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Pupillary dilation reflex and pupillary pain index evaluation during general anaesthesia: a pilot study

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Abstract

Background. Pupillary response by pupillary dilatation reflex (PDR) is a robust reflex, even measurable during general anaesthesia. However, the ability of infrared pupillometry to detect PDR differences obtained by intraoperative opioid administration in anaesthesized patients remains largely unknown. We analyzed the performance of automated infrared pupillometry in detecting differences in pupillary dilatation reflex response by a inbuilt standardized nociceptive stimulation program in patients under general anesthesia with a standardized propofol/fentanyl scheme.

Methods. In this single center, interventional cohort study 38 patients (24-74 years) were enrolled. Patients were anesthetized with propofol until loss of consciousness. Two dynamic pupil measurements were performed in each patient (before opioid administration and after opioid steady state). Automated infrared pupillometry was used to determine PDR during nociceptive stimulations (10-60 mA) applied by a inbuilt pupillary pain index protocol (PPI) to the skin area innervated by the median nerve. Increasing stimulations by protocol are device specific and automatically performed until pupil dilation of > 13%. Pupil characteristics, blood pressure, heart rate values were collected.

Results. After opioid administration, patients needed a higher stimulation intensity (45.26 mA vs 30.79 mA, p = 0.00001). PPI score showed a reduction after analgesic treatment (5.21 vs 7.68, p = 0.000001), resulting in a 32.16% score reduction.

Conclusions. PDR via automated increased tetanic stimulation may reflect opioid effect under general anaesthesia. Further research is required to detect possible confounding factors such as medication interaction and optimization of individualized opioid dosage.

Keywords: analgesia, pain, monitoring

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Introduction

Pain assessment in non-communicative patients is still challenging despite many novel innovative technologies. Under general anaesthesia, communication is impossible due to unconsciousness. Adequate measurement of nociception may allow the anaesthesiologist to individual titration of analgesics (mostly opioids), avoiding over- or underdosage. More and more anaesthesiologists attempt to minimize the dose of opioids, consequently reducing the well-known side effects. Correct nociceptive assessment and therefore appropriate individually based treatment, may be an ideal scenario. Appropriate pain assessment and evidence-based pain treatment may improve patient safety and outcome during hospital stay. Although current research addressing this complex issue provides some promising innovative techniques [1], no standardized objective pain monitoring protocols exist. Many professionals still use vital signs (heart rate, systolic blood pressure) or locomotor response as reliable

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indicators of nociception in the non-communicative patient under general anaesthesia [2].

Infrared pupillometry was introduced decades ago, but only recently used for nociceptive assessment. Concerns of unwanted device movement or subjective pupil diameter evaluation are no longer realistic with the introduction of an automated pupil tracking system [3]. Although recent research revealed a pupil dilation reflex (PDR) effect of antiemetics [4], and respiratory distress with hypoxia and/or hypercarbia [5], little is known about the influence by different opioids, age, or gender. Currently, portable video pupillometry is used for measuring pupil characteristics and the light-induced pupil reflex in response to noxious procedures [6-8].

However, if we want to evaluate the pupil response during noxious procedures (skin incision, pneumoperitoneum, etc.), monitoring of PDR elicited by standardized nociceptive stimulations in anesthesized patients needs to be further examined. Furthermore, there is a need for consensus to use and interpret different pupil assessment features as light-induced PDR, nociceptive stimulation induced PDR, constriction velocity, reaction latency or PPI score. We anticipated that a PDR evaluation, and in addition PPI score, by increasing tetanic stimulation may be related to analgesic treatment in anaesthesized patients.

Materials and methods

This single-center observational cohort study was performed in accordance with the ethical standards of ICH-GCP and the Declaration of Helsinki after study approval by the institutional review board and the Ethics Committee of the Antwerp University Hospital, Belgium (study identifier: 16/40/410). Registration at Clinicaltrials.gov (NCT02942316) was executed before study inclusion.

