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SCIENTIFIC ARTICLE

Use of remifentanil to reduce propofol injection pain and the required propofol dose in upper digestive tract endoscopy diagnostic tests



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Abstract

Background and objectives: The introduction of propofol (2,6-diisopropylphenol) as a sedative agent has transformed the area of sedation for endoscopic procedures. However, a major drawback of sedation with the use of propofol is its high incidence of injection pain. The most widely used technique in reducing propofol injection pain is through the association of other drugs. The aim of this study was to evaluate the effect of remifentanil-propofol combination on the incidence of propofol injection pain and its influence on the total dose of propofol required for sedation in upper digestive tract endoscopy (UDE) diagnostic tests.

Method: One hundred and five patients undergoing upper digestive tract endoscopy were evaluated and randomly divided into 3 groups of 35 patients each. The Control Group received propofol alone; Study-group 1 received remifentanil at a fixed dose of 0.2 mg/kg combined with propofol; Study-group 2 received remifentanil at a fixed dose of 0.3 mg/kg combined with propofol. The incidence of propofol injection pain and the total dose of propofol required for the test were evaluated. The sample was very similar regarding age, weight, height, sex, and physical status. Statistical analysis was performed according to the nature of the evaluated data. Student's *t*-test was used to compare the mean of age, weight, height (cm), and dose (mg/kg) variables between groups. The χ^2 test was used to compare sex, physical status, and propofol injection pain between groups. The significance level was $\alpha < 0.05$.

Results: There was significant statistical difference between the study groups and the control group regarding the parameters of propofol injection pain and total dose of propofol (mg/kg)

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PALAVRAS-CHAVE

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used. However, there were no statistical differences between the two study groups for these parameters.

Conclusion: We conclude that the use of remifentanil at doses of 0.2 mg/kg and 0.3 mg/kg was effective for reducing both the propofol injection pain and the total dose of propofol used.

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Uso do remifentanil para redução da dor à injeção de propofol e a dose necessária de propofol em exames de endoscopia digestória alta diagnóstica
Resumo

Justificativa e objetivos: A introdução do propofol (2,6-di-isopropilfenol) como agente sedativo tem transformado a área da sedação para procedimentos endoscópicos. Entretanto, um grande inconveniente da sedação com o uso do propofol é sua alta incidência de dor à injeção. A técnica mais usada na redução da dor à injeção do propofol tem sido a associação com outros fármacos. O objetivo deste estudo foi avaliar a repercussão da associação do remifentanil com o propofol na incidência de dor à injeção de propofol e a influência na dose total de propofol necessária para sedação em endoscopia digestória alta (EDA) diagnóstica.

Método: Foram avaliados 105 pacientes, submetidos à EDA diagnóstica e divididos aleatoriamente em três grupos de 35. O Grupo Controle foi sedado apenas com propofol. O Grupo de Estudo 1 foi sedado com remifentanil em dose fixa de 0,2 µg/kg associado ao propofol. E o Grupo de Estudo 2 foi sedado com remifentanil em dose fixa de 0,3 µg/kg associado ao propofol. Foram avaliadas a incidência de dor à injeção de propofol e a dose de propofol necessária para o exame. A amostra se mostrou bastante similar em relação às variáveis idade, peso, altura, sexo e estado físico. De acordo com a natureza dos dados estudados, procedeu-se ao tratamento estatístico julgado adequado. Usou-se o teste *t* para comparação, entre os grupos analisados, das médias das variáveis idade, peso, altura (cm) e dose (mg/kg). Foi usado o teste χ^2 para comparação, entre os grupos analisados, das variáveis sexo, estado físico e dor à injeção de propofol. O nível de significância adotado foi $\alpha < 0,05$.

Resultado: Houve diferença estatística significativa entre os grupos de estudo e o grupo controle tanto no parâmetro dor à injeção de propofol quanto no parâmetro dose de propofol usada (mg/kg). Entretanto, não houve diferenças estatísticas entre os dois grupos de estudo para esses parâmetros.

Conclusão: O uso do remifentanil nas doses de 0,2 µg/kg e de 0,3 µg/kg mostrou-se efetivo tanto sobre o parâmetro redução da dor à injeção de propofol quanto sobre o parâmetro dose de propofol usada.

