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ORIGINAL RESEARCH

Foreseeing postoperative pain in neurosurgical patients: pupillometry predicts postoperative pain ratings—an observational study

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Abstract

Pupillary reflex dilation (PRD) is triggered by noxious stimuli and diminished by opioid administration. In the postoperative period, PRD has been shown to be correlated with pain reporting and a useful tool to guide opioid administration. In this study we assessed whether pupillary measurements taken before extubation were related with the patient's reported pain in the Post-Anesthesia Care Unit (PACU) using the Numerical Rating Scale (NRS). Our objective was to evaluate the correlation of PRD and pupillary variables measured intraoperatively with postoperative pain under the same opioid concentration. This was a prospective observational study of 26 neurosurgical patients undergoing general anesthesia exclusively with propofol and remifentanil. A portable infrared pupillometer was used to provide an objective measure of pupil size and PRD (using the Pupillary Pain Index) before extubation. Pain ratings were obtained from patients after recovery of consciousness, while remifentanil was maintained at 2 ng/mL. A significant correlation was observed between NRS scores and pre-extubation PPI ($r_S = 0.62$; $P = 0.002$), as well as between NRS scores and pupil diameter before tetanic stimulation PPI ($r_S = 0.56$, $P = 0.006$). We also found a negative correlation between pupil diameter and age ($r_S = -0.42$, $P = 0.04$). The statistically significant correlation between pre-extubation PPI scores and NRS scores, as well as between the pupillary diameter before tetanic stimulation and NRS scores suggest the possibility of titrating analgesia at the end of the intraoperative period based on individual responses. This could allow clinicians to identify the ideal remifentanil concentration for the postoperative period.

Keywords Pupillary Pain Index · Nociception monitoring · Pupillary reflex dilation · Postoperative pain

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1 Introduction

The importance of personalized medicine is increasingly recognized in anesthesia, and to achieve this, new monitoring devices have been developed, which allow better drug titration. However, there is no widely accepted monitor available for analgesia and thus postoperative pain continues to be a major medical challenge with fewer than 50% of patients receiving adequate pain relief [1].

If inadequately treated, acute postoperative pain not only limits mobility and impairs ventilation, but also increases stress hormones and the risk for chronic postsurgical pain. On the other hand, if opioids are given in excess they can cause respiratory depression, nausea and vomiting, ileus, sedation and even hyperalgesia [2].

In order to titrate analgesia perioperatively, monitors based on surrogate variables of the autonomic nervous system (ANS) have been developed [3]. They rely on changes that noxious stimuli induce in derived cardiovascular and

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respiratory parameters (heart rate variability, patterns of blood pressure and heart rate responses, pulse wave amplitude and pulse beat interval), skin impedance and pupillary parameters [4].

Pupillary reflex dilation (PRD), one of the pupillary reflexes [5], is triggered by noxious stimuli in anesthetized subjects [6, 7] and diminished by opioid administration [8]. Therefore, it has been used as an indirect measure of the nociception/antinociception balance intraoperatively to guide opioid administration [9–12]. In the postoperative period, PRD has been demonstrated to be significantly correlated with pain reporting and is a useful tool in guiding opioid administration [13, 14]. The Pupillary Pain Index (PPI) is an index derived from the PRD, and has been shown to be correlated with postoperative pain [15] and capable of assessing noxious stimulus in sedated patients in the ICU [16]. Although many have studied the utility of PRD as a surrogate indicator of nociception, there are no studies to our knowledge that have investigated the correlation between intraoperative PRD or PPI values and postoperative pain in adults receiving the same dose of opioid.

In this study, we asked whether intraoperative pupillary measurements before emergence from anesthesia correlated with the patient's reported pain in the Post-Anesthesia Care Unit (PACU) using the Numerical Rating Scale (NRS). Our objective was to assess the correlation of (PPI) or other pupillary variables measured intraoperatively with postoperative pain, maintaining the same opioid concentration at both times.

2 Methods

This was a pilot prospective observational study with institutional review board and ethics committee approval (Reference Number 062-DEFI/062-CES) from the Centro Hospitalar Universitário do Porto, Porto, Portugal. All participating patients gave written informed consent.

