anesthesiologist, it is the second most frequent and the tenth most important to be prevented among 33 outcomes surveyed.[11]

In many respects, propofol is an ideal agent for short duration procedures in the outpatient setting.[12] The popularity of propofol among physicians and patients is mostly related to its pharmacokinetic and pharmacodynamics properties, which provide propofol with fast onset and end of action, giving patients a feeling of well-being.[3]

Opioids are anesthetic drugs that provide analgesia during surgery and have a synergistic effect when associated with propofol.[13] Among the most modern opioids, remifentanil stands out, as it presents desired pharmacokinetic properties, with short-lasting pharmacodynamics effects.

In order to provide sedation with a quality and safe technique, education and training are required, in addition to understanding the pharmacokinetics and pharmacodynamics of sedative agents, which enables customizing anesthetic agents and doses.[14] The emphasis regarding the sedation technique for endoscopy procedures is to deliver high-quality low-risk sedation, fast recovery time, superior recovery quality and absence of side effects, aimed at high level patient satisfaction.

The goal of the present study was to assess the impact of the association of remifentanil with propofol on the quality of sedation, hemodynamic parameters, and on the incidence of significant hypoxemia during examination. Concerning patient recovery, we aimed to evaluate both time for spontaneous eye opening and time for post-anesthetic recovery, the quality of post-anesthetic recovery, patient satisfaction regarding the sedation technique, and the incidence of side effects related to drugs and doses used during sedation in diagnostic upper GI endoscopy exams.

Method

The study was a phase IV randomized, controlled, double-blind clinical trial. It was carried out after approval by the Research Ethics Committee of the institution, with a sample analogous to a previously published study.[15] All patients were informed about the protocol and provided an informed consent for each study.

Inclusion criteria

We selected 105 patients, of both sexes, physical status ASA I or II, submitted to diagnostic upper GI endoscopy.

Exclusion criteria

Exclusion criteria were patients under 18 and over 65 years of age, pregnant women, history of allergy to any component of the drugs to be administered, requirement of therapy of any nature in addition to the diagnostic upper GI endoscopy, and any patient ASA class > II.

Assessment and execution

Data: age, weight, sex, height and ASA classification were collected during the pre-anesthetic assessment. Patients to be submitted to diagnostic upper GI endoscopy were randomly assigned to one of three groups: Control Group (CG), consisting of 35 patients who were sedated only with propofol; Study Group 1 (SG1), consisting of 35 patients who were sedated with remifentanil at a fixed dose of 0.2 $\mu g.kg^{-1}$ associated with propofol; Study Group 2 (SG2) consisting of 35 patients who were sedated with remifentanil in a fixed dose of 0.3 $\mu g.kg^{-1}$ associated with propofol. Patients who met inclusion criteria were monitored with cardioscopy, pulse oximetry and non-invasive arterial blood pressure, using a Philips C3 multiparametric monitor; had a glasses-type nasal catheter with 3 $L.min^{-1}$ O_2 flow placed; and were submitted to peripheral venipuncture with a 22G catheter at the antecubital region for infusion of 0.9% isotonic saline solution and administration of sedative medication. Patients were then positioned in the left lateral position for the examination. Patients in the CG received 0.9% isotonic saline solution administered through a 10 mL syringe at the rate of 1 mL every 3 seconds. Patients in SG1 and SG2 received a dose of 0.2 $\mu g.kg^{-1}$ and 0.3 $\mu g.kg^{-1}$ of remifentanil, respectively. Next, propofol was administered through a 20 mL syringe, at a rate of 1 mL every 3 seconds. Propofol was injected until loss of consciousness, checked by absence of response to vocal orders and loss of the ciliary reflex confirmed by all team members. The same endoscopist performed the procedure and graded the quality of sedation during the exam, as shown in Supplementary Material Annex 1.

Data on heart rate, mean arterial pressure, and oxygen saturation through pulse oximetry were assessed at fixed moments (patient admission, after remifentanil 0.9% isotonic saline, after propofol, during examination, upon awakening, and at discharge), along with the incidence of significant hypoxemia (Supplementary Material Annex 2).

