

Objective Assessment of the Immediate Postoperative Analgesia Using Pupillary Reflex Measurement

A Prospective and Observational Study

Mourad Aissou, M.D.,* Aurelie Snauwaert, M.D.,† Claire Dupuis, M.D.,† Arthur Atchabahian, M.D.,‡ Frederic Aubrun, M.D, Ph.D.,§ Marc Beaussier, M.D, Ph.D.||

ABSTRACT

Background: The evaluation of pain intensity during the immediate postoperative period is a key factor for pain management. However, this evaluation may be difficult in some circumstances. The pupillary dilatation reflex (PDR) has been successfully used to assess the analgesic component of a balanced anesthetic regimen. We hypothesized that PDR could be a reliable index of pain intensity and could guide morphine administration in the immediate postoperative period.

Methods: One hundred patients scheduled to undergo general surgery were included in this prospective observational study. Pain intensity was assessed by using a simple five-item verbal rating scale (VRS). After patients awoke from general anesthesia, those experiencing mild or more severe pain (VRS more than 1) received intravenous morphine titration. Before and after intravenous morphine titration, the PDR induced by a standardized noxious stimulus was measured with a portable pupillometer. A receiver-operating curve was built to estimate the accuracy of PDR in objectively detecting patients requiring morphine titration. Results are given as median (95% CI).

* Associate Professor of Anesthesiology, † Anesthesiology Resident, || Professor of Anesthesiology and Intensive Care, Department of Anesthesia and Intensive Care, Assistance Publique, Hôpitaux de Paris, St. Antoine University Hospital, Paris, France, University Pierre & Marie Curie, Paris, France. ‡ Associate Professor of Anesthesiology, Department of Anesthesiology, New York University School of Medicine, New York, New York. § Professor of Anesthesiology and Intensive Care, Department of Anesthesia and Intensive Care, Hospices Civils de Lyon, Hôpital Croix Rousse, Lyon, France.

Received from the Department of Anesthesia and Intensive Care, Assistance Publique, Hôpitaux de Paris, St. Antoine University Hospital, Paris, France. Submitted for publication August 29, 2011. Accepted for publication February 10, 2012. The pupillometer (IDmed Neurolight SN80800®, version 1.2, Marseilles, France) was provided by the manufacturer for the duration of the evaluation. Financial support was obtained solely from departmental sources.

Address correspondence to Dr. Beaussier: Département d'Anesthésie-Réanimation Chirurgicale, Hôpital Steet-Antoine, 184 rue du Fbg Steet-Antoine, 75571 Paris Cedex 12, France. marc.beaussier@sat.aphp.fr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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What We Already Know about This Topic

- The Pupillary Dilatation Reflex (PDR) in response to noxious stimulation is reduced during anesthesia by opioids in a plasma concentration-dependent manner
- The utility of the PDR in titrating opioids for analgesia in the acute postoperative period has not been examined

What This Article Tells Us That Is New

- In 100 patients shortly after general surgery, the PDR to a standard pressure stimulus adjacent to the wound correlated with verbal pain ratings before and after morphine titration
- PDR might be useful in detecting pain and titrating analgesia after surgery in patients in whom direct communication is difficult

Results: On the initial evaluation, a correlation was found between VRS and PDR ($\rho = 0.88$ [0.83–0.92], $P < 0.0001$). In the 39 patients that had a VRS more than 1, PDR before and after morphine titration was respectively 35% (31–43) versus 12% (10–14); $P < 0.0001$. The PDR threshold value corresponding to the highest accuracy to have VRS more than 1 was 23%, with 91% and 94% sensitivity and specificity, respectively.

Conclusion: In the immediate postoperative period, the PDR is significantly correlated with the VRS. The pupillometer could be a valuable tool to guide morphine administration in the immediate postoperative period.

