Non-invasive monitoring of intracranial pressure during midazolam-induced moderate sedation for upper gastrointestinal endoscopy

Monitoramento não invasivo da pressão intracraniana durante a sedação moderada induzida por midazolam para endoscopia digestiva alta

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ABSTRACT
Midazolam is a drug chosen for moderate sedation by many endoscopists, it acts on receptors of the cortex, thalamus and cerebellum to produce the sedation effect, and its effects on intracranial pressure during moderate sedation have been poorly studied. This report provided data on intracranial pressure monitoring before, during sedation application, during upper digestive endoscopy and after examination. From this collected data we evaluated intracranial pressure through its wave morphology and P2/P1 ratio. A small reduction in this last parameter was observed after the exam and may be related to midazolam use. It is suggested this must be investigated in further studies.

Keywords: Midazolam, Moderate Sedation, Intracranial Pressure, Brain Compliance, Non-Invasive Monitoring.

RESUMO
O midazolam é o fármaco de escolha para vários endoscopistas na sedação moderada, ele age em receptores no córtex, tálamo e cerebelo para produzir o efeito sedativo, e seus efeitos na pressão intracraniana durante a sedação moderada foram pouco estudados. Este estudo de caso, fornece dados da pressão intracraniana de antes, durante a aplicação da sedação moderada, durante a endoscopia digestiva alta e após a realização do exame. A partir dos dados coletados nós avaliamos a pressão intracraniana através da morfologia da sua onda e por meio da razão P2/P1. Uma pequena redução neste parâmetro foi observada após a realização do exame e pode ser relacionada ao uso do midazolam. Sugere-se que isto seja investigado em estudos posteriores.

Palavras-Chave: Midazolam, Sedação Moderada, Pressão Intracraniana, Complacência Cerebral, Monitoramento Não-Invasivo.

1 INTRODUCTION

Upper gastrointestinal endoscopy (UGIE) is a diagnostic procedure that allows a thorough evaluation of the esophagus, stomach and duodenum. The exam is quick and safe, but may bring some discomfort to patients, to lessen such discomfort and the

patient's anxiety moderate sedation or also called conscious sedation is used (Lauriola et al.,2019), during this type of sedation, the patient maintains respiratory and cardiovascular function and is able to respond to sound and touch stimuli (J. H. Kim, D. H. Kim, & Kim, 2019).

Midazolam-induced sedation has been the choice of several endoscopists, this benzodiazepine class drug has interesting characteristics for its use in endoscopy, such as: anxiolysis, anterograde amnesia, anticonvulsant and muscle relaxant action, besides its short duration when compared to others benzoadiazepines (Kim, Park, Shin, Y. C. Lee, & Lee, 2018), but there are risks of side effects such as respiratory depression (Kim et al., 2019).

Intracranial pressure (ICP) is a parameter normally monitored in neurocritical patients and is invasively monitored, but there are non-invasive monitoring alternatives that allow investigation of this parameter in other clinical conditions (Harary, Dolmans, & Gormley, 2018). The monitoring method presented by Frigieri et al. (2018) consists in a non-invasive procedure that use a strain gauge sensor to capture skull deformations resulting from changes in ICP, positioned on the scalp in the parietal region lateral to the sagittal suture, which captures skull deformations resulting from changes in ICP, continuously providing ICP waveform information.

The ICP waveform present three characteristic peaks: P1, P2 and P3. The P1 peak (percussion wave) is formed from the displacement of arterial blood from the choroid plexus to the ventricles. The P2 peak (tidal wave) is related to brain compliance, and the last peak, P3 (dichrotic wave), is associated with aortic valve closure. Under normal conditions, these three peaks have the following relationship: P1> P2> P3, in situations where there is a decrease in brain compliance or an increase in ICP, this relationship may be altered with a consequent increase in the P2/P1 ratio (Ballestero, Frigieri, Cabella, S. M. Oliveira, & Oliveira, 2017).

