Measurements of pupillary unrest using infrared pupillometry fail to detect changes in pain intensity in patients after surgery: a prospective observational study

Les mesures des fluctuations du diamètre pupillaire à l'aide de la pupillométrie infrarouge ne permettent pas de détecter les changements dans l'intensité de la douleur chez les patient·es après une intervention chirurgicale : une étude observationnelle prospective

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Abstract

Purpose The pupil displays chaotic oscillations, also referred to as pupillary unrest in ambient light (PUAL). As pain has previously been shown to increase pupillary unrest, the quantitative assessment of PUAL has been considered a possible tool to identify and quantify pain. Nevertheless, PUAL is affected by various states, such as vigilance, cognitive load, or emotional arousal, independent of pain. Furthermore, systematically applied opioids are known to reduce PUAL, thus potentially limiting its usefulness to detect pain or changes in pain intensity. To test the hypothesis that PUAL can reliably identify changes in pain intensity in a clinical setting, we measured PUAL in patients experiencing substantial pain relief when regional anesthesia interventions were applied after surgery.

Methods We conducted an observational study at an academic surgery centre following institutional review board approval. Eighteen patients with unsatisfactory pain control following surgery underwent regional anesthesia procedures to improve pain control. We used infrared pupillometry to assess pupillary unrest before and after the regional block. We then compared the changes in pupillary unrest with the changes in pain scores (numeric rating scale [NRS], range 0–10).

Results Eighteen patients received epidural anesthesia (n = 14) or peripheral nerve blocks (n = 4), resulting in improvement of mean (standard deviation [SD]) NRS pain scores from 7.2 (1.7) to 1.9 (1.8) (difference in means, −2.2; 95% confidence interval [CI], −6.3 to −4.1; P < 0.001). Nevertheless, pupillary unrest did not change as pain decreased; the mean (SD) PUAL was 0.113 (0.062) before analgesia and 0.112 (0.068) after analgesia (difference in means, −0.001; 95% CI, −0.018 to 0.015; P = 0.88).

Conclusion In this prospective observational study, pupillometric measurements of pupillary unrest did not identify changes in pain intensity in a postoperative, predominantly opioid-exposed patient population. While the sample size was small, the use of measurements of pupillary unrest to detect and quantify pain has to be questioned.

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Résumé

Objectif La pupille affiche des oscillations chaotiques, également appelées fluctuations du diamètre pupillaire (FDP). Comme il a déjà été démontré que la douleur augmente les troubles pupillaires, l'évaluation quantitative des FDP a été envisagée comme outil potentiel pour identifier et quantifier la douleur. Néanmoins, les FDP sont affectées par divers états, tels que la vigilance, la charge cognitive ou l'excitation émotionnelle, indépendamment de

la douleur. De plus, nous savons que l'application systématique d'opioïdes réduit les FDP, ce qui limite potentiellement leur utilité pour détecter la douleur ou les changements d'intensité de la douleur. Pour tester l'hypothèse selon laquelle les FDP permettent d'identifier de manière fiable les changements dans l'intensité de la douleur dans un cadre clinique, nous avons mesuré les FDP chez les patient·es manifestant un soulagement substantiel de la douleur lorsque des interventions d'anesthésie régionale ont été appliquées après la chirurgie.

Méthode Nous avons mené une étude observationnelle dans un centre de chirurgie universitaire après avoir obtenu l'approbation du comité d'éthique indépendant. Dix-huit patient·es dont le contrôle de la douleur n'était pas satisfaisant à la suite d'une intervention chirurgicale ont bénéficié d'interventions d'anesthésie régionale pour améliorer le contrôle de la douleur. Nous avons utilisé la pupillométrie infrarouge pour évaluer les fluctuations du diamètre pupillaire avant et après le bloc régional. Nous avons ensuite comparé les changements dans les fluctuations pupillaires avec les changements dans les scores de douleur (échelle d'évaluation numérique [EVA], plage de 0 à 10).