RAPID control of acute postoperative pain at the time patients recover consciousness and the ability to feel noxious stimuli is a critical step in the global process of postoperative pain management.¹ This period is of major importance because it determines the quality of the subsequent analgesia and can largely affect the patient's overall satisfaction about pain management. After emerging from general anesthesia, intravenous morphine titration (IMT), *i.e.*, the administration of repeated small doses of morphine until adequate pain relief is obtained, is usually recommended for

◆ This article is accompanied by an Editorial View. Please see: Larson MD, Sessler DI: Pupillometry to guide postoperative analgesia. ANESTHESIOLOGY 2012; 116:980–2.

acute pain relief in the postanesthesia care unit.² This method of administration allows for a precise determination of the dose of morphine required to obtain pain relief.³ Accuracy of IMT is dependent on the quality of pain assessment and measures of adequate ventilation. However, pain assessment in the immediate postoperative time is often a very difficult task, and the currently available assessment scales are not always reliable during this specific period.⁴ Indeed, most patients are unable to clearly express their pain level in the immediate postoperative period, and to discriminate between objective pain and discomfort feelings. Residual anesthetic effects, blurred vision, or postoperative nausea and/or vomiting make it difficult to use these scales and reduce their clinical relevance. This is especially true in elderly patients.⁵ Moreover, it has been shown that IMT-induced sedation, which could be associated with residual pain intensity, may prevent an accurate evaluation of the delivered analgesia.^{6,7} Lastly, some patients, such as nonverbal or cognitively impaired patients,⁸ are unable to adequately express their pain level, making IMT very difficult to implement. In these circumstances, the use of tools to provide objective evaluation of immediate postoperative analgesia and guide IMT would be of valuable help.

The pupillary dilatation reflex (PDR) was originally described by Budge in 1852 as a sympathetic reflex that dilates the pupil in response to noxious stimuli.⁹ To date, PDR has been successfully used to assess the analgesic component during balanced general anesthesia. Larson *et al.* have demonstrated that alfentanil blocks the PDR in response to noxious stimuli.¹⁰ A good correlation between plasma alfentanil concentration and the magnitude of pupil dilatation was found.^{10,11} Similarly, during propofol anesthesia in healthy patients, it has been demonstrated that an increase of remifentanyl concentration was correlated with a decrease in PDR.¹²

To our knowledge, PDR has never been investigated for the evaluation of immediate postoperative analgesia. In this prospective study, we hypothesized that PDR could be a reliable index of pain intensity and may guide morphine administration in the immediate postoperative period.

Materials and Methods

This prospective and observational study was approved by the Committee for the Protection of Human Subjects in Biomedical Research (CPP Ile de France III, 2009-A01400–39) and performed between January and March 2011 at Saint-Antoine University Hospital in Paris, France. The methodology followed the international guidelines for observational studies.[#]

After written informed consent was obtained, 100 American Society of Anesthesiologists physical status I–III patients scheduled to undergo general surgical procedures were in-

cluded. The surgical procedures performed were cholecystectomy, colonic surgery, abdominal wall surgery, upper abdominal surgery, and thyroidectomy.

Exclusion criteria were ocular diseases, epidural analgesia, administration of anticholinergic drugs, neuromuscular block reversal, preoperative pain treated with opioids, psychiatric diseases, and inability to understand the verbal rating pain scale.

Anesthetic Technique

Patients were premedicated with oral hydroxyzine (1 to 2 mg/kg) given 1 h before the induction of anesthesia. After arrival in the operating room, patients were monitored as usual. Neuromuscular blockade was monitored by train-of-four stimulation. The anesthetic induction was performed using intravenous propofol (2 to 3 mg/kg), sufentanil (0.2 to 0.3 µg/kg), and atracurium (0.5 mg/kg). After tracheal intubation, mechanical ventilation was initiated with a mixture of 50% O₂ and 50% N₂O, and adjusted to keep end-tidal carbon dioxide tension between 30 and 35 mmHg. Anesthesia was maintained with desflurane and continuous infusion or bolus administration of atracurium and sufentanil. The postoperative analgesia plan was left to the discretion of the anesthesiologist. Multimodal analgesia was provided using a combination of acetaminophen and ketoprofen, according to respective contra-indications. In some cases, regional analgesia techniques (wound infiltration or transversus abdominis plane block) were used. At the end of the procedure, volatile agents were discontinued, and 100% O₂ was given with 8 l/min fresh gas flow. Tracheal extubation was performed when the response of train-of-four was more than 90%, the patient was alert, with a respiratory rate between 12 and 30 breaths/min, and a central core temperature greater than 36°C.