Subsequent to propofol discontinuation, we registered the time of patient recovery after eye opening in response to verbal order. Then the patient was taken to the recovery room and followed up to collect the remaining data of the protocol.

In the endoscopy procedure room at the moments proposed by the study protocol, we collected data relating to the total dose of propofol administered measured in $mg.kg^{-1}$, quality of sedation, heart rate, arterial blood pressure, oxygen saturation through pulse oximetry, presence of hypoxemia, time for spontaneous eye opening. In the post-anesthetic recovery room, at the moments proposed by the study protocol, we collected data regarding post-anesthetic recovery time, quality of post-anesthetic recovery, patient satisfaction and incidence of side effects on a specific spreadsheet for later analysis. Both the endoscopist and the professional who collected the data were blind to the group the patient belonged to.

Intervention

In case of significant hypoxemia, according to the predetermined criteria, patient's chin elevation was performed and the endoscopist waited until arterial blood saturation was corrected to above 92% to complete the exam.

Statistical analysis

Quantitative variables were described by mean, median, minimum value, maximum value and standard deviation.

Table 1 Comparison of mean age (years), weight (kg) and height (cm).

Variable	Group	n	Mean	Median	Minimum	Maximum	SD	p^a
Age	CG	35	34.1	33.0	20.0	60.0	9.3	0.566
	SG 1	35	36.2	35.0	18.0	60.0	11.7	
	SG 2	35	33.9	35.0	20.0	52.0	8.0	
Weight	CG	35	74.0	73.0	50.0	110.0	12.2	0.233
	SG 1	35	69.2	67.0	48.0	98.0	13.2	
	SG 2	35	70.1	68.0	50.0	94.0	11.9	
Height	CG	35	167.6	168.0	155.0	184.0	8.5	0.618
	SG 1	35	165.8	165.0	150.0	180.0	7.0	
	SG 2	35	166.3	165.0	150.0	182.0	7.9	

[a] One-way ANOVA, $p < 0.05$.

Table 2 Gender comparison among groups analyzed.

Gender	CG		SG1		SG2	
	n	%	n	%	n	%
Female	22	62.9	25	71.4	27	77.1
Male	13	37.1	10	28.6	8	22.9
Total	35	100.0	35	100.0	35	100.0
p^a	0.419					

[a] Chi-Square test, $p < 0.05$.

Table 3 Comparison of ASA classification among groups analyzed.

ASA	CG		SG1		SG2	
	n	%	n	%	n	%
1	30	85.7	29	82.9	24	68.6
2	5	14.3	6	17.1	11	31.4
Total	35	100.0	35	100.0	35	100.0
p^a	0.168					

[a] Chi-Square test, $p < 0.05$.

Qualitative variables were described by frequencies and percentages. The comparison of the groups in relation to variables age, weight, height, dose, eye opening time and recovery time was performed using the one-way analysis of variance model (ANOVA). The comparison of the groups in relation to the categorical variables was performed using the Chi-Square test. Comparisons of groups two by two were analyzed using Fisher's exact test or the Logistic Regression model and Wald's test. For the analysis of the variables heart rate, mean arterial pressure and arterial oxygen saturation, collected at different moments of the assessment, the comparison of the moments and groups was performed considering the Analysis of Variance (ANOVA) Split-Plot model. In the case of significant interaction between the group and the moment of assessment, groups were compared using the one-way ANOVA model. Multiple post hoc comparisons were made using the LSD (least significant difference) test. The level of significance adopted was 0.05 and corrected by Bonferroni for comparisons of groups two by two ($p < 0.017$ indicated statistical significance). Data were analyzed using the IBM SPSS Statistics v.20.0 computer program. Armonk, NY: IBM Corp.

Results

The groups were homogeneous in relation to variables: age, weight, height, sex and ASA class (Tables 1–3).

On admission, the groups presented homogeneous means in relation to parameters: heart rate, mean arterial pressure and arterial oxygen saturation.

Propofol doses administered ranged from 0.51 to 3.17 $mg.kg^{-1}$.