Résultats Dix-huit patient·es ont reçu une anesthésie péridurale (n = 14) ou des blocs nerveux périphériques (n = 4), ce qui a entraîné une amélioration des scores de douleur moyens (écart type [ET]) sur l'EVA de 7,2 (1,7) à 1,9 (1,8) (différence de moyennes, −2,2 ; intervalle de confiance [IC] à 95 %, −6,3 à −4,1 ; P < 0,001). Néanmoins, les fluctuations du diamètre pupillaire n'ont pas changé à mesure que la douleur diminuait; la moyenne (ET) des FDP était de 0,113 (0,062) avant l'analgésie et de 0,112 (0,068) après l'analgésie (différence de moyennes, −0,001; IC 95 %, −0,018 à 0,015; P = 0,88).

Conclusion Dans cette étude observationnelle prospective, les mesures pupillométriques des fluctuations du diamètre pupillaire n'ont pas permis d'identifier de changements dans l'intensité de la douleur dans une population de patient·es postopératoires, principalement exposé·es aux opioïdes. Bien que la taille de l'échantillon soit petite, l'utilisation de mesures des fluctuations du diamètre pupillaire pour détecter et quantifier la douleur doit être remise en question.

Keywords infrared pupillometry · pain · pupil size fluctuations · pupillary unrest · regional anesthesia

The assessment of pain depends primarily on patient-reported pain scores such as the numeric rating scale (NRS). An objective assessment of pain is still not clinically established but nonetheless desirable because of common clinical challenges such as the under- or over-reporting of pain by patients or the difficulty of assessing pain in nonverbal patients. Experimental studies investigating the objective assessment of pain have applied approaches such as neuroimaging,[1,2] measuring of biopotentials such as electroencephalography and magnetoencephalography,[3,4] as well as measuring autonomic-mediated responses such as heart rate variability or skin-conductance[5] to determine whether the pain experience can be objectively quantified.

Pupil size and movements are strongly influenced by the autonomic nervous system, and measurements of pupillary changes have frequently been considered potential tools to objectively measure pain.[6] Pupillary measurements can be performed in clinical settings with the use of a portable infrared pupillometer[7] and can include the assessment of pupil size, changes in pupillary reflexes such as the pupillary light reflex and the pupillary reflex dilation, or changes in the amplitude of pupillary oscillations, also known as pupillary unrest in ambient light (PUAL).[8]

Pupillary unrest has previously been shown to correlate with pain scores after surgery,[9] but since pupillary unrest is extremely sensitive to the effects of systemically applied opioids,[8] the observed changes could have been influenced by prior opioid administration. We tested the hypothesis that changes in pain intensity after effective pain treatment with regional anesthesia can reliably be detected by measurements of pupillary unrest in patients that had undergone surgery. If pupillary unrest responds to pain, we expected to detect the substantial reduction in pain intensity that can be achieved with regional anesthesia with infrared pupillometry.

Methods

Setting

This study was a prospective, observational study in an academic surgery centre. The study was approved by its institutional review board and the manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patient population

The study participants were patients who had undergone various types of surgery between October 2020 and

Table 1 Characteristics of study participants

Characteristic	Data $N = 18$
Sex (F/M), n (%)	14/4 (78%/22%)
Age (yr), mean (SD)	53 (15)
Baseline pain score (NRS 0–10), mean (SD)	7.2 (1.7)
Baseline PUAL (arbitrary units), mean (SD)	0.114 (0.062)
Baseline pupil diameter (mm), mean (SD)	2.51 (0.68)
Block procedure (epidural/peripheral nerve block/fascial plane block), n (%)	13/4/1 (72%/ 22%/6%)

F = female; M = male; NRS = numeric rating scale; PUAL = pupillary unrest in ambient light; SD = standard deviation

January 2023 and were subsequently experiencing unsatisfactory pain control despite the administration of systemic analgesics (Table 1). Inclusion criteria were uncontrolled pain following surgery and a planned analgesic intervention using regional anesthesia. The only exclusion criteria were refused consent, existing eye disease, and prior eye surgery. A pain management team performed regional anesthesia techniques that covered the surgical site to achieve improved pain control. We performed pupillary measurements before and after block performance. We obtained written consent to use the scans for research purposes from the individuals after pain control was achieved and the study was explained in detail.