After written consent, patients planned for elective abdominal or gynaecological surgery with the American Society of Anesthesiologists physical status classification system (ASA) I or II were recruited for study inclusion from November 2016 until March 2017. History of ophthalmologic surgery, known pupil reflex disorders, cranial nerve lesions, expected difficult airway management, chronic opioid use (> 3 months) and preoperative use of topical interfering eye drops (atropine, phenylephrine) or antiemetics were defined as exclusion criteria.

Enrolled subjects underwent two consecutive pupil measurements under general anaesthesia. By convention the left eye was assessed after confirmation of pupil syndrome disorder absence. Patients were anaesthetized in a fully equipped operation room. No premedication was administered before surgery. On arrival in the operation theatre, standard monitoring and safe surgery checklist was executed. Venous catheter was inserted in a cubital vein. Non-invasive blood pressure was recorded every 5 minutes, and heart rate, ECG, oxygen saturation (SpO_2), end-tidal-carbon dioxide concentration were recorded continuously.

Induction was established after preoxygenation by administration of a propofol bolus of 2 mg · kg^{-1} followed by continuous target controlled infusion (TCI) of propofol with effect-site concentration 5 µg · ml^{-1} (Marsh-Model; injectomat TIVA Agilia, Fresenius Kabi, Germany) [9, 10]. Manually assisted ventilation with 100% oxygen began as soon as the subjects became apneic. To facilitate orotracheal intubation rocuronium 0.6 mg · kg^{-1} was given when considered necessary by the attending anaesthesiologist. No deep neuromuscular block was used during surgery. Airway management was performed by laryngeal mask (LMA UniqueTM, LMA Deutschland GmbH, Bonn, Germany) placement or endotracheal intubation (Tracheal Tube MallinckrodtTM, CovidienTM, Tullamore, Ireland). First PDR measurement was performed when Richmond Agitation and Sedation Scale (RASS) $\leq$ -4 was achieved. If not, the rate of propofol was adjusted. Sedation depth by RASS classification was controlled by the attending anaesthesiologist, a resident in anaesthesiology and the principal investigator for PDR measurement approval. A second pupil assessment was executed after fentanyl 2 µg · kg^{-1} administration with a stabilization period of five minutes for airway management and opioid effect site equilibration [11, 12].

For PDR measurement, we used CE-approved NeuroLight AlgiScan® (IDMed, Marseille, France) pupillometer using infrared video recording allowing quantitative pupil size assessment during the steady state anaesthesia; i.e. no propofol adjustments were made during pupil analyses.

For nociceptive stimulation, two Ag-AgCl electrodes were placed at the skin area innervated by the median nerve. Optimal skin contact with low electrode impedance was defined on the touchscreen display. Constant current stimulations were generated during pupil measurement, increasing automatically the voltage according to the resistance. Voltage is limited to a maximum of 300 V. Therefore, at a current fixed at 60 mA, the maximum acceptable resistance is 5 KOhms. Patient movements during the stimulation were recorded.

The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup placed to the orbit ensures optimal device position, pupil-camera distance and environmental darkness. There was never direct contact with the cornea. The contralateral eye was closed, reducing the effect of the consensual light response. Via the touch screen display the *PPI-modus* was selected for dynamic pupil measurement. This in-built measurement protocol generates an automatic

electric stimulation pattern. Operating principle is the application of a standardized noxious stimulation (from 10 mA to 60 mA by incremental steps of 10 mA, with a duration of 1s, and pulse width of 200 μs) in increasing intensity, until pupillary dilation of more than 13% ([maximal diameter – minimal diameter]/maximal diameter × 100). When the defined criteria are reached, stimulation is automatically stopped and PPI score is determined (Table 1). The measurable pupil size (diameter) ranges between 0.1-10 mm. Furthermore, baseline (minimum) and maximum amplitude are recorded. Depending on necessary stimulation intensity, pupil measurement duration is between 2 and 16 seconds.

Statistical analysis

In this pilot study, no data were available to make assumptions for the sample size calculation.

Variables were reported as means ± standard deviation (SD). Pupil size variation was tested using non parametric analysis methods, as a normal distribution is unlikely in the study population. Mean stimulation intensity before and after opioid administration were compared using the Wilcoxon signed rank test in our paired data. Statistical analyses were performed with SPSS Statistics software, version 20.0 for Mac (IBM Corp., Armonk, NY, USA) and reviewed by a statistician member (E. Roelant, University Hospital Antwerp, Wilrijkstraat 10 – 2650 Edegem, Belgium) Statistical significance was considered with $p < 0.05$.