Comparison of groups in relation to quality of sedation

Appropriate quality sedation was significantly higher in SG1 compared to the CG. There was no statistical difference in the quality of sedation between SG1 and SG2, and neither between the CG and SG2 (Tables 4 and 5). When using the Bonferroni correction on the level of significance, only p-values < 0.017 appointed statistical significance. Thus, the difference between CG and SG2 was not significant.

Table 4 Comparison of quality of sedation among groups analyzed.

Quality of sedation	CG		SG1		SG2	
	n	%	n	%	n	%
Good	11	31.4	1	2.9	4	11.4
Optimal	24	68.6	34	97.1	31	88.6
Total	35	100.0	35	100.0	35	100.0
p[a]	0.003					

[a] Chi-Square test, $p < 0.05$.

Table 5 Comparison of quality of sedation among groups analyzed two by two.

Comparison of groups	p[a]
CG × SG1	0.011
CG × SG2	0.049
SG1 × SG2	0.197

[a] Logistic Regression Model and Wald test, $p < 0.017$ (Bonferroni's correction).

Comparison of groups in relation to heart rate (HR)

When assessing the interaction between group and time of assessment for heart rate, statistical significance was found ($p < 0.001$). Thus, the groups were compared in each of the assessments (admission, after remifentanil, after propofol, during the exam, upon awakening and at discharge). In the case of statistical difference between the groups, they were compared two by two.

The table below shows means and standard deviation obtained for each combination of group and time of assessment (Table 6).

There was no significant difference: at admission ($p = 0.201$), upon awakening ($p = 0.141$) and at discharge ($p = 0.250$).

There was a statistical difference among them at three moments: after remifentanil, after propofol and during the exam (Table 7).

Between CG and SG1, there was a statistical difference only after propofol and during the exam.

Between CG and SG2 there was a statistical difference after remifentanil and during the exam.

Between SG1 and SG2 there was a statistical difference after remifentanil.

Comparison of groups regarding mean arterial blood pressure (MAP)

When assessing the interaction between group and time of assessment for mean arterial pressure, statistical significance was found ($p < 0.001$). The table below shows means and standard deviation obtained for each group combination and time of assessment (Table 8).

There was no significant difference: at admission ($p = 0.902$), after remifentanil ($p = 0.144$), after propofol ($p = 0.202$) and at discharge ($p = 0.090$).

There was a statistical difference among them at two moments: during the exam and upon awakening (Table 9).

Table 6 Mean and standard deviation of heart rate by group and assessment times.

Group	Admission	After remifentanil	After propofol	During exam	Upon awakening	At discharge
CG	72.2 ± 14.1	67.6 ± 11.9	76.0 ± 9.8	75.8 ± 12.2	70.3 ± 12.2	73.6 ± 11.1
SG1	71.5 ± 9.4	67.5 ± 10.2	68.8 ± 8.6	66.4 ± 8.7	65.1 ± 8.8	69.3 ± 8.0
SG2	75.9 ± 13.9	73.9 ± 14.7	73.2 ± 12.5	69.2 ± 9.5	67.3 ± 10.5	70.8 ± 9.7

Table 7 Comparison of heart rate among groups analyzed.

Comparison of groups	After remifentanil	After propofol	During exam
CG × SG1	0.957	0.006	< 0.001
CG × SG2	0.017	0.290	0.012
SG1 × SG2	0.014	0.092	0.290

LSD test, $p < 0.017$ (Bonferroni's correction).

Table 8 Mean and standard deviation of arterial blood pressure by group and observation times.

Group	At admission	After remifentanil	After propofol	During exam	Upon awakening	At discharge
CG	95 ± 13.4	94.1 ± 11.2	79.6 ± 9	84.4 ± 11.5	80.3 ± 9.7	85.6 ± 9.9
SG1	95.9 ± 9.4	91.9 ± 11.8	75.8 ± 9.8	73.6 ± 10.2	73.6 ± 8.5	83.8 ± 8.9
SG2	95.9 ± 10.1	96.5 ± 9.3	76.2 ± 7.1	75.1 ± 7.2	75.9 ± 8.3	80.6 ± 8.7

Table 9 Comparison of mean arterial blood pressure among different groups analyzed.