Sample size justification

We performed no *a priori* sample size calculation as preliminary data were lacking, and enrolled a sample size of convenience of 20 patients. Based on Charier's earlier findings that epidural analgesia during labour contractions reduced pupillary unrest, reported as the variation coefficient of pupillary diameter, by about 70%,[9] we were conservatively expecting a reduction of pupillary unrest by 50% in our study population by the analgesic interventions.

We analyzed a sample size of 18 patients in whom an effect size of 0.021 would have been statistically different at a significance level of 0.05 with a power of 0.8. This would equal a decrease in PUAL of about 20% with improved pain control. The detection of smaller changes in pupillary unrest seems unlikely in a clinical setting using portable infrared pupillometry.

Study interventions

We used infrared pupillometry to assess pupillary unrest and pupil diameter with two measurements performed before and after regional block and their mean calculated.

We compared changes in pupillary unrest and pupil diameter subsequently with the observed changes in pain. We performed the pupillary measurements at the start of the block procedure and the moment the patients reported substantial pain relief after the block procedure. At the same time, we asked the individuals to report pain scores (NRS; range, 0–10) and to provide a verbal descriptor of the level of pain relief experienced.

We report opioid use in the four hours preceding the block to provide a rough estimate about the opioid use before the intervention. Opioid use is reported in oral morphine equivalents using the University of California, San Francisco opioid equivalence table.[A]

The analgesic interventions performed included epidural analgesia following abdominal procedures, two brachial plexus blocks for upper extremity procedures, a truncal block and peripheral nerve blocks following two lower extremity procedures as detailed in Table 2. No other medication was administered between the pupillometric recordings.

All regional anesthesia procedures were performed according to routine standard practice. Peripheral nerve blocks were performed as single-shot blocks or following the placement of a peripheral nerve catheter. All peripheral nerve blocks were performed using ropivacaine 0.5% with a volume appropriate for the block location and patient weight. Epidural analgesia was achieved following placement of a thoracic epidural catheter at the appropriate dermatomal level for the procedure. Administered medications were a test dose of 3 mL lidocaine 1.5% with epinephrine 1:100,000, followed by careful titration of ropivacaine 0.2% until the patients reported substantial improvement of their pain symptoms. In the case of two patients who had received intravenous lidocaine before placement of the epidural catheters, we carefully considered the administered dose and time since intravenous administration and applied epidural local anesthetic in small, divided doses to minimize the risk of local anesthetic systemic toxicity.

Infrared pupillometry

We performed pupillary measurements with a modified commercial portable infrared pupillometer (PLR^{TM}-3000; NeurOptics$^{®}$, Inc.; Irvine, CA, USA).[8] Ambient light was excluded from the investigated eye with a rubber cup projecting from the lens of the pupillometer. The pupillometer incorporated light-emitting diode provided a


