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Effects of moderate sedation induced by propofol or midazolam on intracranial pressure

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ABSTRACT

Introduction: Propofol and midazolam are the main options for moderate sedation in clinical practice. In addition, these drugs are used to reduce intracranial pressure in cases of intracranial hypertension, and their use in these situations is guided by limited evidence. **Objective:** To compare the effects of propofol and midazolam on intracranial pressure wave morphology in moderate sedation in patients undergoing upper digestive endoscopy. **Methods:** Sixty patients were included in this study, being divided into two groups, propofol and midazolam group. Intracranial pressure was monitored during and after upper digestive endoscopy, using non-invasive monitoring equipment developed by the company Brain4care. Arterial pressure was measured before and after the exam. **Results:** The propofol group had lower intracranial pressure (p=0.037) during moderate sedation compared to intracranial pressure after endoscopy and a significant decrease in systolic (p=0.0001) and diastolic pressure (p=0.001) after sedation. Midazolam, on the other hand, reduced systolic pressure (p=0.001), but didn't change the other parameters after the procedure. There wasn't a significant difference between the propofol and midazolam groups. **Conclusion:** There was no significant difference between the groups studied, however, analyses within the propofol and midazolam groups indicate that propofol, but not midazolam, causes changes in intracranial pressure in moderate sedation.

Keywords: arterial pressure; conscious sedation; opioids; receptors, GABA-A.

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INTRODUCTION

Sedation is a depression at the level of consciousness, induced and maintained by drugs, which act on the central nervous system. The use of moderate sedation in upper gastrointestinal endoscopy (UGIE) is routine in most hospitals and clinics, as it provides tolerance to the discomfort of the procedure and optimal conditions for the exam[1]. Endoscopy is a common procedure frequently used in the treatment and diagnosis of gastrointestinal disorders[2].

Among the drugs used at this level of anesthesia, propofol and midazolam stand out. Propofol is a dialkylphenol, which has become the most common agent for inducing

anesthesia, as well as a popular intravenous sedative. This drug enhances the response to GABA in GABA-A receptors and directly activates its function[3]. When administered, it has a rapid onset of action, about 0.5 - 1.0 minutes, lasting about 4-8 minutes and a rapid recovery profile, however, there are adverse effects such as respiratory depression and hypotension[4].

Midazolam belongs to the benzodiazepine class and also acts on GABA-A receptors, as an agonist, producing anxiolytic, sedative-hypnotic, anticonvulsant, and myorelaxative action[2]. Its lipophilicity provides a quick distribution through the blood-brain barrier, with its action beginning in about 1-2.5 minutes after administration. The main side effects associated with its use are respiratory depression, respiratory arrest and hypotension[1], which occur due to the depressant effects on the respiratory center, decreasing the ventilatory response to CO_2[5].

Anesthetic agents have variable effects on intracranial pressure (ICP) and the rate of cerebral oxygen metabolism (CMRO2)[6,7]. In the literature, these effects caused by propofol and midazolam are still not fully understood, as some authors point out that propofol and midazolam have equivalent effects on the reduction of ICP[6,8], others claim that midazolam has a less visible effect on ICP about propofol[9,10] and some relate midazolam to non-significant effects on ICP[11].

Variations in ICP are expected under physiological conditions, but maintaining normal levels is important for preventing complications[12]. Exhaustion of compensatory mechanisms and increased ICP can cause symptoms such as papilledema, nausea, and vomiting, in addition to lethargy and irritability, symptoms that usually precede the Cushing reflex, a condition that occurs with the decompensation of ICP and includes bradycardia, bradypnea, and hypertension, signs that indicate the potential occurrence of cerebral herniation. Another serious condition caused by the increase in ICP is the occurrence of cerebral ischemia due to the decrease in cerebral perfusion pressure (CPP)[13,14].

Frigieri et al.[15] developed a non-invasive monitoring system (Brain4care® methodology), in which a sensor (mechanical strain gauge) is positioned externally under the scalp in the lateral parietal region and detects small deformations of the skull resulting from variations in the ICP. ICP waves are directly related to brain compliance. The simplicity of applying this method and its low cost, allow the monitoring of ICP in patients, situations and environments never studied before.

Using the Brain4care® methodology, in about 3 minutes it's possible to make an accurate assessment of intracranial pressure, based on the results of this research in the comparison of propofol and midazolam, this monitoring methodology can help in choosing the type of sedation, or the option for not using sedation, according to the information collected regarding the intracranial pressure of each patient, for greater safety.

Thus, this research aims to contribute to advances in this area of knowledge, exploring the effects of midazolam and propofol on intracranial pressure in sedation for upper digestive endoscopy.