Twenty-six neurosurgical patients undergoing general anesthesia exclusively with propofol and remifentanil were included. No premedication was given. Patients with ocular diseases with the exception of refractive errors were excluded. Patients who were taking opioids preoperatively were also excluded. Inclusion in the study also required absence of anisocoria, assessed by a portable infrared pupillometer.

Surgeries included craniotomies (biopsies, tumor resections and external ventricular drainage) and lumbar spinal surgeries (laminectomies, decompressions and fusions).

2.1 Measurement of pupillary reflex dilation

A portable infrared pupillometer (AlgiScan, IDMed, France) was used to provide an objective measure of pupil size and pupillary reflex dilation. A light-emitting diode of infrared light is first directed toward the eye, and a sensor then detects the reflected infrared light from the iris, allowing the area and diameter of the pupil to be calculated. Application of a noxious stimulus elicits the PRD [5].

To assess the PRD, we used the Pupillary Pain Index (PPI) setting in AlgiScan. The PPI measures the changes in pupillary dilation in response to a continuously increasing electric stimulus discharge from 10 to 60 mA at 1 s intervals. Once it reaches 60 mA, a 3 s 60 mA stimulus is applied. The response is then classified on a scale from 1 (when pupillary dilation is < 5% after the 3 s of 60 mA tetanic stimulation) to 9 (when pupillary dilation rises above 13% with just 10 mA) [9, 17]. If the pupillary dilation is inferior to 13% even after the 3 s stimulus, a classification of 1 is assigned. If the pupil dilates more than 20%, the PPI rating increases by 1 point.

Using PPI instead of a fixed tetanic stimulus of 60 mA avoids excessive stimulation by standardizing the stimulation threshold. In our study the electrodes were placed on the volar surface of the forearm.

The AlgiScan records measurements at a frequency of 67 Hz. To calculate the pupillary diameter, we averaged the first second of measurements (67 measurements) of the PPI recording where there was no concurrent stimulation. A rubber cup was used around the measured eye, while the contralateral eye was closed to exclude ambient light.

2.2 Protocol

General anesthesia was induced and maintained with a propofol infusion until a loss of behavioural response was attained, and was subsequently titrated to maintain a BIS value between 40 and 60 (BIS Vista™ monitor - Medtronic, Ireland). A target control infusion (TCI) of remifentanil (Minto PKPD model) in a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany) was used as well. Rocuronium boluses were administered for the neuromuscular blockade at the anesthesiologist's discretion.

At the end of the surgical procedure, after the surgical dressing was complete and before the emergence phase, the effect-site concentration (EC) of remifentanil was set to 2 ng/ml. When both the plasmatic and EC of remifentanil reached 2 ng/ml, and with propofol still being administered to keep the patient unconscious, a PPI measurement

was performed. After this, sugammadex was administered, the propofol infusion was stopped, and the patient was allowed to recover consciousness and be extubated. The remifentanil infusion was maintained at 2 ng/ml, in order to provide analgesia and a smooth extubation. The patient was then transferred to the Post-Anesthesia Care Unit (PACU) while the remifentanil infusion was maintained at 2 ng/ml. Besides the remifentanil, no additional analgesia was given until pain could be assessed clinically.

Once the patient was able to provide a pain rating within 15 min upon arrival to the PACU, the Numerical Rating Scale (NRS) [18] was measured. The NRS was registered by the attending anesthesiologist or by the PACU nurse, who were unaware of the PPI value obtained before extubation. After providing the pain rating, patients received paracetamol and NSAIDs, if applicable. If pain was rated as moderate or severe (NRS 4–10), a bolus of remifentanil was given with a concomitant bolus of IV morphine. If the pain was mild or non-existent, IV morphine was given, and the remifentanil infusion was gradually decreased.

The only reversal agent used was sugammadex. In the craniotomies no cranial nerve blocks were performed. In spinal surgery cases, the patients had the site of skin incision infiltrated with ropivacaine 0.75% before skin closure.

