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ORIGINAL ARTICLE

Comparison between pupillometry and numeric pain rating scale for pain assessments in communicating adult patients in the emergency department

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Abstract

Objective: The adequate assessment of pain in the emergency department (ED) can be challenging. Two dynamic pupillary measures used in conscious subjects after a surgical procedure were previously shown to correlate to the magnitude of ongoing pain. The objective of this study was to test the ability of dynamic measures derived from pupillometry to evaluate pain intensity in conscious adult patients admitted to the ED.

Methods: This prospective, interventional, single-centre study was performed between August 2021 and January 2022 (NCT05019898). An assessment of self-reported pain intensity was performed on ED admission by the triage nurse using a numeric rating scale (NRS). This was followed by two dynamic measures derived from pupillometry that were previously correlated with pain perception: the pupillary unrest under ambient light (PUAL) and the pupillary light reflex (PLR).

Results: Among the 313 analysed patients, the median age was 41 years, and 52% were women. No correlation was found between self-reported pain ratings and PUAL ($r = 0.007$) or PLR (baseline diameter $r = -0.048$; decrease $r = 0.024$; latency $r = 0.019$; slope $= -0.051$). Similarly, the pupillometry measures could not discriminate patients with moderate to severe pain (defined as NRS ≥ 4).

Conclusions: Pupillometry does not appear to be an effective tool to evaluate pain in the ED environment. Indeed, too many factors influencing the sympathetic system—and thus the dynamic pupillary measures—are not controllable in the ED.

Significance: Pupillometry does not appear to be an effective tool to evaluate pain in the ED environment.

There are several possible explanations for these negative results. The factors influencing the sympathetic system—and thus the PD fluctuations—are controllable in the postoperative period but not in the ED (e.g. full bladder, hypothermia). In addition, numerous psychological phenomena can impact pupillometry measurements such as emotional reactions or cognitive tasks. These phenomena are particularly difficult to control in the ED environment.

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1 | INTRODUCTION

1.1 | Background

Pain represents nearly 70% of admissions to the emergency department (ED). Studies nevertheless show that less than half of patients receive an analgesic during their ED stay and that almost a third leave the ED in pain (Gueant et al., 2011; Todd et al., 2007).

Effective pain relief depends on the origin and intensity of the pain in addition to an accurate pain assessment. Self-assessment pain scales are the gold standards for evaluating pain in patients admitted to the ED, with the most frequently used and validated tools being the numeric rating scale (NRS) and the visual analogue scale (VAS) (Karcioglu et al., 2018; Mohan et al., 2010). However, both self-assessment scales require the healthcare professional to accept the pain intensity reported by patients, and studies have demonstrated that this is often not the case. Indeed, healthcare professionals in the ED tend to underestimate patients' pain, particularly when it is reported as severe (Rupp & Delaney, 2004; Wooldridge & Branney, 2020), and instead they tend to trust their own evaluation of pain as a more stable and objective reference (Vuille et al., 2018). This attitude can negatively impact the effectiveness of pain relief. For this reason, the use of pupillometry as a pain assessment tool could reduce the influence of caregiver subjectivity and minimize preconceptions about patient-reported pain, especially in situations where patients have difficulty or are unable to express their pain.

Pupil dilation (Kyle & McNeil, 2014) which is a response of the sympathetic nervous system to acute pain, has been shown to be correlated to the intensity of controlled noxious stimuli (Chapman et al., 1999). Pupil diameter (PD) at rest depends mostly on ambient light and is not correlated with the level of pain. However, two dynamic pupillary measures obtained in conscious subjects were shown to relate to the magnitude of their ongoing pain in different contexts, namely, during and after a surgical procedure: the pupillary light reflex (PLR) and spontaneous PD fluctuations. PD fluctuations can be quantified by two different measures: the pupillary unrest under ambient light (PUAL) and the variation coefficient of pupillary diameter (VCPD). For technical reasons, we chose to use the PUAL measure in our study.

Therefore, the measurement of PLR and PD fluctuations using a portable pupillometer may be a promising pain assessment tool in the ED.