Study Protocol and Pupil Measurement

In the first 10 min after tracheal extubation, upon arrival in the postanesthesia care unit, pain intensity was assessed by using a five-item verbal rating scale (VRS, with 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = extreme pain). All patients were educated about the VRS before surgery. Patients experiencing VRS more than 1 received intravenous 2-mg boluses of morphine as titration, with 5-min intervals between two injections, until pain returned to VRS of 1 or fewer. Patients experiencing an initial VRS = 0 or VRS = 1 did not receive morphine titration.

During pain assessment, before and after IMT, pupil size was monitored and recorded using an infrared portable dynamic pupillometer (NeuroLight SN80800®, version 1.2, IDMed, Marseilles, France). The pupillometer was used in STIMN mode. This consists in evaluating for 10 s the variation of the pupillary diameter synchronized with a standardized noxious stimulus. The standardized stimulus consist of a constant pressure (200 kPa) applied during 10 s at a distance of 2 to 3 cm from the edge of the skin incision using an

[#] http://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf. Accessed March 16, 2012.

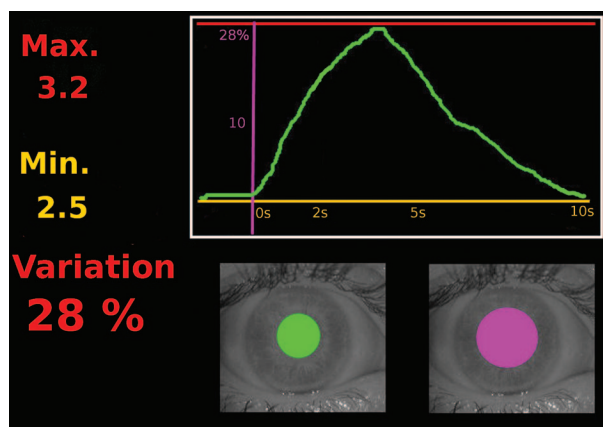


Fig. 1. A typical time course of pupillary dilation reflex measurement.

algometer (Algometer; Somedic® Production AB, Sollen-tuna, Sweden). Wound closure was performed using suture, a topical skin adhesive 2-octyl cyanoacrylate, and covered with sterile dressing. For the purpose of stimulation, the sterile dressing was removed. The topical skin adhesive 2-octyl cyanoacrylate allows for a protection against cutaneous infection. Moreover, the algometer was appropriately cleaned between each patient according to the recommendations of the health services of our hospital with a medical detergent (Surfa'Safe®; ANIOS Laboratory, Lille, France).

Patients stayed in a half-sitting position, with their eyes open and looking straight ahead. The pupillometer was applied to the orbit. Patients were asked to close the contralateral eye. Before standardized painful stimulation, the VRS was evaluated and the initial basal pupil diameter was measured. The painful stimulus was then applied for 10 s and the maximal pupil diameter was recorded. The precision of the measure was 0.01 mm. The pupillometer estimated the amplitude of the PDR, defined as the difference between the pupil size before and after stimulation, divided by the initial basal pupil size. The noxious stimuli were applied by the same nurse who checked the VRS score. The PDR measurement was performed by a physician blinded to the VRS score (fig. 1).

In order to avoid artifacts related to ambient light, the pupillometer includes a preformed silicone membrane surrounding the orbit under investigation. Moreover, patients were asked to close the contralateral eye. Another potential artifact to avoid could be a deformation of the pupil caused by the pupillometer itself. During the measurement, two infrared sensors ensure that the sphericity of the eyeball is not compromised; otherwise, pupil size measurement cannot be performed and the pupillometer has to be repositioned.