Table 2 Detailed patient list

Participant age, sex, and baseline NRS score	Chronic medication prior to admission	Type of surgery	Analgesics given within four hours before block procedure	Block procedure
1. 40 yr, female, 10	Diazepam, baclofen	Exploratory laparotomy	36 OME, ketamine, *iv* lidocaine	Epidural analgesia
2. 60 yr, female, 8	Duloxetine, gabapentin	Ventral hernia repair	27 OME, ketamine	Epidural analgesia
3. 57 yr, female, 4	Citalopram, zolpidem	Revision elbow arthroplasty	44 OME, ketamine, *iv* lidocaine	Infraclavicular brachial plexus block
4. 50 yr, female, 10	None	Gastrectomy	24 OME	Epidural analgesia
5. 68 yr, female, 8	Acetaminophen, buproprion, clonazepam, labetolol, oxycodone	Exploratory laparotomy	48 OME	Epidural analgesia
6. 38 yr, female, 8	Bupropion, clonazepam, fluoxetine, zolpidem, lithium	ORIF humerus fracture	24 OME	Interscalene brachial plexus block
7. 52 yr female, 4	Ibuprofen, oxycodone	Lower extremity amputation	41 OME	Epidural analgesia
8. 70 yr, female, 5	Venlaxafine, diazepam, hydrocodone/ acetaminophen, rizatriptan	Cholecysto-duodenal fistula takedown	43 OME	Epidural analgesia
9. 71 yr, female, 8	Donepezil, duloxetine, fentanyl patch, memantine, acetaminophen, hydromorphone	Inguinal hernia repair with mesh	139 OME	Ilioinguinal block
10. 72 yr, male, 8	None	Whipple	51 OME	Epidural analgesia
11. 38 yr, female, 6	None	Lung transplant	0 OME	Epidural analgesia
12. 56 yr, male, 7	Acetaminophen, gabapentin, ibuprofen	Revision esophagectomy	75 OME	Epidural analgesia
13. 49 yr, female, 8	Gabapentin, ibuprofen, oxycodone	Sigmoidectomy	113 OME, ketamine	Epidural analgesia
14. 62 yr, male, 6	Acetaminophen, gabapentin, ibuprofen, oxycodone	Lower extremity amputation	4 OME	Popliteal + adductor canal block
15. 61 yr, female, 8	Diphenhydramine, naproxen, hydromorphone	Abdominal wall reconstruction	14 OME	Epidural analgesia
16. 56 yr, female, 7	Metoprolol, risperidone, sertraline, tizanidine, tramadol, amitriptyline, lamotrigine	Exploratory laparotomy	27 OME	Epidural analgesia
17. 21 yr, male, 7	Levetiracetam	Lower extremity tumour resection	31 OME	Femoral and sciatic nerve block
18. 27 yr, female, 7	None	Thoracotomy, esophagus perforation repair	25 OME	Epidural analgesia

NRS = numeric rating scale (0–10); OME = administered opioids in oral morphine equivalents

consistent light source of 350 lux. Pupil size was measured for ten seconds, by measuring the reflection of infrared light (Fig. 1). Recordings were taken at a frequency of 33 samples per second (0.03 sec between sample times). The average pupil diameter over the ten-second measurement was calculated and reported as pupil size for that measurement.

Measurements taken with infrared pupillometry are prone to artifacts that arise from blinks, partial lid closures, and eye movements. We modified the computerized methods as described by McLaren *et al.,*[10] Merritt *et al.,*[10,11] and Lüdtke *et al.*[12] to remove artifacts that did not arise from actual movements of the pupil, as well as to slow drifts in diameter that do not constitute pupillary unrest. Drift in pupil size was reduced by eliminating low-frequency components of the scan with a Gaussian filter, and blinks or partial closures were eliminated automatically by identifying discontinuities in the pupil scan. Following this, we used fast Fourier transformation (FFT) to analyze the frequency components of each measurement. Our measure of pupillary unrest was the sum of amplitudes across a frequency range from 0.3–3 Hz.[13]
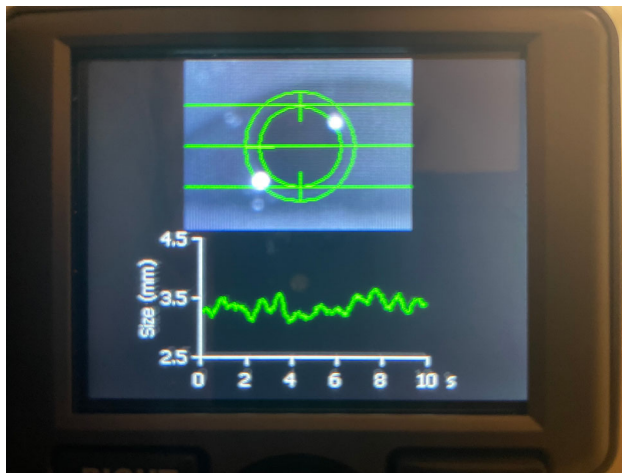
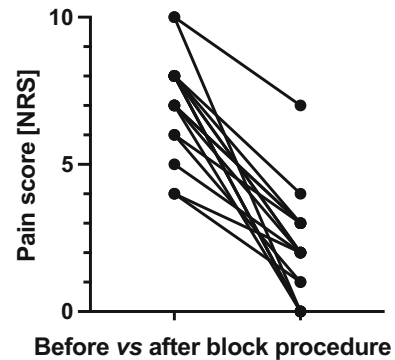Fig. 1 Display of the portable infrared pupillometer used, showing a 10-sec scan of pupillary unrest in ambient light