2 CLINICAL PRESENTATION

This clinical case is part of the research approved by the Ethics and Research Committee of the State University of Ponta Grossa (CEP-UEPG) under the number opinion 2.788.026. The volunteer was informed about the research procedures and, agreeing to participate, signed the free and informed consent form. The patient LLS, 72-years-old male, was attended for the upper gastrointestinal endoscopy (UGIE) in march 2019, following a 12-hour fasting required for the examination. He declared having

vomited with blood and the requesting doctor confirmed that the patient had been undergoing digestive bleeding treatment for about 20 days. Prior to the the upper gastrointestinal endoscopy, the patient took 30 drops of simethicone, and received 10% lidocaine spray jets as a local anesthetic for the oropharynx. The blood pressure measured before the UGIE was 130/90 mm Hg, after the exam, the blood pressure was measured again and it was found that there was no change.

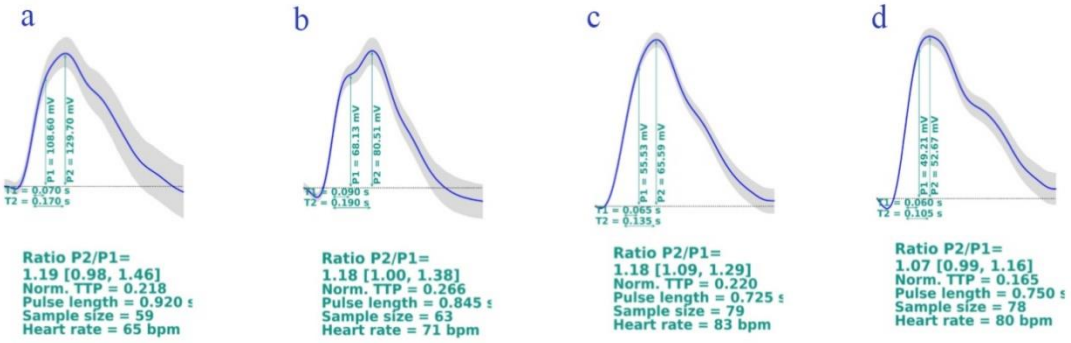
Intracranial pressure monitoring was performed with the device developed by Brain4care® (model BcMM-1500-R) before examination, during patient preparation for examination, during upper digestive endoscopy and after examination, during recovery from the patient. The acquisitions were analyzed by the Brain4care Analytics® platform that generated a report with the P2/P1 ratio and other informations for each monitored minute (for monitoring with more than one minute these values were averaged). The data are presented in Table 1 and Figure 1.

Table 1. Intracranial pressure monitoring data.

	Before UGIE	**During patient preparation**	**During UGIE**	**After UGIE**
Monitoring Time (min)	1	1	4	4
Mean ratio P2/P1	1,19	1,18	1,16	1,07
Mean TTP (time to peak)	0,218	0,266	0,211	0,163
Mean heart rate (bpm)	65	71	83	81

* UGIE: Upper gastrointestinal endoscopy.

Figure 1. ICP waveform. (a) ICP monitored before UGIE; (b) ICP monitored during patient preparation for UGIE; (c) ICP monitored during UGIE; (d) PIC monitored after UGIE.



The examination and all monitoring were done with the patient in the left lateral decubitus. Exam preparation includes i) finding venous access, ii) application of sedation by endoscopist, and iii) waiting for midazolam action (1.2 mL midazolam was used for moderate sedation). The procedure was performed with a Fujinon gastroscope, model EG 250, and lasted about 4 minutes. After the exam, the patient remained in recovery for

about 30 minutes. The findings of the examination found the presence of hiatal hernia due to small-volume sliding (2 cm above the diaphragmatic clamping), and moderate enanthematous pangastritis. Body and antrum biopsy were also performed for the urease test.

3 DISCUSSION

Invasive ICP monitoring guidelines indicate the use of ICP averaging as the main parameter to guide therapy, but reliance on this single parameter makes clinical treatment reactive rather than proactive, and many authors claim that this is why ICP monitoring has not yielded the expected clinical benefits, making it interesting to determine how the pressure/volume curve is at a given time, as well as to measure brain compliance and compensatory system reserve. An increase in ICP not only changes the average ICP, but also changes the ICP waveform, specifically there is an increase in the P2 peak that is associated with low brain compliance (Harary et al., 2018).

The method used in this research (Brain4care) provides ICP waveforms and they are shown in Figure 1, where P1 and P2 peaks were indicated and identified by a system developed by the same company. This method was used before to monitor other conditions such as elderly (Bueno et al., 2021) or hemodialysis (Rickli et al, 2021). In the presented case study, it is observed in the waveforms (a), (b) and (c) similar P2/P1 ratios.