Results

Forty-one patients were enrolled for study inclusion; one patient dropped out due to an electrode impedance problem. Two subjects were excluded from statistical analysis because of outline baseline pupillary data (maximal stimulation intensity for primary measurement). Enrolled patients consisted of 27 women and 11 men, with a mean age of 46.53 ± 13.27 year, and mean BMI 26.01 ± 4.78 kg · m^{-2}. No anti-emetic treatment was administrated prior to pupil analyses. All pupil measurements were taken in the absence of hypoxia (SpO_2 awake: 98.34 ± 1.85%; SpO_2 first PDR assessment: 99.11 ± 1.62%; SpO_2 second PDR assessment: 99.20 ± 0.83%). Hypercarbia in the participants was excluded via end-tidal carbon dioxide monitoring with a target of ≤ 45 mmHg. Pupil characteristics are presented in Table 2.

Baseline pupil diameter decreased by 39% by analgesic treatment. Pupil variation increased significantly after noxious stimulation without opioid, although the stimulation stops when 13% dilation is achieved. The necessary stimulation intensity increased significantly after opioid administration, correlating with a 32% reduction in PPI score. Fourteen patients needed a maximal stimulation intensity of 60 mA (37%) during PDR evaluation after fentanyl administration.

Stimulations were well tolerated without significant variation in vital signs (Table 3).

Discussion

This pilot study suggests that PDR measurement by infra-red pupillometry with an inbuilt standardized noxious stimulation protocol may be related to opioid administration in patients under general anaesthesia. An additional automatically generated PPI-score, in accordance with the standard pain assessment by a numeric rating scale (NRS) in communicative adults, reflects differences in PDR response after analgesic treatment. Larger pupil variation percentages before opioid administration indicates the fast mydriatic effect after tetanic stimulations via an automated inbuilt program.

Table 1. PPI scoring algorithm

Maximun intensity reached by the stimulation (mA)	PPI Score	Pupil reactivity level of the patient
10	9	The pupil's dilatation is over 13% during the stimulation 10 mA
20	8	The pupil's dilatation is over 13% during the stimulation 20 mA
30	7	The pupil's dilatation is over 13% during the stimulation 30 mA
40	6	The pupil's dilatation is over 13% during the stimulation 40 mA
50	5	The pupil's dilatation is over 13% during the stimulation 50 mA
60	4	The pupil's dilatation is over 13% during the stimulation 60 mA
60	3	The pupil's dilatation is over 13% during the second level of 60 mA
60 mA (5% < pupil dilatation < 13%)	2	The pupil's dilatation is over 13% during the third level of 60 mA stimulation
60 mA (pupil dilatation ≤ 5%)	1	The pupil's dilatation is over 13% during the last stimulation of 60 mA

Table 2. Changes in pupil characteristics before and after opioid administration

Parameter	No opioid	After opioid	p value**
Baseline pupil diameter (mm)	3.57 ± 1.09	2.17 ± 0.38	< 0.0001
Stimulation intensity (mA)	30.79 ± 10.24	45.26 ± 14.66	0.000016
Pupil variation (mm)	1.09 ± 0.53	0.35 ± 0.21	< 0.0001
Pupil variation (%)	31.39 ± 14.81	15.97 ± 7.01	< 0.0001
PPI score*	7.68 ± 1.17	5.21 ± 2.16	0.000001

Data are expressed mean ± SD
* PPI = pupillary pain index; ** stat. sign. for $p < 0.05$

Table 3. Variation in vital signs induced by opioid administration

	Before analgesia	After analgesia	p value*
Systolic blood pressure (mmHg)	121.55 ± 18.47	100.95 ± 18.75	0.000001
Heart rate (bpm)	70.66 ± 10.95	69.26 ± 12.25	0.094