Before *vs* after block procedure

Fig. 2 Reduction of pain, measured by numeric rating scale (0–10) achieved with regional anesthesia. The mean (standard deviation) pain score decreased from 7.2 (1.7) to 1.9 (1.8) ($P < 0.001$).

NRS = numeric rating scale

Our main endpoint, PUAL, was quantified by calculating the area under the curves of the FFTs of pupil diameter over the selected range of frequencies and reported as arbitrary units.

Statistical analysis

All continuous variables are presented as mean (standard deviation [SD]). The primary endpoint was change in PUAL with improved pain control. Changes in pain scores, pupil diameter, and PUAL were analyzed using a paired *t* test. Differences between measurements are presented as effect sizes, 95% confidence intervals (CIs) of the effect size, and *P* values. To determine whether patients with higher pain scores had higher baseline PUAL, the correlation of PUAL and pain scores before the block procedure was assessed by calculating the Pearson correlation coefficient. We used Prism 9.5.1 for the statistical analysis (GraphPad Software, LLC; Boston, MA, USA), and *P* values < 0.05 were considered statistically significant.

Results

We identified 20 patients that reported insufficiently controlled pain within the first 24 hr after surgery. Numeric rating scale scores ranged from 4 to 10, with all individuals requesting additional analgesic interventions to improve pain control. All individuals experienced satisfactory pain control following the analgesic intervention. We removed two patients from the study because the quality of pupillary scans or missing data did not allow analysis. The surgical procedures and the subsequent analgesic interventions performed are outlined in Table 1.

At the time of entering the study, all patients had received opioids, four were receiving continuous ketamine infusions, and two were receiving additional continuous intravenous lidocaine infusions. Oral morphine equivalents in the four hours preceding the block ranged from 0 to 139 mg, and three of the patients were using long-acting opioids (extended-release oxycodone, methadone) for either chronic pain or an opioid use disorder, making a reliable estimate of opioid serum concentrations challenging, if not impossible. In no case were opioids administered between the first and second series of pupillary measurements.

There was no observable linear correlation ($r = 0.191$; 95% CI, −0.303 to 0.604; $P = 0.45$) between pupillary unrest and pain scores before the block procedure. All patients included in the analysis reported that their pain had improved substantially or disappeared following the block procedure. None of the patients developed a Horner's syndrome following block performance.

The reported mean (SD) NRS pain scores were 7.2 (1.7) before the block procedures and 1.9 (1.8) after the block procedures (difference in means, −5.2; 95% CI, −6.3 to −4.1; $P < 0.001$; Fig. 2). The mean (SD) PUAL was 0.113 (0.062) before analgesia and 0.112 (0.068) after analgesia (difference in means, −0.001; 95% CI, −0.018 to 0.015; $P = 0.88$; Fig. 3), and the mean (SD) pupil diameters were 2.51 (0.68) mm before analgesia and 2.48 (0.66) mm after analgesia (difference in means, −0.03; 95% CI, −0.14 to 0.08; $P = 0.56$; Fig. 4).