Statistical Analysis

The statistical analysis was performed using Medcalc® version 11.2.1.0 (MedCalc Software, Mariakerke, Belgium). We hypothesized that PDR would be correlated with VRS and morphine consumption. The correlation and comparison was obtained by Spearman rank test and Wilcoxon rank

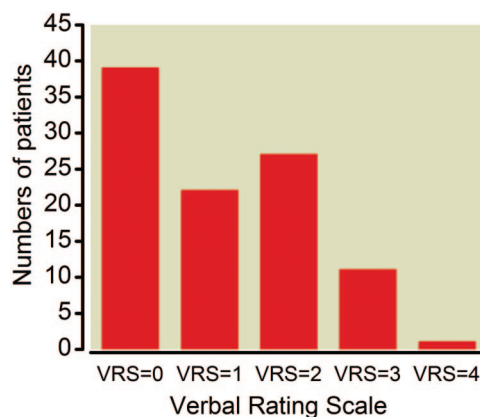


Fig. 2. Distribution of the initial five-item verbal rating scale in the immediate postoperative period. VRS = verbal rating scale.

sum test, respectively. The results are expressed as median with 95% CI. The threshold for statistical significance was set at $P < 0.05$.

A receiver-operating curve was built by plotting the sensitivity, or true positive rate, as a function of the false positive rate (100-specificity) at different PDR points. The software generated the PDR value with the highest sensitivity and specificity to conclude that a patient had adequate pain relief (VRS = 0 or 1) that does not require IMT.

Results

One hundred patients were included and analyzed. The median age was 58yr (52–62). Forty-two were male, and the median body mass index was 24 kg/m² (23.5–25.2). Respectively 32, 62, and six patients were classified as American Society of Anesthesiology physical status 1, 2, or 3.

Pain assessment was performed within 10 min after tracheal extubation in all cases. Measurements of PDR and VRS were easily performed in all cases. There were no missing data.

The distribution of initial pain intensity is shown in figure 2. During this first pain evaluation, 39 patients did not have pain (VRS = 0), all of them having benefited from effective regional analgesia. Only one patient reported a pain intensity at VRS = 4.

During the initial evaluation, in the absence of noxious stimulus, basal pupil diameter was 2.3 mm (2 to 2.8) in patients with VRS of 1 or fewer and 2.5 mm (2.3 to 2.7) in patients with VRS more than 1 ($P = 0.45$). No correlation was found between VRS and basal pupil diameter ($P = 0.17$). A significant correlation was found between VRS and maximal pupil diameter ($\rho = 0.46$ [0.29 to 0.6], $P < 0.0001$) and PDR ($\rho = 0.88$ [0.83 to 0.92], $P < 0.0001$) as illustrated in figure 3.

The receiver-operating curve determining the predictive value of PDR for a VRS of 1 or fewer is shown in figure 4. The cutoff point, corresponding to the PDR value with the highest sensitivity/specificity to conclude to adequate pain

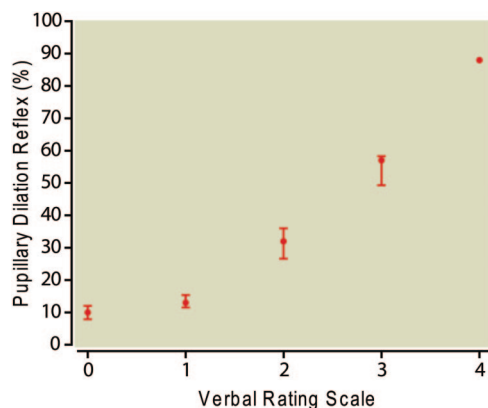


Fig. 3. Correlation of the verbal rating scale and the pupillary dilatation reflex. Pupillary dilatation reflex is shown as median (large horizontal bars) and 95% CI (small horizontal bars). Only one patient reported pain intensity at verbal rating scale = 4.

relief that does not require IMT (VRS = 0 or 1), was calculated to be 23%. At this value, the sensitivity, the specificity, the predictive positive value, and the negative predictive value of the PDR to discriminate between patients with VRS of 1 or fewer and VRS more than 1 were 91% (82–97), 94% (86–99), 96% (88–99) and 88% (74–96), respectively.