Data are expressed mean ± SD
* stat. sign. for $p < 0.05$

Despite the ongoing debate of opioid free anaesthesia, mainly in patients at risk such as obstructive sleep apnoea syndrome or gastrointestinal surgery [13], no large trials were conducted for optimizing pain assessment in non-communicative patients during surgery. The lack of nociceptive evaluation in patients under general anaesthesia, impedes adequately treating pain and therefore under – or overdosing still occurs, further compromising the patient outcome. The stress response evoked by pain can have deleterious negative consequences. Increased circulating catecholamines can cause arteriolar vasoconstriction, impair tissue perfusion, and reduce tissue-oxygen partial pressure [14]. Furthermore, catabolic hypermetabolism resulting in hyperglycemia, lipolysis, and breakdown of muscle to provide protein substrate, impairs wound healing and increases the risk of wound infection [15-17]. Moreover, pain compromises postoperative comorbidities causing delay in early rehabilitation and prolongues the hospital stay. On the other hand, overdosing opioids are also associated with negative consequences such as opioid-induced hyperalgesia, ileus or nausea and vomiting.

Recently, De Jonckheere et al. presented some technological solutions for nociception monitoring [18]. The choice of assessment device relies, however, on the clinical context and general purpose. Nociceptive assessment in non-communicative patients remains challenging for health care providers.

PDR is known as a robust reflex, parasympathetically mediated during general anesthesia [19]. Barvais et al. found that PDR upon a painful tetanic (100 Hz) stimulus was a better indicator for remifentanil titration than a haemodynamic response or BIS measurements during propofol TCI in healthy individuals [20]. Moreover, PDR evaluation recently showed promising results in awake and unconscious patients. Administration of classically used sedatives showed no depression of the PDR after activation of nociceptive A-delta and C-fibers [21]. It should be noted that during chronic opioid treatment, tolerance occurs in analgesic effect and respiratory depression effect, in contrast to the elicitation of miosis. This should be taken in account when interpreting PDR results.

Propofol, lidocaine and neuromuscular blocking agents do not affect pupil reactivity in contrast to modern used inhalation anaesthetics such as sevoflurane and desflurane [22, 23], and nociceptive stimulation still induces mydriasis under general anaesthesia. Up to now, all the mechanisms of blocking this pupil reflex are not fully understood. Furthermore, drug-effect measurements are still evaluated either as pupil variation from baseline or as an absolute effect by extreme accurate equipment [21]. Our results indicate that PRD measurements during standardized nociceptive stimulation of the skin may perceive the effects of endogenous opioid response in patients receiving propofol anaesthesia. To determine the effect of fentanyl we used a gradual increase in stimulation intensity in anaesthetized patients by protocol. An advantage of this automated schedule is that there is no need for unappropriated high stimulation. When the device detects a pupil variation of > 13%, nociceptive stimulation is interpreted and stopped. The use of automated pupillometry for nociceptive PRD evaluation in non-communicative adults may provide the caregiver the possibility to measure the reactivity of the autonomous system to nociceptive stimuli. Recently, Jakuscheit et al. used the PDR among others as nociceptive reflex and concluded this assessment as a reflection of the analgesia-nociception balance under general anaesthesia [24].

There are, however, some limitations to our pilot study such as the unequal gender distribution caused by including a majority of gynaecological patients. Evaluation of the heart rate, systolic blood pressure and the application of an anaesthesia depth device, as additional standard parameters for each nociceptive stimulation category would have been of particular

value. To determine the effect of opioid administration, patients should obtain an equal anaesthesia depth prior to the first pupil measurement. Moreover, opioid administration with estimated effect site concentrations would define steady state analgesic plasma concentrations even more superior.

Conclusions

In conclusion, if caregivers would be able to improve opioid titration based on individual and more objective reflex parameters, adequate analgesic administration would be performed with less over – and underdosing. As a fast, straightforward and easy to use bedside device, PDR measurement in response to noxious stimulation may help the anaesthesiologist to evaluate the autonomous component of nociception in anaesthetized adults undergoing painful procedures. Whether this technique, including PPI scoring, may be helpful in recruiting perioperative opioids necessitates more clinical research.

Conflict of interest

Nothing to declare

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