To address the concern that the ketamine and lidocaine infusions could have affected PUAL, we performed a subgroup analysis, excluding the four patients who receive the infusions from the analysis. The results for the remaining 14 patients were unchanged when compared with the complete cohort: the mean (SD) NRS in the
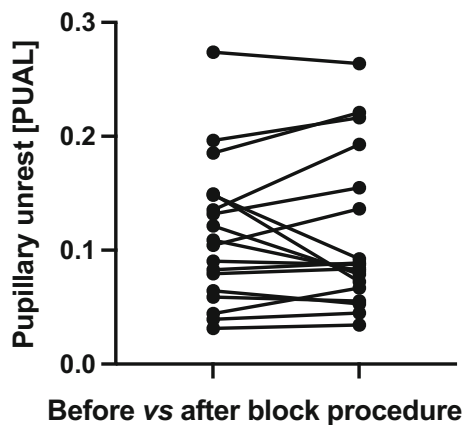
Fig. 3 Pupillary unrest in ambient light did not change when pain was managed by regional anesthesia

PUAL = pupillary unrest in ambient light
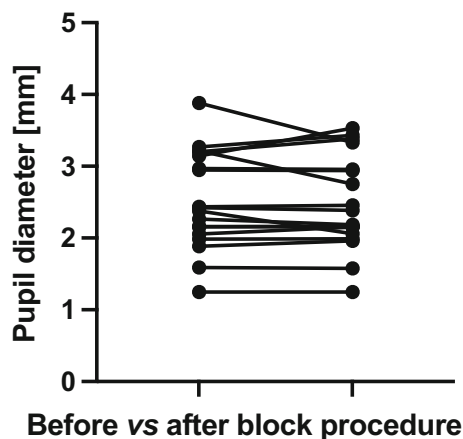
Fig. 4 Pupillary diameter did not change when pain was managed by regional anesthesia

remaining 14 patients decreased from 7.1 (1.5) to 1.9 (1.3) following the block procedures (difference in means, −5.1; 95% CI, −6.4 to −3.9; $P < 0.00$). The mean (SD) PUAL was 0.110 (0.068) before the block and 0.106 (0.070) after the block (difference in means, −0.004; 95% CI, −0.025 to 0.016; $P = 0.66$). The mean (SD) pupillary diameter did not change, from 2.47 (0.73) mm before the block to 2.43 (0.69) mm after the block (difference in means, −0.05; 95% CI, −0.19 to 0.10; $P = 0.49$).

An additional subgroup analysis investigated whether the amount of opioids used before the start of measurements affected the changes in PUAL and pupil diameter. Both low and high opioid users, based on opioid use in the four hours before the baseline measurements, displayed similar behaviour and did not show decreases in pupillary unrest and pupil diameter with improved pain control.

Discussion

Based on earlier reports,[9] we expected that measurements of pupillary unrest would be able to detect changes in pain after surgery. Nevertheless, our findings in patients experiencing substantial pain relief by regional anesthesia showed that our measure of pupillary unrest (PUAL) did not change with changes in pain intensity in a postsurgical patient population.

The first published investigation on the interplay of pupillary unrest and pain reported that painful contractions during labour and delivery increased pupillary unrest.[9] Following epidural analgesia, with improved pain control, the contractions failed to increase pupillary unrest. A subsequent study by the same investigators reported that in recovery room patients following surgery, pupillary unrest correlated with reported pain scores, suggesting that the extent of pupillary unrest may indeed be a measure of pain.[14]

Pupillary unrest is a potential marker of pain as it is affected by opposing inhibitory and excitatory influences on the Edinger–Westphal (EW) nucleus. Sympathetic stimulation caused by pain could alter this balance and increase pupillary unrest by inhibition of the EW nucleus. Nevertheless, arousal caused by nonpainful stimuli has also shown to increase pupillary unrest.[15] Opioids are known to block the inhibitory input to the EW nucleus, thus causing pupillary constriction and suppression of pupillary unrest.[8,16] In this study, we tried to confirm that measurement of PUAL can still detect changes in pain intensity in a patient population that is likely to have been exposed to opioids.