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Introduction

In many countries, sedation has become routine in patients undergoing colonoscopy and diagnostic upper digestive tract endoscopy (UDE).¹ According to a survey from the American College of Gastroenterologists, sedation is used in over 98% of colonoscopy exams and UE in the United States.² The term sedation is used for depression of an individual's level of consciousness. Sedation is used to promote anxiolysis, amnesia, and, in some instances, analgesia.³

The introduction of propofol (2,6-diisopropylphenol) as a sedative agent has transformed the area of sedation for endoscopic procedures.³ Much of propofol's popularity between physicians and patients is related to its

pharmacokinetic and pharmacodynamic properties, which gives the drug a quick start and end of its effects and provides the patient a sense of well-being.³ In many respects, propofol is an ideal agent for short procedures in outpatients. However, because of its pharmacological profile, one of its recommendations is to be used only by professionals trained in the administration of general anesthesia.⁴ A major drawback of sedation using propofol is its high incidence of injection pain.^{5,6} The presence of propofol injection pain ranges from 28%⁷ to 90%⁸ of cases.

Macario et al.⁹ questioned among American anesthesiologists which anesthetic clinical outcomes are common and necessary to avoid. Propofol injection pain during anesthetic induction was ranked as the seventh most important

among 33 clinical outcomes, when taking into account frequency and clinical significance together. Many studies have been conducted seeking to minimize or resolve this problem.¹⁰ Even after changing the original formulation of propofol, the cremophor thinner, which was linked to anaphylactic reaction,¹¹ to a lipid emulsion, the pain remained. This shows that it is due to the drug itself, not the formulação.¹² That is to say that the use of lipid emulsion almost abolished the pain associated with diazepam and etomidate injection.^{13–15} Optional propofol formulations with changes in the composition of the lipid emulsion, different fractions of medium- and long-chain triglycerides, and use of different preservatives, such as ethylenediaminetetraacetic acid (EDTA) and sodium metabisulfite, did not eliminate the injection pain.¹⁶ However, it has been suggested that increased lipid solvent content may reduce the concentration of free propofol in the aqueous phase and its contact with free nerve endings, which could reduce propofol injection pain during.^{17–22} Recommendations such as using large-caliber veins help reduce propofol injection pain. However, the most widely used technique to reduce propofol injection pain has been the combination of other drugs such as lidocaine,^{23–25} ephedrine,²⁴ magnesium sulfate,²⁶ thiopental,²⁵ ketamine,²⁷ acetaminophen,²⁸ and tramadol,²⁹ among others.

Opioids are the drugs most commonly used in combination with propofol for anesthesia. Its use in the reduction of propofol injection pain is widespread and has proved to be effective in most clinical studies,^{30,31} although it was proved ineffective in the study by Basaranoglu et al.³² It is known that intravenous anesthetics, such as hypnotics, opioids, and benzodiazepines, combine synergistically during anesthesia.³³ These drugs are associated in order to potentiate the effects of the interaction between propofol and opioids³⁴; thus, the desired effects can be achieved with lower doses of drugs. In very short outpatient procedures, such as endoscopic examinations or lumbar puncture in pediatric patients,³⁵ the association of remifentanil and propofol enables extremely fast recovery with short duration pharmacodynamic effects.

The aim of this study was to evaluate the effects of remifentanil associated with propofol in the incidence of propofol injection pain and, concomitantly, the influence of the remifentanil association on propofol dose required for sedation in diagnostic UDE.

Method

The study was conducted after approval by the Research Ethics Committee of the institution, and all patients were informed about the project and signed the informed consent.

A total of 105 patients of both genders, physical status ASA I or II, undergoing diagnostic UDE was selected. Exclusion criteria were patients aged under 18 and over 65, pregnant women with a history of allergy to any component of the study drugs, in whom it was necessary, in addition to the diagnostic test, any kind of therapy during the procedure, and any patient with physical status ASA > II.

The patients were randomly divided into three groups by drawing lots:

Control Group ($n=35$), received sedation with propofol alone for diagnostic UDE.

Study Group 1 ($n=35$), received sedation with remifentanil at fixed dose of $0.2 \mu\text{g}/\text{kg}$ combined with propofol for diagnostic UDE.