In the 39 patients that had an initial VRS of more than 1, the average initial PDR value was 35% (31–43) versus 11% (9–13) in patients having VRS of 1 or fewer initially ($P < 0.0001$). In these patients, the morphine dose required to return to VRS of 1 or fewer was 8 mg (7–10). Morphine consumption was significantly correlated with the initial VRS value ($\rho = 0.90$ [0.85 to 0.93], $P < 0.0001$), as well as with the initial PDR values ($\rho = 0.88$ [0.82 to 0.91], $P < 0.0001$, fig. 5).

After morphine titration, VRS of 1 or fewer was obtained in all patients and the corresponding PDR was 11% (10–13). A significant difference was found between PDR before

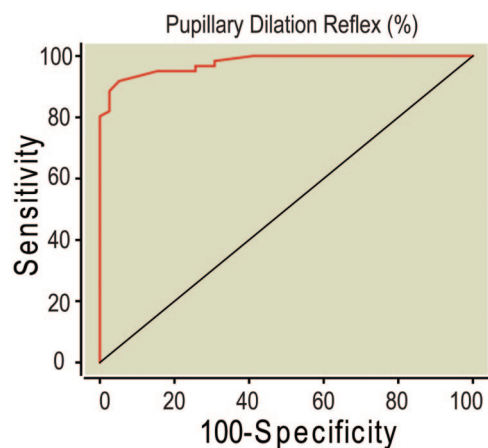


Fig. 4. Receiver-operating curve showing the relationship between sensitivity (true-positive) and 100-specificity (true-negative) in determining the value of the pupillary dilatation reflex values that predict a verbal rating scale of more than 1 requiring intravenous morphine titration.

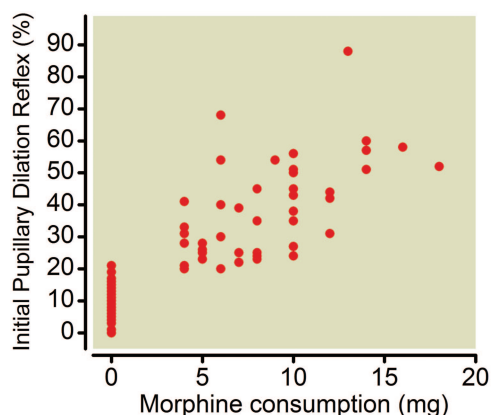


Fig. 5. Correlation between the initial pupillary dilatation reflex and the morphine consumption to achieve verbal rating scale of 1 or fewer.

and after morphine titration (35% [31–43] vs. 12% [10–14]; $P < 0.0001$). Pupillary diameter at the end of the IMT, without any noxious stimulation, was 2.4 mm (2.3 to 2.7). This value was not significantly different from initial baseline values, whatever the initial level of pain. PDR after IMT was not statistically different from that measured in the patients who had no pain on initial evaluation.

Discussion

The results of this study suggest that the measurement of the pupillary diameter variation induced by a standardized noxious stimulus may provide a useful objective index of analgesia. A PDR value of more than 23% is associated with a high probability to have VRS more than 1, and therefore to require morphine titration.

The incidence of severe pain upon awakening from anesthesia has been emphasized in previous studies.^{3,13} In a study by Aubrun *et al.* performed in orthopedic surgical patients, the mean initial visual analog scale score after tracheal extubation was 73 ± 19 mm, with a high number of patients complaining of pain intensity rated as 90 mm.³ In the current study, 61% of the patients rated their initial pain as absent or mild. This could be ascribed to the use of a multimodal analgesic regimen, including regional techniques, and to the preemptive administration of nonopioid analgesics before the end of the surgery. Regardless, 39 patients out of 100 experienced pain of moderate to severe intensity and required IMT for immediate postoperative analgesia.