2.3 Statistical analysis

We categorized pain ratings from NRS scores as mild (1–3), moderate (4–6), or severe (7–10). For PPI categorization, we divided the 9-point scale into proportional categories: low (1–3), intermediate (4–6) and high (7–9).

Data were compiled and analyzed using IBM SPSS Statistics (Version 25.0). For the comparison between independent groups of patients Kruskal–Wallis and Mann–Whitney tests were performed where appropriate. Spearman correlation was used to assess the relations between variables; an ordinal regression was performed on the NRS categories considered, using pupillometry variables. $P \leq 0.05$ was considered significant. Data are presented as mean ± standard-deviation and median (interquartile range).

As this is a pilot study and our objective was to assess if intraoperative pupillary measurements were correlated with the patient's reported pain in the PACU using the NRS, we assumed a large effect size for the correlation (0.5, power 0.8, alpha 0.05) and determined a sample size of 23 to be sufficient for our study.

3 Results

Of the 26 patients enrolled in this study, 3 were excluded due to artifacts in the PPI records. For the 23 patients included in the analysis (10 craniotomies and 13 spinal surgeries), the mean age was 54.7 ± 12.4 years and 14 were female (60.9%). Mean pupillary diameter before stimulation was 2.3 mm ± 0.6 (interquartile range 0.6), median PPI value before extubation was 6 (3 to 7) and median NRS at PACU was 5 (3 to 6).

The PRD curves for each patient are plotted in Fig. 1. Individual PRD trends were normalized according to the baseline diameter at the beginning of data acquisition, and averaged for patients with the same PPI (Fig. 2). A significant correlation was observed between NRS at PACU and pre-extubation PPI ($r_S = 0.62$; $P = 0.002$), as well as between NRS at PACU and pupil diameter before tetanic stimulation PPI ($r_S = 0.56$, $P = 0.006$)—Figs. 3 and 4. We also found a negative correlation between pupil diameter and age ($r_S = -0.42$, $P = 0.04$).

No correlation was observed between the other variables, namely between PPI and BIS value at the time of measurement, nor between PPI and pupil diameter. There were no statistical differences in PPI, NRS and pupil diameter values between craniotomies and spinal surgeries.

Dividing PPI and NRS values into classes yielded an association between pain ratings and PPI measurements ($r_S = 0.74$, $P = 0.001$ (Fig. 3). There were no demographic differences across classes.

An ordinal regression was performed on the NRS categories using different pupillometry variables, namely pupil diameter and PPI. The ordinal regression obtained using these variables (Nagelkerke $R^2 = 0.684$) correctly classified 80% of patients reporting severe pain, and 72.7% reporting moderate pain; if we consider moderate and severe pain together, classification was correct in 87.5% of patients reporting pain in these categories (Fig. 4).

4 Discussion and conclusions

In our study we found a statistically significant correlation between pre-extubation PPI score and NRS scores, as well as between the pupillary diameter before tetanic stimulation and NRS scores. An ordinal regression correctly classified 87.5% of patients reporting moderate to severe pain at the PACU. These preliminary results show that the information retrieved from the pupillometer may aid in the prediction and prevention of postoperative pain. Further validation studies would be necessary to test the regression model on independent data and also evaluate the impact of different analgesic doses on the pupillometer variables. In addition, we also found that patients with low PPI scores (0–3) or intermediate PPI scores (4–6) were less likely to report severe pain in the postoperative period.

The type of study we carried out has been previously reported using other commercially available nociception monitors [19–21]. For example, with the Analgesia