Study Group 2 ($n=35$), receive sedation with remifentanil at fixed dose of $0.3 \mu\text{g}/\text{kg}$ combined with propofol for diagnostic UDE.

Patients who met the inclusion criteria were monitored with cardioscopy, pulse oximetry, and noninvasive blood pressure, using the multiparameter Philips C3 Monitor, type glasses nasal catheter placement with O_2 flow (3L/min) and peripheral 22G venous puncture catheter in antecubital region for 0.9% isotonic saline and sedatives infusion. The patients were then placed in the left lateral position for the exam.

Using a syringe, 10 mL isotonic 0.9% saline at a rate of 1 mL every 3 s was administered to the Control Group; remifentanil $0.2 \mu\text{g}/\text{kg}$ to the Study Group 1; and remifentanil $0.3 \mu\text{g}/\text{kg}$ to the Study Group 2. Subsequently, propofol was administered using a 20 mL syringe at a rate of 1 mL every 3 s. During propofol injection, the patient was asked if he felt any pain in the arm with the catheter and if it was located at the injection site. All patients were asked identically. Propofol was injected to loss of consciousness, checked by the lack of response to verbal stimulation and loss of ciliary reflex and confirmed by all team members. All examinations were performed by the same endoscopist, and the time of the patient's recovery was verified by spontaneous eye opening in response to verbal stimulation.

Data on age, weight, sex, height, physical status, presence or absence of propofol injection pain and propofol dose at mg/kg were recorded in specific worksheet at the proposed time points.

According to the nature of the data studied, the appropriate statistical analysis was performed. We used the t test to compare between groups the mean of the variables age, weight, height (cm), and dose (mg/kg). The χ^2 test was used to compare gender, physical status, and propofol injection pain between groups. The significance level was $\alpha < 0.05$.

Results

The groups were homogeneous with respect to age, weight, height, sex, and physical status. A descriptive summary of each group is shown in [Tables 1–3](#).

The incidence of propofol injection pain in Control Group was present in 40% of patients and significantly lower in the study groups pre-medicated with doses of remifentanil $0.2 \mu\text{g}/\text{kg}$ (14.28%) and remifentanil $0.3 \mu\text{g}/\text{kg}$ (14.28%). There was no statistical difference between the Study Groups 1 and Study Group 2 regarding the incidence propofol injection pain ([Table 4](#) and [Figs. 1–3](#)).

The mean dose of propofol used was 2.07 mg/kg in Control Group, with a range from 0.93 to 3.17 mg/kg, and it was

Table 1 Comparison of mean age, weight, and height (cm) in the analyzed groups: *t* test.

Groups	<i>n</i>	Idade		<i>p</i>
		Min-max	Mean ± SD	
Study 1	35	18-60	36.17 ± 11.73	0.34
Study 2	35	20-52	33.89 ± 7.99	
Study 1	35	18-60	36.17 ± 11.73	0.43
Control	35	20-60	34.14 ± 9.28	
Study 2	35	20-52	33.89 ± 7.99	0.90
Control	35	20-60	34.14 ± 9.28	

Groups	<i>n</i>	Weight		<i>p</i>
		Min-max	Mean ± ± SD	
Study 1	35	48-98	69.20 ± 13.19	0.77
Study 2	35	50-94	70.09 ± 11.87	
Study 1	35	48-98	69.20 ± 13.19	0.12
Control	35	50-110	74.00 ± 12.18	
Study 2	35	50-94	70.09 ± 11.87	0.18
Control	35	50-110	74.00 ± 12.18	

Groups	<i>n</i>	Height (cm)		<i>p</i>
		Min-max	Mean ± SD	
Study 1	35	150-180	165.77 ± 7.01	0.75
Study 2	35	150-182	166.34 ± 7.88	
Study 1	35	150-180	165.77 ± 7.01	0.34
Control	35	155-184	167.57 ± 8.51	
Study 2	35	150-182	166.34 ± 7.88	0.53
Control	35	155-184	167.57 ± 8.51	

n, number of patients; min-max, minimum and maximum values; SD, standard deviation; *p*, *p*-value probability.

significantly higher than that required in the study groups. The mean dose of propofol in the premedicated group with remifentanil 0.2 µg/kg was 1.25 mg/kg, with a range from 0.89 to 2.17 mg/kg. And the average dose of propofol in the group premedicated with remifentanil 0.3 µg/kg was 1.19 mg/kg, with a range of 0.51-1.91 mg/kg. There was no statistical difference in the mean mg/kg dose of propofol used between the two study groups (Table 5 and Fig. 4).