Comparison of groups	During exam	Upon awakening
CG × SG1	< 0.001	0.004
CG × SG2	< 0.001	0.062
SG1 × SG2	0.534	0.315

LSD test, $p < 0.017$ (Bonferroni's correction).

Table 10 Mean and standard deviation of SpO_2 by group and observation times.

Group	Admission	After remifentanil	After propofol	During exam	Upon awakening
CG	98.8 ± 1.3	98.8 ± 1.5	98.1 ± 2.3	96.2 ± 4.1	98.5 ± 1.4
SG1	98.4 ± 1.5	98.9 ± 1.4	96.7 ± 3.6	95.9 ± 4.3	98.7 ± 1.6
SG2	98.9 ± 1.1	99.3 ± 1.3	97.1 ± 3.7	96.5 ± 3.3	98.7 ± 1.7

Table 11 Comparison of presence of hypoxemia among groups analyzed.

Hypoxemia	CG		SG1		SG2	
	n	%	n	%	n	%
No	29	82.9	31	88.6	30	85.7
Yes	6	17.1	4	11.4	5	14.3
Total	35	100.0	35	100.0	35	100.0
p[a]	0.792					

[a] Chi-Square test, $p < 0.05$.

Between CG and SG1 there was a statistical difference during the exam and upon awakening.

Between CG and SG2, there was a statistical difference only during the exam.

Between SG1 and SG2 there was no statistical difference at any time (Table 9).

Comparison of groups in relation to oxygen saturation (SpO_2)

For saturation, no significant interaction was found between group and time of assessment, indicating that the three groups had a similar behavior of SpO_2 over time ($p = 0.364$). There was no evidence that the groups differed from the mean over the follow-up periods ($p = 0.587$).

The table below shows means and standard deviation obtained in the study for each combination of group and time of assessment (Table 10).

The lowest SpO_2 in the three groups was during the exam, when the peak effect of the drug used is expected.

Comparison of groups in relation to hypoxemia

There was no statistical difference regarding the incidence of significant hypoxemia among the three study groups (Table 11).

Comparison of groups in relation to variables eye opening time and post-anesthetic recovery time

Eye opening time was significantly shorter in SG1 and SG2 compared to the Control Group. There was no statistical difference in eye opening time between SG1 and SG2 (Tables 12 and 13).

Post-anesthetic recovery time was significantly shorter in SG1 and SG2 compared to the Control Group. There was no statistical difference in post-anesthetic recovery time between SG1 and SG2 (Tables 12 and 13).

Comparison of groups regarding patient satisfaction

There was no statistical difference regarding patient satisfaction among the three groups (Tables 14 and 15).

Table 12 Comparison of eye-opening time (seconds) and post anesthetic recovery time (seconds) among groups analyzed.

Variable	Group	*n*	Mean	Median	Minimum	Maximum	SD	*p*[a]
Eyes opening time	CG	35	311.1	280.0	139.0	596.0	96.6	< 0.001
	SG1	34	189.5	175.5	86.0	305.0	59.9	
	SG2	35	178.4	181.0	60.0	405.0	75.9	
Post-anesthesia recovery time	CG	35	732.5	715.0	441.0	1196.0	184.2	< 0.001
	SG1	35	583.1	510.0	393.0	1210.0	184.3	
	SG2	35	560.3	510.0	337.0	997.0	172.9	

[a] One-way ANOVA, $p < 0.05$.

Table 13 Comparison of means of eye-opening time and post anesthesia recovery time among groups analyzed two by two (*p*-values).

Comparison of groups	Variable	
	Time to open eyes	Post-anesthesia recovery time
CG × SG1	< 0.001	0.001
CG × SG 2	< 0.001	< 0.001
SG1 × SG2	0.567	0.597

LSD Test, $p < 0.017$ (Bonferroni's correction).

Comparison of groups regarding quality of post-anesthetic recovery and incidence of side effects

All patients reached the maximum score for quality of post-anesthetic recovery, with no statistical difference among the three groups.

There were no cases of side effects in the three groups, and no statistical difference among them.