Our finding that in a postsurgical, predominantly opioid-exposed patient population, PUAL was not able to detect changes in pain raises the question whether factors other than pain could explain the correlations previously observed between pupillary unrest and pain, or which factors could have masked the impact of pain on pupillary unrest in our patient population. There are several possible explanations for the findings of the present study and why they appear to contradict findings from earlier studies.

Pupil diameter and pupillary unrest reflect the activity of the locus coeruleus,[17] the noradrenergic nucleus that controls arousal.[18] It is possible that the observed increases in pupillary unrest were not caused by pain itself, but rather by the arousal triggered by pain, the associated stress response, or the emotional response caused by the painful experience. Such responses would not be expected to last long because they cannot be maintained for an extended period.[19,20] Our findings are compatible with the hypothesis that pain is not able to sustain arousal and that the observed increases in pupillary

unrest are short-lived, even if pain persists. Therefore, the subsequent relief from pain does not alter PUAL.

An alternative explanation for our findings is that pupillary unrest does change with pain, but that the pain-evoked effects on pupillary unrest were masked in our patients by opioids and other centrally acting agents. The effects of opioids on the EW nucleus could have masked the stimulatory effects of pain on pupillary unrest. Nevertheless, the observation that pupillary unrest at baseline was not severely depressed in our study population and that even dramatic changes in pain intensity did not alter pupillary unrest in these patients make it unlikely that the administration of opioids is solely responsible for the inability of pupillary unrest to accurately reflect increased pain. Furthermore, even in patients who had received smaller doses of opioids, the analgesic interventions failed to effect PUAL. If even small doses of administered opioids would be able to mask the association between pain and pupillary unrest, measurement of PUAL would have very little utility as a measure of pain in most clinical scenarios involving patients with substantial pain.

A recently published study supports and complements the findings of our study. In patients admitted to an emergency room with pain, no correlation was observed between patient-reported NRS and PUAL. Measurements of PUAL also failed to identify patients with moderate to high pain scores, even though opioid use prior to admission was an exclusion criterion for the study. Our finding that reducing pain is not associated with changes in PUAL in patients who have been experiencing sustained pain expands on these findings.

The present investigation used a simple methodology and has limitations. We were not able to quantify whether or to which extent PUAL was suppressed at baseline by the administered opioids as we were not able to measure opioid plasma concentrations. As already discussed, pain-evoked changes in pupillary unrest may become masked once a certain amount of opioids has been administered or pupillary unrest is depressed below a certain threshold. Nevertheless, the baseline values of PUAL in our study were comparable to those observed in opioid-naïve patients in their respective age group.[21]

Some patients received additional analgesics such as intravenous ketamine and lidocaine, whose effects on pupillary unrest are not well investigated. Nevertheless, excluding those patients who received these drugs in a subgroup analysis revealed identical findings. We decided to not exclude these patients, as their use reflects the clinical scenarios any tool designed to assess pain would be operated in.

This observational study was not preregistered on ClinicalTrials.gov at study start, which may raise concerns about bias, thus potentially limiting the impact of the findings. The results are also not supported by a sample size estimate at the time of study start because preliminary data were lacking. To address this limitation, we conducted a post hoc power analysis to show that our final sample size—while small—would have been large enough to detect relevant changes in pupillary oscillations with analgesia had they occurred.

It should also be noted that we are contrasting our findings to the earlier findings of Charier *et al.* who used a different algorithm to quantify pupillary oscillations,[9] which has been termed the "variation coefficient of pupillary diameter." Although both approaches are based on different algorithms, they both attempt to quantify pupillary unrest and the findings of investigations using these measurements should be comparable.

In summary, measurements of pupillary unrest did not identify changes in postsurgical pain in predominantly opioid-exposed patients when regional anesthesia was used to manage pain. Pupillary unrest has not been shown to be a reliable marker for pain in clinical settings of sustained pain. While pupillary unrest seems to be a useful indicator for the extent of central opioid effects, it does not appear, in clinical scenarios associated with pain, to be a promising tool to objectively measure pain.

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