Table 2 Comparison of sex in the analyzed groups: χ^2 test.

Groups	Sex		Total	<i>p</i>
	Male	Female		
Study 1	10	25	35	0.78
Study 2	8	27	35	
Study 1	10	25	35	0.61
Control	13	22	35	
Study 2	8	27	35	0.30
Control	13	22	35	

p, *p*-value probability.

Table 3 Comparison of physical status in the analyzed groups: χ^2 test.

Groups	ASA		Total	<i>p</i>
	1	2		
Study 1	29	6	35	0.26
Study 2	24	11	35	
Study 1	29	6	35	1.0
Control	30	5	35	
Study 2	24	11	35	0.15
Control	30	5	35	

p, *p*-value probability.

Table 4 Comparison of propofol injection pain in the analyzed groups: χ^2 test.

Groups	Propofol injection pain		Total	<i>p</i>
	Yes	No		
Study 1	5	30	35	0.73
Study 2	5	30	35	
Study 1	5	30	35	0.03
Control	14	21	35	
Study 2	5	30	35	0.03
Control	14	21	35	

p, *p*-value probability.

Discussion

For diagnostic UDE, the ideal characteristics of the drugs would be a quick connection with the effect site, reduced accumulation in the body, and rapid elimination, which would promote rapid pharmacodynamic effects, such as early hypnosis, deep sedation, rapid and efficient control use of autonomic responses, and early awakening.

Anesthetics with these characteristics have a higher predictability of its pharmacodynamic effects, which gives a

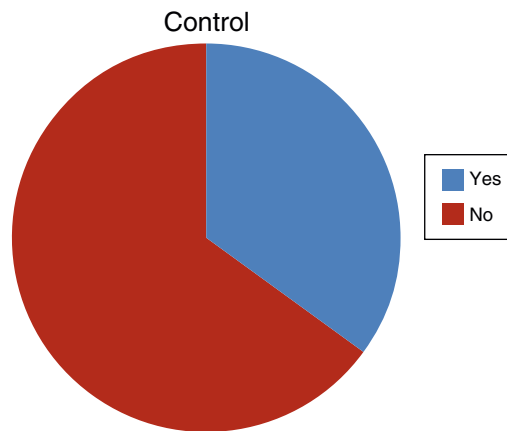


Figure 1 Frequency of propofol injection pain in Control Group.

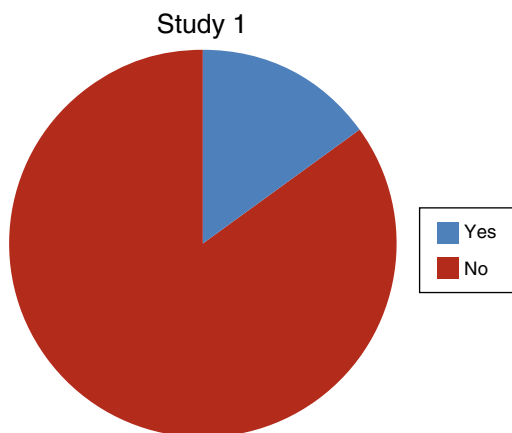


Figure 2 Frequency of propofol injection pain in Study Group 1.

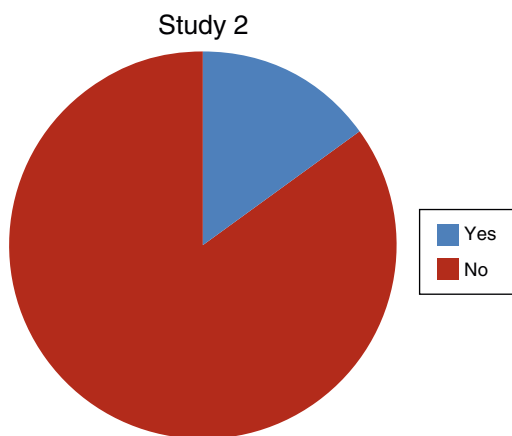


Figure 3 Frequency of propofol injection pain in Study Group 2.

greater safety margin to the anesthesiologist and prevents, for example, a prolonged awakening or late respiratory depression.