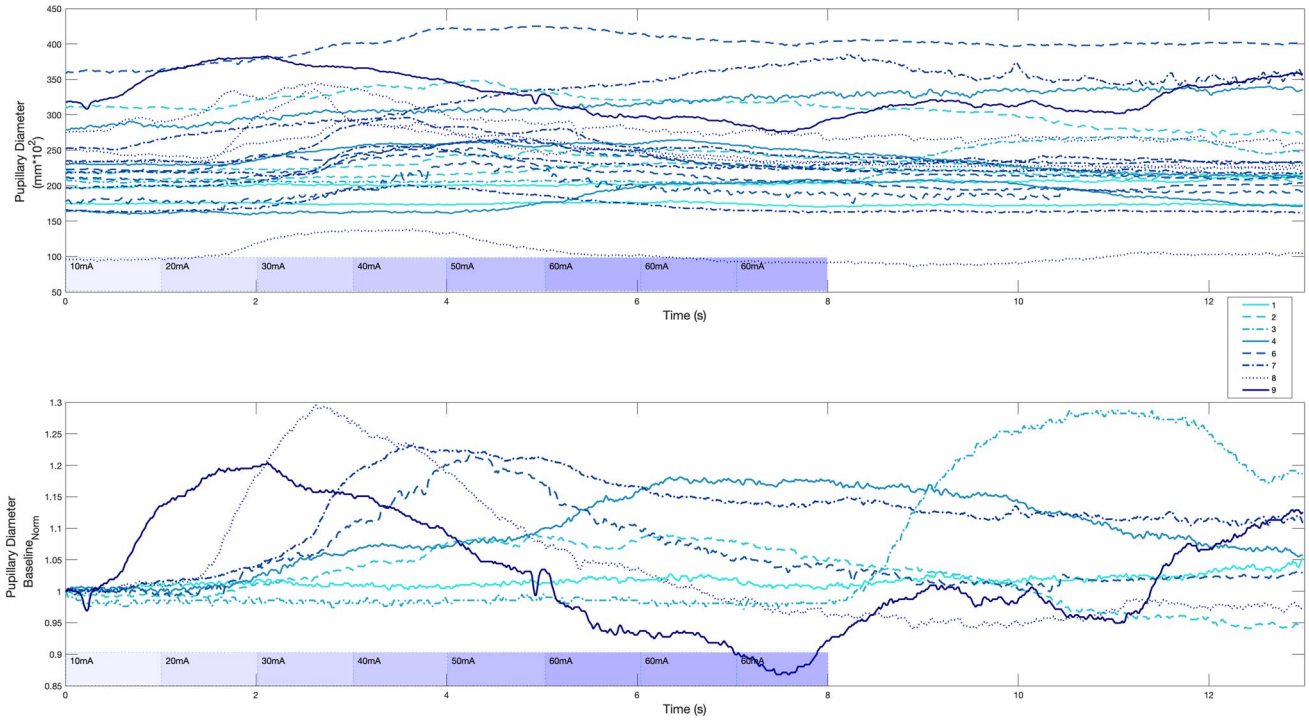

Fig. 1 Superior: plot of each patient's PRD curve, colored according to the PPI class. Inferior: mean normalized PRD curves for each PPI score

Nociception Index (ANI), measurements taken immediately before extubation after inhalation-remifentanil anesthesia were significantly associated with pain intensity on arrival in PACU, yielding a good performance for the prediction of immediate postoperative pain [19]. Our objective was to assess if the same was true for the PRD in order to have additional means to optimize postoperative analgesia.

PRD during anesthesia is generated through inhibition of the Edinger–Westphal nucleus without a sympathetic contribution. When the Edinger–Westphal nucleus is inhibited, the pupil dilates passively as sphincter tone is lost. [5]. This reflex has been used before to assess postoperative pain. In one study, PRD measurements were taken after patient's recovery of responsiveness [13]. However, contrary to unconscious patients where PRD is a supraspinal parasympathetic reflex, PRD is primarily a sympathetic reflex in unanesthetized patients [2]. Thus, it is likely that other factors capable of eliciting a sympathetic response besides the noxious stimulus can interfere with this reflex. In another study [14], PRD measurements were taken while the patient was still unconscious, but the analgesic dose varied, and was not the same during the moment of PRD measurement and pain rating assessment. These authors also individualized the stimuli to each patient by creating a PRD threshold, which resulted in 4 classifications (vs the 9 classifications of PPI), which correlated significantly with the intensity of immediate postoperative pain. This methodology might have contributed to a lower correlation with postoperative pain compared to our study. In our protocol, the PRD measurement using the PPI mode was taken while patients were unconscious under general anesthesia prior to extubation, without concomitant stimuli. Remifentanil EC were also the same during PPI measurement and when NRS were obtained.