Besides leading to poor patient satisfaction, acute postoperative pain has general consequences that can lead to postoperative morbidity and have detrimental effect on patients recovery course.¹⁴ Current guidelines promote aggressive treatment of acute pain.^{1,14} In this setting, IMT allows for the provision of rapid and efficient analgesia, with a dose closely adapted to individual cases, thereby minimizing the incidence of morphine-related adverse events.^{2,3,15} In the current study, all patients that benefited from IMT reached a

VRS score of 1 or fewer at completion, with a median morphine dose of 8 mg.

Morphine titration is conceptually based on the accuracy of pain level evaluation at the time of emergence from anesthesia. The evaluation of pain is therefore the cornerstone of this approach. Pain scales are commonly used for this purpose. In this study, VRS was chosen because of its simplicity and ease of use.¹⁶ Although visual analog scale is considered as the gold standard for pain assessment, it is sometimes difficult to implement in the immediate postoperative period and its clinical pertinence in this setting remains questionable.¹⁷ It should be noted that the final aim of IMT is commonly to provide a visual analog scale score of less than 30 out of 100 mm, which closely corresponds to the threshold we choose (VRS of 1 or fewer) in the current study.¹⁸ However, in clinical daily practice, physicians experience major problems to reliably evaluate immediate postoperative analgesia using a patient's self-reporting pain scales. Initial evaluation is complicated by the postoperative perceptual cognitive impairment experienced by patients who have undergone general anesthesia. Anxiety, drowsiness, postoperative nausea and vomiting, and blurred vision, which frequently occur after general anesthesia, make it difficult to use pain scales. During IMT, many patients experience morphine-induced sedation despite having residual pain, which is difficult to evaluate in these circumstances.^{6,7} Lastly, analgesia evaluation is of primary importance in patients having communication impairment, making adequate pain relief quite impossible to provide.¹⁹ Pupillary dilatation in response to a noxious stimulus has been well characterized.^{9–12,20,21} It is considered a reliable index of the adequacy of the analgesic component during a balanced general anesthesia. In anesthetized healthy volunteers,¹⁰ surgical patients,¹² and children,²¹ opioid administration reduces PDR in a dose-dependent manner.

The current results suggest for the first time a correlation between the magnitude of the PDR induced by a noxious stimulus and the level of pain reported by the patient on VRS during the immediate postoperative period. Comparisons of the current findings with studies of anesthetized patients are difficult. Mechanisms for PDR seem to be different in anesthetized and unanesthetized conditions, with the sympathetic component being predominant during the conscious state.²² Indeed, it has been shown that the sympathetic pupillary reflex was under the dependence of rostral brain centers that maintain consciousness.²³ Regardless of the mechanism, which remains poorly understood, it can be concluded from our results that the measurement of PDR in conscious patients following emergence from anesthesia is a reliable indication of the level of analgesia.

It should be stressed that PDR is strictly speaking a measurement of the level of analgesia (pain elicited by stimulation) rather than a measurement of pain. Although conceptually distinct, these two parameters are closely correlated, as illustrated in the present study. In order to better quantify

this relationship and the ability for PDR to discriminate between patients experiencing pain with a VRS more than 1 and therefore requiring IMT, and those that do not, a receiver-operating curve was constructed. The value of 23% was determined to be the value with the highest sensitivity and negative predictive value, meaning that PDR values above this threshold have a high probability to be associated with patients reporting pain intensity requiring IMT. In addition, a correlation was shown between morphine requirements and initial PDR and VRS. At the time of IMT completion, PDR values were reduced as compared with initial values. This is consistent with the observation drawn from intraoperative studies that showed a correlation between opioid systemic concentration and PDR values.^{10,12,21,24} The fact that PDR values at the end of IMT were nearly the same as those obtained in patients who did not report pain upon awakening provides further evidence of the accuracy of PDR to evaluate pain relief. This could make this technique useful in guiding IMT, especially in patients with communication impairments, in drug-seeking patients, in patients who refuse pain medications either because of fear of addiction or because any admission of pain is thought to be a sign of weakness, or also in the case of morphine-induced side effects that could mask residual pain.