Propofol is a safe and effective drug for gastrointestinal endoscopic procedures and is associated with shorter recovery period and earlier hospital discharge, higher scores

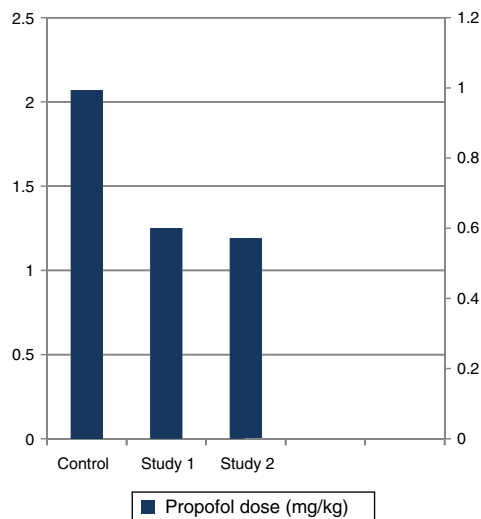


Figure 4 Comparison of propofol dose used in Control Group and Study Groups.

of post-anesthetic recovery, better sedation and increased patient compliance regarding traditional sedation, without a increase in cardiopulmonary complications.³⁶ However, it is a drug that has a high rate of injection pain, especially with smaller caliber veins, such as the back of hands.³⁷ To reduce propofol injection pain, puncture of larger caliber veins, such as the antecubital region, should be recommended for induction and maintenance of anesthesia techniques based on the use of this drug.

In our study, it was shown that even with the puncture of larger caliber veins, the incidence of propofol injection pain still remained very high, around 40%.

Although the pain etiology is not exactly established, different methods and different drugs have been used to reduce its incidence and severity.²⁴ The combination of drugs with the aim to reduce propofol injection pain is an effective and technically easy method and independent of the punctured vein location. Most drugs associated with propofol to reduce injection pain or was not studied or do not significantly reduce the propofol dose required for induction of anesthesia.^{29,38} In some studies, the use of lidocaine combined with propofol decreased the anesthetic potency of propofol.^{39,40}

Opioids are drugs used in association with propofol for general anesthesia and sedation. An important reason for this choice in the present study is that opioids are synergistically combined with propofol and effectively reduce its total dose during anesthesia. Fentanyl and alfentanil, although widely used in anesthesia, have the disadvantage of extending its clinical to the postoperative period, particularly in short procedures. A reasonable goal would be to reduce propofol injection pain without the appearance of other adverse effects, such as delayed recovery from anesthesia.

The choice of remifentanyl was based on its rapid onset and offset of action, which decreases the incidence of residual side effects. However, due to the pharmacodynamic characteristics, during general anesthesia it should be administered as a continuous infusion. The use of bolus

Table 5 Comparison of mean dose (mg/kg) in the analyzed groups: *t* test.

Groups	<i>n</i>	Dose (mg/kg)		<i>p</i>
		Min-max	Mean ± SD	
Study 1	35	0.89-2.17	1.25 ± 0.29	0.48
Study 2	35	0.51-1.91	1.19 ± 0.32	
Study 1	35	0.89-2.17	1.25 ± 0.29	<0.0001
Control	35	0.93-3.17	2.07 ± 0.53	
Study 2	35	0.51-1.91	1.19 ± 0.32	<0.0001
Control	35	0.93-3.17	2.07 ± 0.53	

n, number of patients; min-max, minimum and maximum values; SD, standard deviation; *p*, *p*-value probability.