Discussion

Several studies have already shown that propofol offers significant advantages over benzodiazepines and opioids for sedation during endoscopic procedures. Gasparović et al. indicated that propofol was safer and more effective than midazolam and meperidine to achieve and maintain an adequate level of sedation during endoscopy, resulting in better control of level of sedation and fast recovery.[16]

Hendrickx et al.,[17] in 2008, in a review on the interaction between anesthetics, classified the interaction between two anesthetic drugs as synergistic, additive and infra-additive, when their combined effect exceeds, equals, or is below, respectively, the sum of the effects of the drugs individually.

Table 15 Comparison of patient satisfaction among groups analyzed two by two.

Comparison of groups	*p*[a]
CG × SG 1	1
CG × SG 2	0.493
SG 1 × SG 2	0.493

[a] Fisher's exact test, $p < 0.017$ (Bonferroni's correction).

Interactions of drugs that act on the same site of action usually produce an additive effect. Synergistic effects are due to different mechanisms and sites of action. Acknowledging these concepts of interaction enables us to use lower doses of each drug, potentiating their anesthetic effects and reducing their adverse effects. Propofol and opioid are combined to take advantage from the enhanced effects that result from their interaction.

Based on the known synergism between propofol and remifentanil, one can expect potentiation of their desired pharmacodynamic effects and reduction of their side effects. In 2006, Fidler and Kern[18] had already observed the relative level of interaction between propofol and remifentanil, and proposed a flexible drug interaction model for their pharmacodynamic effects. Accordingly, the combination of doses between propofol and remifentanil can be done asymmetrically depending on the desired effect. Hayes et al.,[12] in 2008, analyzing the combination of remifentanil with propofol, found that increasing the remifentanil dose and reducing the propofol dose increased the duration of apnea and decreased recovery time. When the remifentanil dose was reduced and the propofol dose increased, there was reduction in apnea time and increase in recovery time.

In our study, we opted for low doses of remifentanil compared to previous studies,[12,19] as both drugs are powerful ventilation depressants.

As previously mentioned, endoscopists were more satisfied with the propofol sedation technique.[8,20] Due to the

Table 14 Comparison of patient satisfaction among groups analyzed.

Patient satisfaction	CG		SG 1		SG 2	
	n	%	n	%	n	%
7 and 8	0	0	0	0	2	5.7
9 and 10	35	100	35	100	33	94.3
Total	35	100.0	35	100.0	35	100.0

wide range drug arsenal available, the objective of the present study was to associate an opioid to optimize the response to the stimulus associated with endoscope insertion and maneuvers performed during the exam. Using remifentanil in the proposed doses was accompanied by statistically confirmed better quality of sedation and higher satisfaction of endoscopists. There was no difference in the quality of sedation between the two groups that used different doses of remifentanil.

Kho et al. found that the propofol-remifentanil association, when compared to the administration of propofol alone, significantly reduced the dose of propofol required. They also found a significant reduction in arterial blood pressure when propofol was combined with remifentanil compared to propofol used alone.[21] However, the methodology used was different in terms of administration regimen, dose of remifentanil and time of data collection.

All anesthetic drugs or drug associations cause hemodynamic changes, which also occur in response to pain stimulus. Upper GI endoscopy is often accompanied by tachycardia, suggesting the occurrence of an endocrine response to the stress caused by the exam.[22]

When comparing the three groups, one can observe that the moment with the greatest number of parameters with a statistical difference occurred during the exam, that is, when painful stimulus was applied: there was simultaneous statistical difference for HR and MAP values of the CG compared to both SG1 and SG2. During the examination, the control group was characterized by higher heart rate and mean arterial pressure than in the two study groups. There was no statistical difference between SG1 and SG2 in any of these parameters. Probably, even when remifentanil is used in small doses, it promotes analgesia, prevents adrenergic response and contributed to our findings.