The availability of a portable pupillometer allows for a convenient and reliable objective measurement of PDR and may promote the development of this technique in clinical practice. Other parameters, such as the patient's own report of elicited pain, the sinus variability of the electrocardiogram, the pupillary response latency, or the peak velocity of pupillary movement could have been used.²⁵ We choose to focus on PDR for practical reasons. Absolute values of pupil sizes have also been recorded. The basal pupil size is under the dependence of the interaction between the parasympathetic and the sympathetic nervous system, but it is also influenced by several other factors, such as ambient light, vision accommodation, or drug interactions. Although the explanation remains unclear, no correlation was found between basal nonstimulated pupil sizes and initial VRS, suggesting that in the immediate postoperative period, a constant level of pain does not significantly dilate the pupil. Similarly, no difference on basal pupil sizes was found before and after IMT, although the pupillary constrictor effect of opiate drugs is well recognized.²⁶ It had been demonstrated, in anesthetized patients without surgical stimulation, that fentanyl could depress PDR without any action on basal pupil diameter.²⁷ The present results tend to show that in patients awakening from anesthesia, PDR is depressed by opiate administration, without any effect on pupil diameter; however, this deserves further evaluation. The only relevant impact of the pupillary diameter on PDR measurement might have been the fact that any changes could have altered the mechanical range available for iris motion.²⁸ However, in the present study, no significant variations in the pupillary diameter were observed before and after IMT.

The existence of a continuous physiologic oscillation of the pupillary diameter, regardless of any external stimulation, called pupillary hippus, should be taken into account.^{29,30} Indeed, the magnitude of the pupillary variation induced by physiologic hippus is about 10%, which corresponds approximately to the PDR value recorded in patients who had no pain. The probability of physiologic hippus to impact PDR measurements in the present study is low because the periodicity of hippus variations (0.04 to 0.1 Hz) is far less than the period of measurement. However, it cannot be ruled out that part of the variability in our results might be ascribed to physiologic hippus.

Several limitations of this study should be addressed. The accuracy of PDR measurement is a matter of concern. In the present study, all patients were informed about the PDR measurement and able to collaborate appropriately. Measurement was correctly performed in all patients without any missing values. Standardization of noxious stimuli was insured by using an identical pressure applied for the same time, in a similar fashion, in all patients. Medications known to alter PDR (*e.g.*, dopaminergic receptor antagonists used as antiemetics, or anticholinergic drugs) were avoided.³¹ Local anesthetics are not known to interfere with PDR measurements, supporting the validity of the PDR values obtained in patients who benefited from regional analgesia and did not experience pain on initial evaluation.³² Administration of neuromuscular blocking drugs was closely monitored, allowing residual neuromuscular weakness to be prevented without the use of reversal agents and the associated anticholinergic medications that could have interfered with PDR.

In order to avoid potential interactions with ambient light in the postanesthesia care unit, likely to interfere with PDR measurement,²⁴ the pupillometer includes a preformed silicone membrane surrounding the orbit, and the patients were asked to close the contralateral eye. Another possible limitation of our results could be that the examinations were performed only during a very short period of time after surgery. During this time point the processing of nociceptive stimulation and pain experience may be still affected by anesthetic medications. Further investigations are needed to explore the interest of PDR measurement at later time-points after awakening from anesthesia. Finally, it should be stressed that other parameters, such as age, gender, and type of surgery might have influenced the current results.³³ This should be taken into account before translating the current results in another setting.

In conclusion, the assessment of the level of analgesia during the immediate postoperative period by the measurement of the PDR induced by a noxious stimulus is significantly correlated with the pain intensity and the morphine requirements to obtain pain relief. In this context, a PDR value above 23% has a high probability to be associated with moderate to severe pain requiring ITM. The portable pupillometer appears to be an objective method not only to assess postoperative analgesia but also to guide IMT. In this per-

spective, it could be used to improve immediate postoperative pain management, especially in patients with communication impairments.

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