Pre-extubation PPI and postoperative pain was previously assessed in children, where a pediatric acute pain scale, the LLANTO scale, showed a statistically significant correlation while the Visual Analog Scale did not [15]. The use of pain reporting in children may be confounded by variation in a child's ability to communicate complex feelings such as pain, whereas our adult patients were instructed preoperatively on the use of the NRS scale. The aforementioned study also does not control for the analgesic concentration during PPI measurements and pain assessment.

One interesting finding was the correlation of pupillary diameter with the NRS. One explanation for this might be that pain at the end of surgery dilated the pupil, even before the tetanic stimulation was applied. This could be a better predictor of postoperative pain in cases where regional anesthesia or wound infiltration was performed, because there will be a difference in antinociception between the region of placement of the electrodes and the surgical site.

Another factor that should be considered in our results is the synergism between propofol and remifentanil, as propofol EC was not the same across patients. A previous study has shown that PRDs measured under the same EC of

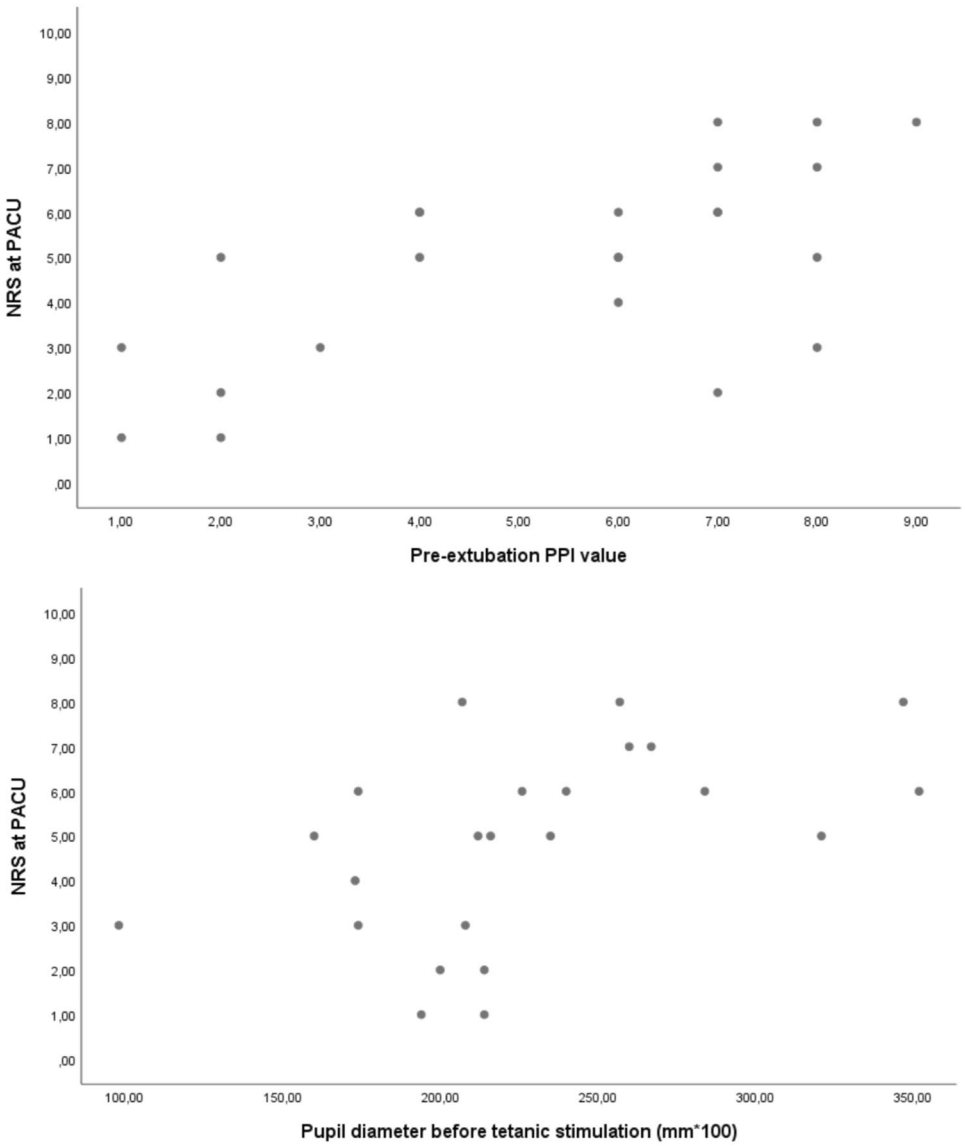

Fig. 2 Superior: representation of NRS at PACU and pre-extubation PPI. Inferior: representation of NRS at PACU and pupil diameter before tetanic stimulation

remifentanil can be influenced by depth of hypnosis assessed by the BIS [22]. This synergism is difficult to control and could have some influence in our results. To account for this matter, we recorded the BIS values at the time our PPI measurements were taken, and our statistical analysis did not show any correlation of BIS values with PPI values nor diameter.

The correlation found between pupil size and age is in accordance with literature, as a reduction in the size of the pupil with age has been described in both light and dark conditions [23] and during anesthesia [24].

Analgesia titration in the PACU, consisting mostly of morphine, is usually standard for all patients due to a lack of understanding of factors responsible for the large inter-individual variability in its analgesic effect [25]. A study reported an inter-subject variability in the effective opioid dosages to be above 300% [25, 26]. Our observed correlation between pre-extubation PPI and pupillary diameter with the NRS suggests that it may be possible to titrate analgesia in the end of the intraoperative period according to the individual response. This would then allow clinicians to identify the ideal remifentanil EC and administer other opioids for the postoperative period in equipotent doses. However, a subsequent study should be designed, including the measurement of pupillary unrest [10] in addition to the PRD, to assess if titration of the remifentanil EC according to PPI/pupillary diameter would allow clinicians to decrease or prevent post-operative pain.

The limitations of these findings reside on the extrapolations we try to make, which share distinct physiologic mechanisms. We sought to describe the relationship between the nociception–antinociception balance of an unconscious patient and postoperative pain generated by surgical aggression. The postoperative pain response is