A recent meta-analysis demonstrated that using propofol in simple endoscopic procedures was associated with a reduction in the number of complications when compared to other anesthetic agents.[23] Opioids are known as powerful respiratory depressants, thus, one of the main study goals was to learn the repercussion that the association with remifentanil would have on oxygen saturation and on the incidence of significant hypoxemia when compared to the isolated use of propofol. It was shown that neither remifentanil doses assessed changed the values of oxygen saturation or the incidence of significant hypoxemia in relation to the Control Group. The low doses of remifentanil were not enough to cause a higher incidence of hypoxemia. Oxygen saturation less than 92% for more than 15 seconds was chosen to define significant hypoxemia, according to a previous study.[24] An oxygen saturation value below 85% was added to this criterion, for being potentially harmful.[25] We found the significant hypoxemia rates of 17.1% in the CG, 14.3% in SG2, and 11.4% in SG1. Li et al. used a different methodology and found an incidence of hypoxemia ranging from 10% to 40% in upper GI endoscopies with propofol-only sedation. The variation was associated with the rate of infusion and the dose used. Higher infusion rates and higher doses were related to higher incidence of hypoxemia and was the most common complication in their study.[26]

Remifentanil has shorter pharmacodynamic effects than propofol. This explains why both SG1 and SG2 had a statistically shorter spontaneous eye-opening time compared to the control group, with no significant difference found between the two study groups.

The scale proposed by Salim[27] (Supplementary Material Annex 3), which assesses three clinical parameters (Airways, Behavior, Consciousness), was adopted to assess time and quality of post-anesthetic recovery. The author established and validated the minimum score of 8 for patients to be discharged from the post-anesthetic recovery room.

Both spontaneous eye opening and post-anesthetic recovery time were shorter in the groups in which the remifentanil and propofol combination was used when compared to the propofol-only control group. The result is also explained by remifentanil's shorter pharmacodynamic effects.

Given both drugs have desirable pharmacokinetic characteristics and very short pharmacodynamic effects, the quality of anesthetic recovery was very satisfactory, reaching a maximum score in all patients.

In any patient-centered treatment, patient satisfaction and quality of recovery are essential measures.[28] When comparing different management strategies, one should consider these two aspects. We chose to use low doses of remifentanil because using opioids might reduce the quality of the recovery period due to side effects. Nausea, vomiting, and itching are among the most recurrent side effects of opioids and they are addressed by the present study. Propofol, in turn, has a widely documented antiemetic effect. In patients undergoing upper GI endoscopy under sedation, an increase in the rate of side effects can have several implications such as delayed hospital discharge, increased costs and reduced patient satisfaction. None of the patients assessed during the proposed study period reported side effects after the exam.

Reichheld[29] created a method to assess the level of customer satisfaction with a particular product or service (Supplementary Material Annex 4). The author demonstrated that customers that are satisfied with the service provided, in addition to remaining customers, function as promoters, that is, they make positive references and recommend the product or service to other potential customers.

The level of satisfaction among patients was found to reach the highest projected level. There was no statistical difference among the groups studied. Only two patients in SG2 graded their satisfaction as 7 and 8.

Our study assessed all proposed goals. Possible differences in the results found in relation to previous studies may be due to several factors such as sample with a different population age and ASA physical status, variable rate of injection, distinct drug doses, or even different criteria used in the classification of a given clinical outcome.

Conclusions

The ideal quality of sedation was statistically higher in SG1 than in the CG.

There was no statistical difference in mean arterial pressure at any time between SG1 and SG2. There was a statistically significant difference in heart rate between the two groups, only after administration of remifentanil. The Control Group showed statistical differences for mean

arterial pressure and heart rate at some point in relation to both SG1 and SG2.

The association of remifentanil with propofol did not change oxygen saturation or the incidence of hypoxemia.

The association of remifentanil with propofol reduced the time for spontaneous eye opening after propofol discontinuation.

The association of remifentanil with propofol reduced post-anesthetic recovery time.

The association of remifentanil with propofol showed no significant differences in the quality of post-anesthetic recovery, in patient level of satisfaction, or in the incidence of side effects.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2020.03.003.