METHODS

This research was approved by the Ethics and Research Committee of the Universidade Estadual of Ponta Grossa (UEPG) through Plataforma Brasil, under the opinion of number 2.788.026. All volunteers were informed of the research procedures and, agreeing to participate, signed the free and informed consent form. This research included 60 volunteers, admitted for the examination of upper gastrointestinal endoscopy at the Acras Gastroenterology and Digestive Endoscopy Clinic, between November 2018 and August 2019. Patients who underwent the examination without the use of sedation were excluded, as those who didn't have the completed exam and those who didn't have a sufficient sample for analysis. The choice of sedation for each patient was made by the responsible endoscopist using medical criteria, and from this choice, the two groups analyzed in this research were defined, the propofol group, and the midazolam group. From this choice, the two groups analyzed in this research were defined, the propofol group (n=37), and the midazolam group (n=23).

Patients' sedation was performed in the same room where the UGIE was performed. Patients who received propofol were sedated and followed up by an anesthesiologist. In some patients in this group, small doses of fentanyl were used to help induce anesthesia according to medical criteria. Patients who received midazolam were sedated by the endoscopist. The UGIE was initiated after a short time interval, depending on the patient's response to sedation.

All patients had their blood pressure measured with the aid of a sphygmomanometer before the sedation and after performing an upper digestive endoscopy. Intracranial pressure was monitored during and after endoscopy (about 5 minutes after), for about 3 minutes.

The monitor used for non-invasive ICP monitoring was developed by Brain4care®, model BcMM-1500-R. All patients remained in the left lateral position during monitoring, the sensor was positioned on the right side of the head in all cases. The files containing the ICP wave data were stored on a computer and subsequently uploaded to the Brain4care Analytics platform of the same company, this system generated reports for each monitoring, showing an average of the P2/P1 ratio for each minute of monitoring, as well as the Time to Peak (TTP) values, the number of cardiac pulses and the sample size used by the system, minutes containing insufficient samples, or of inadequate quality due to patient movements, these data weren't calculated. In monitoring where data were calculated in more than one minute, such information was expressed by their average.

The ICP wave has three peaks, P1, P2, and P3, which respectively represent the percussion wave, caused by the transmission of the arterial pressure from the choroid plexus to the ventricles; the tidal wave, related to intracranial compliance; and the dicrotic wave, resulting from the closing of the aortic valve. The relationship under normal conditions of homeostasis between these peaks is P1>P2>P3. This relationship between peaks is altered when there is an increase in ICP and a decrease in cerebral compliance. Thus, an analysis of the amplitude ratio of the two main ICP wave peaks (P2/P1 ratio) provides a parameter directly related to ICP[16]. A P2/P1 ratio <1.0 is considered an indication of normal cerebral compliance[17].

TTP is a new parameter proposed by the Brain4care® Methodology to assist in the determination of cerebral compliance, it indicates in the ICP wave what is the time until the appearance of the highest peak. The higher the value, the greater the chances of the highest peak being the P2 peak[17].

Statistical analysis

The sample size was defined as a convenience sample. The data referring to the general characteristics of the sample, such as age, gender, and quantity of medication administered, were compared with the unpaired student t-tests (quantitative variables) and χ^2 (nominal variable).

For the analysis of patients who used propofol and midazolam, considering blood pressure (systolic and diastolic), non-invasive intracranial pressure (P2/P1), and TTP (time to peak), the Mann-Whitney test (comparison between groups) and Wilcoxon (comparison between the same group at different times of measurement). The option for non-parametric models applied to these quantitative variables was made, since the data, even after logarithmic transformation, predominantly did not present a normal distribution (Kolmogorov-Smirnov test, $p<0.05$).

The significance level adopted was 5%. All calculations were performed with two specific programs (IBM®-SPSS® version 21, IBM Corp. Released 2012. IBM SPSS, Armonk, NY: IBM Corp, USA; and GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla, California, USA).

RESULTS

Eighty patients participated in the study, 60 of which were divided into two groups, 37 volunteers were included in the propofol group and 23 in the midazolam group. Figure 1 shows the flowchart of the participants of the two research groups. Twenty patients were excluded due to a lack of sample quality (Figure 1).

The general characteristics of the sample, such as gender and age are shown in Table 1. There was no significant difference in the average age or gender between the two groups.