dose of emifentanil without an infusion is suitable only for clinical procedures that require intense analgesia, such as in diagnostic and therapeutic procedures performed outside the operating room and lasting only a few minutes.⁴¹ It requires less preparation time of anesthesia, has a lower cost because it does not require infusion pumps and specific infusers. In 2004, Egan et al. used remifentanil at dose bolus of up to 200 μg , which showed more significant ventilatory effects in the elderly than in young patients.⁴¹ These effects were short-lived and easily managed only with verbal stimulation and oxygen addition (2 L/min). The interaction model and ventilatory involvement proposed by La Pierre et al.⁴² in 2012, suggests the occurrence of greater airway obstruction with higher concentrations of propofol and an intolerable ventilatory depression with high concentrations of remifentanil. The same author also proposes a significant synergism between both drugs. This indicates that lower doses of each are required to achieve the same effect. The results found by Hayes et al., in 2008, indicate that in the propofol-remifentanil combination, the option of increasing the remifentanil dose (1.5 $\mu\text{g}/\text{kg}$) and decreasing the propofol dose (2 mg/kg) increased the duration of apnea and reduced the recovery time; with reduced remifentanil dose (0.5 $\mu\text{g}/\text{kg}$) and increased propofol dose (4 mg/kg), the time of apnea was reduced and the recovery period increased.³⁵

The use of pre-injection bolus doses of remifentanil (0.2 and 0.3 $\mu\text{g}/\text{kg}$) considered low compared to doses previously studied^{30,32,35,41} is justified because it is a diagnostic test of short duration, in which there is a restriction regarding airway management, with the greatest stimulus during the device introduction, the peak time of the opioid effect that, according to Egan et al., 2004, occurred 2.5 min after injection.⁴¹ The option for a lower dose of remifentanil was similar to that suggested by Drover et al.,⁴³ in 2004, because in their study during esophagogastroduodenoscopy in children, lower doses minimized episodes of oxygen desaturation. Increasing the dose of remifentanil does not diminish the need for propofol and increases the risk of side effects related to opioid. Jeong et al.,⁴⁴ in 2011, showed that a dose of 0.3 $\mu\text{g}/\text{kg}$ was effective in reducing propofol injection pain even with the use of the dorsal hand veins when mixed with lidocaine; however, doses of 0.5 and 1.0 $\mu\text{g}/\text{kg}$ were more effective.

Because both drugs are potent depressant of ventilation and based on the principle of an asymmetric interaction curve between the drugs, as the one proposed by Fidler et al.,⁴⁵ in 2006, and on the results previously found by Hayes et al.,³⁵ in 2008, we decided in this study to use a low dose of remifentanil and assess the pharmacodynamic interaction with propofol during endoscopic examinations. Another reason for choosing these doses is due to the fact that large veins of the antecubital region were chosen for venous access, which would be a reduction factor of propofol injection pain.

In our study, as in many others,⁴⁶⁻⁵⁰ it is shown that remifentanil is effective in reducing propofol injection pain; however, our study also quantifies the effect of two doses of remifentanil over the propofol dose required to achieve a pharmacodynamic effect during the proposed procedure.

At doses of 0.2 and 0.3 $\mu\text{g}/\text{kg}$, remifentanil did not cause sedative effect that could alter the patient's perception and

his responsiveness to the incidence of propofol injection pain.

Previous studies that used remifentanil to reduce propofol injection pain have methodological differences from the present study. Roehm et al.,⁴⁶ in 2003, collected data from patients pretreated with midazolam, using venous catheter on the dorsum of the hand and continuous infusion of remifentanil. Batra et al.,⁵¹ in 2004, used bolus doses, but with venipuncture in the back of the hand of pediatric patients, in addition to using behavioral parameters for measurement of pain, such as presence of grimace, cry, and hand removal, and not by patient's objective response. Although propofol the time of balance is greater than the remifentanil, remifentanil was given first because one of the study's objectives was precisely to assess the interference in the propofol dose required for the exam.

The objectives were effectively proven. In addition to a significant reduction in propofol injection pain, we also found a significant reduction in the propofol dose required for diagnostic UDE.

The difference in results compared with previous studies may be due to non-use of premedication, different injection rate, different age population sample, choice of larger caliber veins of the antecubital region, and pre-injection of remifentanil in different doses to previous studies.

In this study, the assessment of sedation with propofol in combination or not with remifentanil in patients undergoing diagnostic UDE allowed the following conclusions:

Pretreatment with remifentanil significantly reduced propofol injection pain.

Pretreatment with remifentanil significantly reduced the propofol dose required for sedation.

There was no statistically significant difference between the groups receiving pretreatment with remifentanil at doses of 0.2 $\mu\text{g}/\text{kg}$ and 0.3 $\mu\text{g}/\text{kg}$ regarding propofol injection pain and interference in the used dose of propofol.

Conflicts of interest

The authors declare no conflicts of interest.

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