Analyzing the relationship between the peaks, we noticed that the P2 peak was high in all monitoring stages. Table 1 shows the average P2/P1 ratio of the patient, and this ratio was higher than 1 in all monitoring, indicating low brain compliance and increased ICP. When there is high brain compliance and good compensatory reserves, changes in volume produce none or little increase in ICP, but in situations of low brain compliance and depleted compensatory mechanisms, any increase in volume leads to a rapid increase in ICP. This process can be dangerous because increased ICP decreases brain perfusion, leading to ischemia, as well as herniation of the brain stem and other vital structures (Oertel & Antes, 2018).

Time to Peak (TTP) can be an auxiliary parameter in assessing brain compliance, it indicates in the pulse of the ICP wave, which time to the highest peak, the higher the value is the chance of being the peak P2. The values for TTP are presented in Table 1, the smallest value happens in the pulse with the lowest P2/P1 ratio, but the largest value does not happen in the pulse with the highest P2/P1 ratio, but it is possible to notice a

relationship, but larger conclusions cannot be drawn yet because there is few information about this parameter.

Under normal physiological conditions, variations in ICP occur, such as changes in posture, brain activity, cardiovascular and respiratory function, but maintenance of ICP at physiological levels is essential for the prevention of brain damage (Harary et al., 2018). Understanding the factors that led to the increase in ICP is the first step of this prevention. In UGIE, in order for the gastric mucosa to be properly observed, patients undergoing endoscopy must have a complete fast for 6 to 8 hours (Pessoa, Ferreira, Viana, & Alencar, 2018). This factor eliminated the possibility that the findings found in the ICP were due to other medications.

Midazolam, the drug used in sedation, is a gamma-aminobutyric acid receptor (GABA-A) agonist, which by conformational alteration increases the affinity for the neurotransmitter GABA, this binding induces hyperpolarization of the neuron. There are different binding site isoforms in this receptor, the BZ1 receptor is found in the cortex, thalamus and cerebellum, and is responsible for the sedative effects of midazolam, the BZ2 receptor is found in the limbic system, spinal cord dorsal horn and motor neurons, generating relaxing muscle effects. This drug also generates a depressing action on the respiratory center, causing a decreased ventilatory response to CO_2 (Shteamer & Dedhia, 2017). Recently, several studies have pointed to neuroprotective effects of midazolam such as: anticonvulsant activity, antineurotoxic function (reducing hydrogen sulfide-induced mortality), attenuating action of ketamine-induced toxicity in the hippocampus, preventing motor and cortical neuronal death due to oxidative stress attack, and the prevention of death of hippocampal neurons by sevoflurane exposure (Yu, Zhu, Cui, Long, & Ma, 2019).

However, Abdalla (2018) states that this drug has no neuroprotective activity, in his text he also discusses the activity of midazolam on cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF), according to him there is a decrease on these two parameters but there are no significant effects on ICP. The data obtained in this case study (Table 1) show a slight decrease in P2/P1 ratio values after midazolam administration (during patient preparation) and during its sedative action (during upper digestive endoscopy). Figure 1 allows another important observation, immediately after midazolam administration (b) there was a delineation of peaks P1 and P2. The largest reduction in the P2/P1 ratio occurred during patient recovery, after sedative drug action, the reduction was not enough to turn P2/P1 to normal range, but these peaks were

distinguishable in the pulse waveform. As the patient did not undergo any intervention at this stage of monitoring, and since there was no decrease in blood pressure, we believe that this behavior of the P2/P1 ratio may be related to the use of midazolam.

According to Whelton et al. (2018) blood pressure values characterize the patient as stage 1 hypertensive, blood pressure is closely linked with ICP: cerebral perfusion pressure (CPP) is the result of the difference between mean arterial pressure (MAP) and ICP, when ICP is elevated, to maintain CPP there is an increase in MAP mainly caused by increased cardiac output (Harary et al., 2018). Thus, the increase in blood pressure may be the cause of the increase in ICP, but similarly the increase in blood pressure may be due to the increase in ICP. Unfortunately, the present data do not allow us to conclude what was the primary reason for the increase in P2/P1 ratio.

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