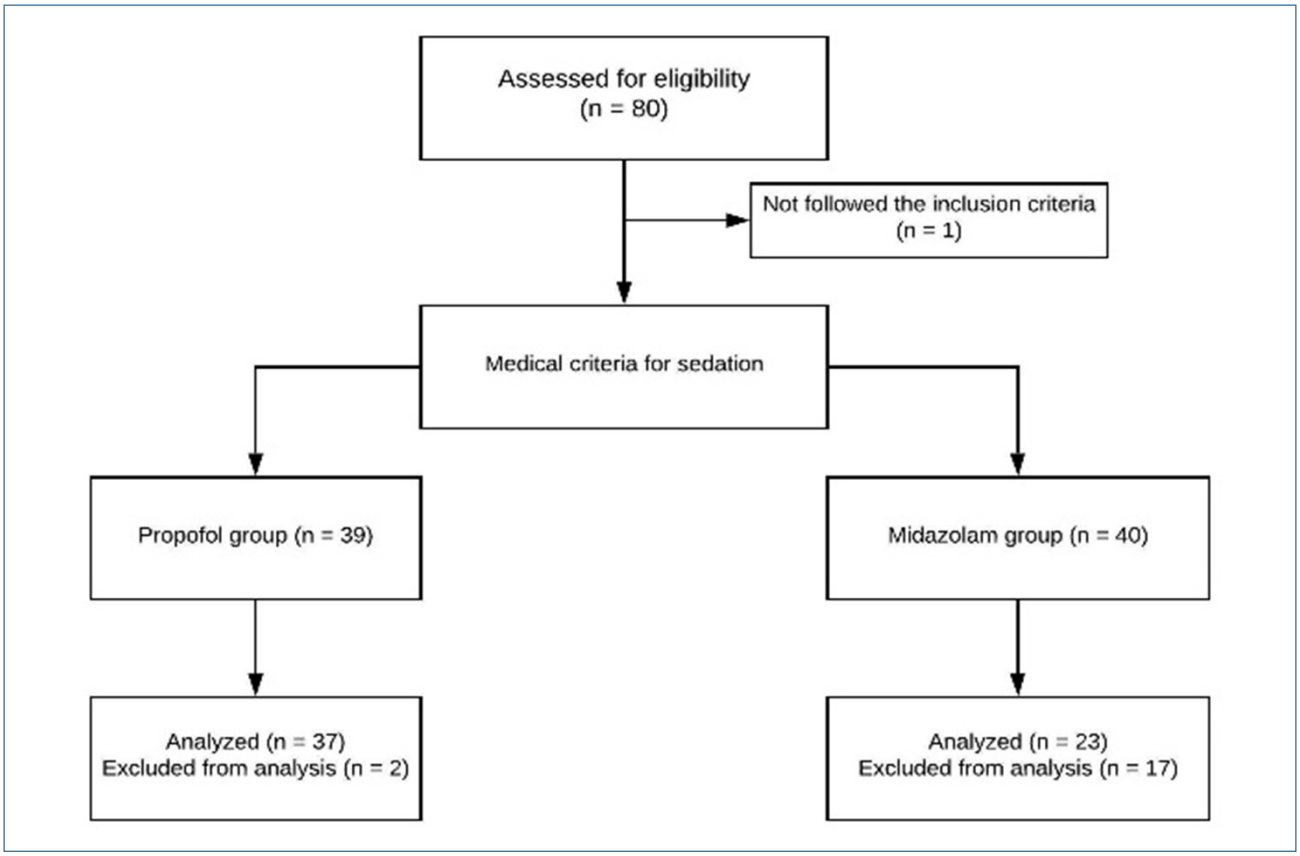

Figure 1: Flowchart of research participants

The comparison between the P2/P1 ratio, TTP, systolic pressure and diastolic pressure in an intergroup way (comparison between the propofol and midazolam groups) (Figure 2), shows that there wasn't a significant difference between the two groups (Figures 2A, B, C, and D respectively).

In the intragroup comparison (comparison between parameters during and after UGIE for the P2/P1 and TTP ratio, and comparison between before and after UGIE for systolic and diastolic BP), there was a significant difference for the four parameters in the propofol group (Figures 2A, B, C, and D). In the midazolam group, there was a significant difference between the two moments only for systolic BP (Figure 2C).

DISCUSSION

Figures 2A and 2B show, respectively, the TTP and the P2/P1 ratio, with the absence of significant difference between the propofol and midazolam groups being observed. This result corroborates the studies by Alnemari et al.[8] and Desai et al.[6], who claim that both drugs have similar effects in reducing ICP.

However, the results of the comparison within each group (propofol and midazolam group), the monitoring of the P2/P1 and TTP ratio during and after the UGIE (Figure 2 A and B, respectively) are observed in the same graph, showing a different profile between the two drugs. Because there was a significant difference in these parameters with the use of propofol, compared to the moment after sedation, there was a significant decrease in the P2/P1 ratio, which can be associated with a significant decrease in intracranial pressure, and the same didn't occur with the use of midazolam.