References

1. Triantafillidis JK, Merikas E, Nikolakis D, et al. Sedation in gastrointestinal endoscopy: current issues. World J Gastroenterol. 2013;19:463–81.
2. Lin OS. Sedation for routine gastrointestinal endoscopic procedures: a review on efficacy, cost and satisfection. Intest Res. 2017;15:456–66.
3. Lewis JR, Cohen LB. Update on colonoscopy preparation, premedication and sedation. Expert Ver Gastroenterol Hepatol. 2013;7:77–87.
4. Pambianco DJ, Vargo JJ, Pruitt RE, et al. Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study. Gastrointest Endoscopy. 2011;73:765–72.
5. Heuss LT, Froehlich F, Beglinger C. Changing patterns of sedation and monitoring practice during endoscopy: results of a Nationwide survey in Switzerland. Endoscopy. 2005;37:161–6.
6. Porostocky P, Chiba N, Colacino P, et al. A survey of sedation practices for colonoscopy in Canada. Can J Gastroenterol. 2011;25:255–60.
7. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: a nationwide web survey in Italy. Dig Liver Dis. 2011;43:726–30.
8. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a Nationwide survey. Am J Gastroenterol. 2006;101:967–74.
9. Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anestesia in GI endoscopy. Gastrointest Endosc. 2008;68:815–26.
10. Macario A, Weinger M, Carney S, et al. Which clinical anesthesia outcomes are importante to avoid? The perspective of patients. Anesth Analg. 1999;89:652–8.
11. Macario A, Weinger M, Truong P, et al. Which clinical anesthesia outcomes are both common and importante to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg. 1999;88:1085–91.
12. Hayes JA, Lopez AV, Pehora CM, et al. Coadministration of propofol and remifentanil for lumbar puncture in children. Anesthesiology. 2008;109:613–8.
13. Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. Anesthesiology. 2000;92:1603–16.
14. Harris ZP, Liu J, Saltzman JR. Quality assurance in the endoscopy suíte: sedation and monitoring. Gastrointest Endosc Clin N Am. 2016;26:553–62.
15. Uliana GN, Tambara EM, Baretta GAP. Use of remifentanil to reduce propofol injection pain and the required propofol dose in upper digestive tract endoscopy diagnostic tests. Rev Bras Anestesiol. 2015;65:437–44.
16. Gasparović S, Rustemović N, Opacić M, et al. Clinical analysis of propofol deep sedation for 1104 patients undergoing gastrointestinal endoscopic procedures: a three year prospective study. World J Gastroenterol. 2006;12:327–30.
17. Hendrickx JFA, Eger EI, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg. 2008;107:494–506.
18. Fidler M, Kern SE. Flexible interaction model for complex interactions of multiple anesthetics. Anesthesiology. 2006;105:286–96.
19. Egan TD, Kern SE, Muir KT, et al. Remifentanil by bolus injection: a safety, pharmacokinetic, pharmacodynamic, and age effect investigation in human volunteers. Br J Anaesth. 2004;92:335–43.
20. Zhang R, Lu Q, Wu Y. The comparison of midazolam and propofol in gastrointestinal endoscopy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech. 2018;28:153–8.
21. Koh JC, Park J, Kim NY, et al. Effects of remifentanil with or without midazolam pretreatment on the 95% effective dose of propofol for loss of consciousness during induction. Medicine. 2017;96:49.
22. Yetkin G, Oba S, Uludag M, et al. Effects of sedation during upper gastrointestinal endoscopy on endocrine response and cardiorespiratory function. Braz J Med Biol Res. 2007;40:1647–52.
23. Wadhwa V, Issa D, Garg S, et al. Similar risk of cardiopulmonary adverse events between propofol and traditional anesthesia for gastrointestinal endoscopy: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2017;15:194–206.
24. Kauling ALC, Locks GF, Brunharo GM, et al. Conscious sedation for upper digestive endoscopy performed by endoscopists. Rev Bras Anestesiol. 2010;60:577–83.
25. Bell GD. Premedication, preparation, and surveillance. Endoscopy. 2000;32:92–100.
26. Li Q, Zhou Q, Xiao W, et al. Determination of the appropriate propofol infusion rate for outpatient upper gastrointestinal endoscopy – a randomized prospective study. BMC Gastroenterol. 2016;16:49.
27. Salim M. Transfer from recovery room to ward. Br J Anaesth. 1988;61:241.
28. Bruder N, Auquier P. Integration of satisfaction and quality of recovery. Best Pract Res Clin Anaesthesiol. 2018;32:269–76.
29. Reichheld FF. The one number you need to grow. Harv Bus Rev. 2003;81:46–54.