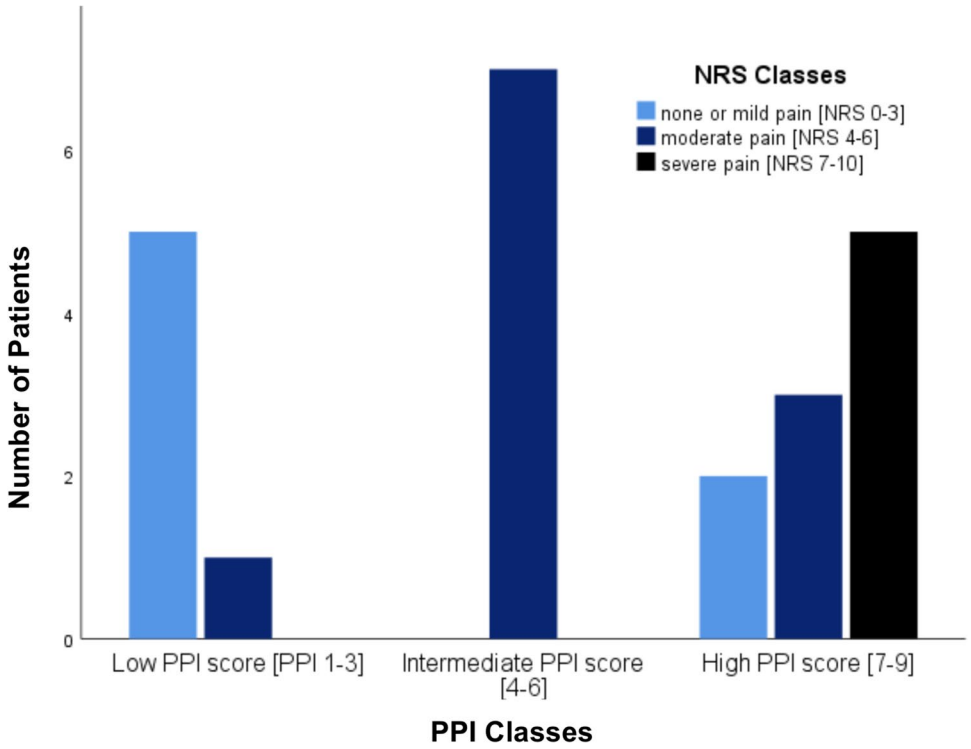

Fig. 3 PPI measurements grouped into classes and the respective PACU NRS class

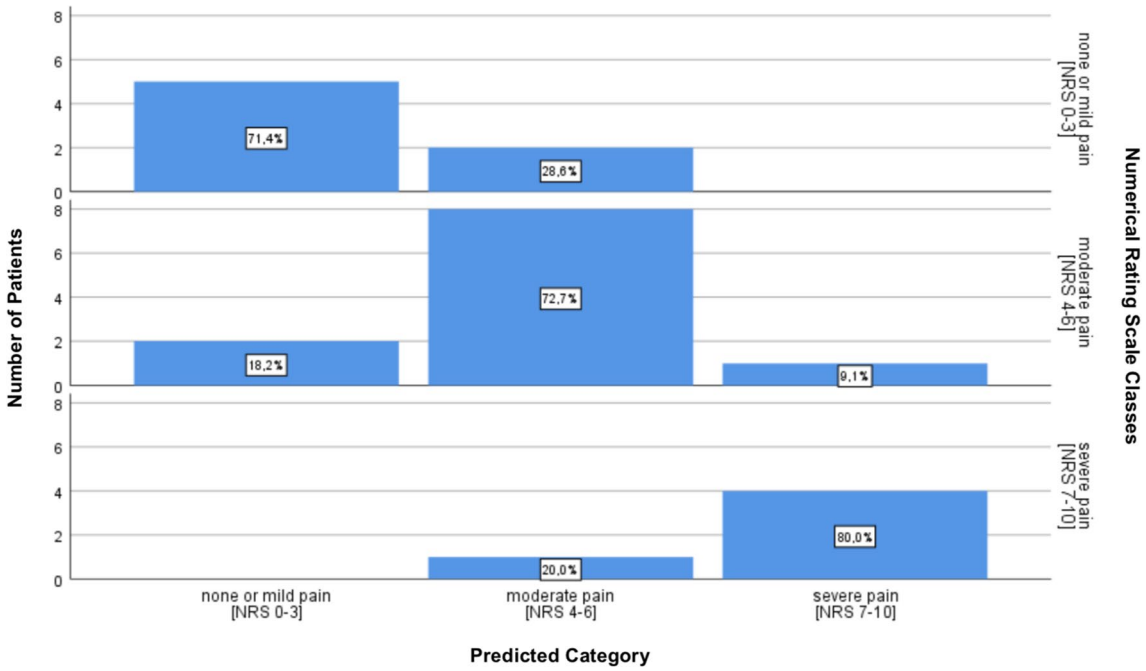

Fig. 4 Predicted category using ordinal regression and each respective category

a far more complex phenomenon that involves cortical processing. Additionally, the type of fibers responsible for the transmission of these two types of pain are not equal. The PRD, and subsequently the PPI, is initiated primarily by activation of nociceptors served by the faster conducting A-delta fibers [27], whereas the postoperative pain depends not only on A-delta fibers, but also C fibers [28]. Furthermore, these observations depend on a very controlled and cumbersome protocol that might not be feasible in daily clinical practice.

For future research, it would be interesting to determine if the variation coefficient of pupillary diameter, which is a measure of pupillary diameter fluctuations and has been correlated with the visual analog scale in awake patients [29], could also be used intraoperatively to predict postoperative pain. Nevertheless, these observations may incentivize additional research into predicting the degree of postoperative pain, and allowing preventative measures to take place.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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