The result is in line with the description of the action of these two drugs made by Abdalla[11], in which propofol causes systemic hypotension through arteriolar and venous vasodilation, and decreases the rate of cerebral oxygen metabolism, causing vasoconstriction in the brain, decreased CSF, cerebral blood volume and ICP. The hypotension that accompanies the use of propofol can also decrease cerebral blood flow (CBF). Midazolam, on the other hand, causes a lower rate of brain oxygen metabolism lower than that caused by propofol, without altering the ICP.

Additionally, Figures 2C and D show that there wasn't a significant difference in systolic and diastolic pressure between the two groups, but there was a difference within the groups. In the propofol group, there was a significant difference in

Table 1: General characteristics of the sample of patients undergoing upper gastrointestinal endoscopy.

Variable	Sedation		P value
	Propofol	Midazolam	
Age in years (mean±SD)‡	54.2 ± 18.6	54.8 ± 17.6	0.896ns
Gender (%)†			
Male	13 (35)	10 (43)	0,518ns
Female	24 (65)	13 (57)	
Total	37 (100)	23 (100)	
Medication volume in mL (mean±SD)‡	16.7 ± 5.2	1.6 ± 0.4	

‡t *student;* †χ^2; ˢsignificant; nsnot significant

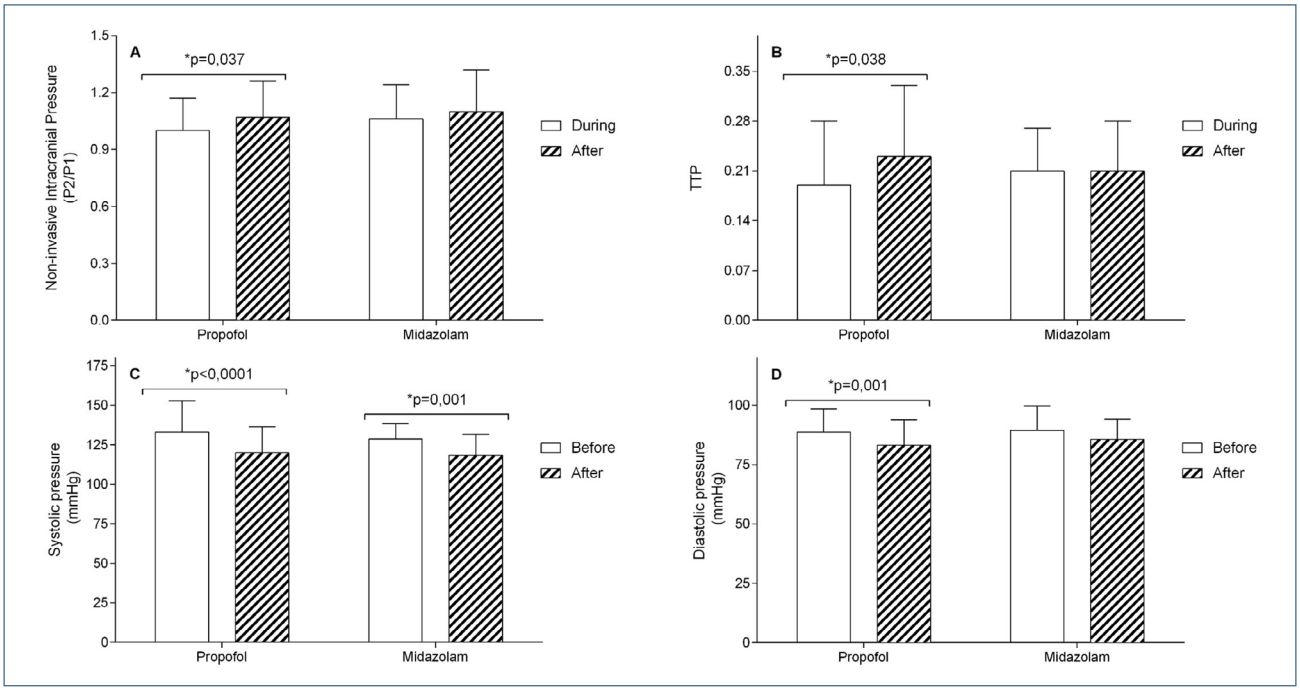

Figure 2: Mean and standard deviation of non-invasive intracranial pressure values (A); time to peak (TTP) (B); systolic (C) and diastolic (D) blood pressure obtained from patients undergoing upper gastrointestinal endoscopy.

systolic and diastolic pressure, and in the midazolam group, there was a difference only in systolic pressure. This difference is expressed by the decrease in systolic and diastolic pressure after UGIE to the blood pressure values before UGIE.

Unlike propofol, midazolam is considered a drug that causes minimal hemodynamic effects; however, it has the potential to cause apnea, respiratory depression and loss of ventilatory response, which are dose-dependent effects. The use of this drug tends to benefit a large number of patients, especially those anxious, with severe or uncooperative phobias[18].

It's known that patients are usually afraid of medical appointments, as well as, fear of undergoing procedures, anesthesia, or even fear of the possibility of discovering a poor prognosis with an exam. These factors can cause anxiety in patients and this condition must be considered. Ifeagwazi et al.[19] states that emotional reactivity is implicated in blood pressure and inadequate emotional responses to stressful stimuli establish psychophysiological changes, which can eventually raise blood pressure.

Thus, the increase in blood pressure recorded before the exam may have been a consequence of the anxiety caused by the prospect of the exam, and its decrease after the exam, as a result of the end of the anxiety stimulus. It isn't possible to quantify how much the anxiolysis caused by midazolam had an impact on those patients who used this drug.

Another divergent point between the action of the two drugs is their action on the baroreceptors. Abdalla[11] also states that the hypotension commonly caused by propofol is not accompanied by an increase in heart rate, due to the attenuation of the baroreceptor reflex. In contrast, Franchi et al.[20] point out that midazolam does not affect the sympathetic response of the baroreflex to hypotension, with an almost immediate increase in heart rate and contractility, with the mobilization of blood, such as the spleen, for the central circulation.

This divergence of effects on the baroreceptors caused by propofol and midazolam can be reflected in figure 2C and D. Because the significant decrease in systolic and diastolic pressures observed after the use of propofol may be associated with the action of this drug in attenuating the baroreceptors, and in the case of midazolam, the significant decrease only in systolic pressure may be related to the normal response of the baroreceptors to hypotension.

Blood pressure (BP) and ICP are closely linked and this relationship is dependent on the capacity for self-regulation of cerebral blood flow. When the capacity for self-regulation is full, decreases in BP below the regulatory plateau cause vasodilation to maintain CBF, and increases in BP therefore don't increase ICP, as vasoconstriction occurs, preventing hyperperfusion. When there's deregulation in this system of self-regulation, an increase in BP can directly alter the volume of cerebral blood, and a decrease can impair CBF[6].

Olesen et al.[21], point out that the literature estimates the regulatory plateau between a 60 to 150 mmHg variation in BP, in which the CBF wouldn't change. However, his recent study that assessed the impact of increased BP on the blood flow of the internal carotid artery during propofol-remifentanil anesthesia, found that the blood flow of the internal carotid artery increases by 15% when there is an increase in BP of 60-65 mmHg to 80-85 mmHg.

The relationship between BP and ICP can also be related to the Cushing's reflex, which is a pathophysiological phenomenon that occurs in patients with intracranial hypertension, when hypertension, bradycardia, and respiratory abnormalities develop, but which aren't necessarily observed together in all patients[22]. This event usually occurs in extreme conditions of ischemia in the brain stem, however, there is debate whether the Cushing's reflex is an acute pathological response, or is part of a physiological mechanism of blood pressure regulation, as some evidence points to this possibility, such as the interdependence between ICP and heart rate, modest and gradual increases in ICP in awake patients produce increases in blood pressure and heart rate, and a supposed ability of the central nervous system to modulate the setpoint of the baroreceptor reflex, an important BP control mechanism[23].

Limitation

During the research, it wasn't possible to monitor the ICP before the start of UGIE, which prevented further exploration of the results, in addition, data on weight, lifestyle, and pre-existing diseases weren't collected for analysis of the interference of these factors in the results.

Conclusion

Based on the results obtained, we conclude that in moderate sedation for upper digestive endoscopy, there aren't significant differences in blood pressure and intracranial pressure, regarding the use of propofol and midazolam. Propofol changes the ICP, decreasing the P2/P1 ratio and TTP during the endoscopic procedure about the post-endoscopic moment, as well as reducing systolic and diastolic BP at the end of the endoscopic procedure. Midazolam reduces systolic BP but doesn't change diastolic BP or ICP parameters after UGIE. This research presents an analysis never done before and, therefore, innovative. The results indicate great potential for applicability of the Brain4care® Methodology, which, with just three minutes of monitoring, provides real-time data on patients' intracranial pressure in a safe manner, which can be complementary information for the physician's decision in the risk assessment-benefit of each type of sedation for each patient.

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