The objective of this study was to compare these two dynamic tests with the NRS evaluation in conscious and communicating adult patients presenting to the ED with acute pain. Anxiety was shown to play an important role in the nociceptive response (Thompson et al., 2008; Van Wijk & Hoogstraten, 2009), and according to some studies, it may influence pupillary parameters (Bakes et al., 1990; Bertrand et al., 2013). As the pupillary response to anxiety is poorly studied, we also observed the influence of anxiety on the values obtained with pupillometry as secondary objectives.

1.2 | Importance

To the best of our knowledge, no study to date has explored the use of pupillometry as a tool for the assessment and management of pain in patients presenting to the ED. In this setting, pupillometry could be an effective pain assessment tool for ED patients.

1.3 | Goals of this investigation

The main goal of this study was to compare the performance of pain assessments by the NRS and pupillometry in adult patients presenting to the ED. The primary end point was the correlation between the PD fluctuations and the patients' self-reported NRS values.

2 | METHODS

2.1 | Study design and setting

We conducted this prospective, interventional, single-centre study in the ED of the Cliniques Universitaires Saint-Luc, a university hospital in Brussels, Belgium, with 78,000 annual admissions. The ethics committee of the hospital approved the study (2021/15JUI/279). A trial registration number assigned to the study was NCT05019898.

2.2 | Selection of participants

All consecutive patients aged 18 years and older who presented to the ED with stable haemodynamic and respiratory status and were able to communicate were eligible for this study. The exclusion criteria were the following: refusal to participate in the study; inability to obtain informed consent; consumption of opioid drugs with immediate (<12 h) or extended release (<24 h); consumption of clonidine (<24 h); consumption of dopamine antagonists (<24 h); administration of topical ocular medications affecting the pupil parameters (<24 h); any acute eye condition; bilateral eye surgery modifying the PD variations; and a history of glaucoma, Parkinson's disease,

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Alzheimer's disease, diabetes or chronic alcoholism with dysautonomia.

Five emergency physicians trained in pupillometry performed the patient inclusion and measurements.

2.3 | Interventions

The ED triage nurse conducted patient triage according to the Manchester Triage Scale. Patients assessed their level of pain using the NRS from 0 (no pain) to 10 (worst pain imaginable). The physician-investigator was not present in the triage room.

After triage, the physician-investigator approached the eligible patients for recruitment. After obtaining written informed consent, the following data were collected:

1. A measurement of patient anxiety with the NRS-A from 0 (not anxious) to 10 (worst possible anxiety).
2. Two dynamic measurements with video pupillometry (NeuroLight, iDmed): PD fluctuations and PLR. All measurements were performed on the same eye.

2.4 | Measurements

2.4.1 | Pupil diameter fluctuations

The pupil undergoes continuous physiological changes under the influence of the sympathetic and parasympathetic systems (Schumann et al., 2020). The PUAL can quantify these changes (McKay et al., 2022; Neice et al., 2017). To perform these measurements, the pupillometer illuminates the filmed eye using a 100 lux white light. The patient closes the contralateral eye and covers it with a hand. The illumination of the eye begins 3 s before recording and lasts for 8.5 s (256 points at 30 Hz). The algorithm of the pupillometer calculates the PUAL using the area under the curve (AUC) of the Fourier transform for the PD fluctuations. The measure is expressed in arbitrary units comprised of the sum of the oscillatory amplitudes between 0.2 and 2.5 Hz (McKay & Larson, 2021).

2.4.2 | Pupillary light reflex

The PLR refers to the miosis that occurs during the illumination of the eye. This measurement is split into four parameters: baseline PD, decrease in PD during calibrated illumination, time between the luminous flash and the contraction of the pupil (latency) and rate of PD decrease (slope) (Charier, Bertheaux, et al., 2017).

To take the measurements, the patient closes and covers one eye with a hand, while the pupillometer covers the open contralateral eye. To reach pupil equilibrium, there is a delay of 6 s before taking the measures. Then, a 320 lux-calibrated flash lasting for 1 s allows the recording of the PLR.

The physician-investigator took all the measures in less than 1 min. The patients then returned to standard care without any changes to their management.

One hour after taking the first measurements, the nurse performed a second pain assessment (NRS), and the physician-investigator took a second series of pupillometry measures.

2.5 | Outcomes

2.5.1 | Primary outcome

The ability of dynamic pupillary measures to assess pain was determined on the correlation between the first PUAL measure and the first NRS.

2.5.2 | Secondary outcomes

A first secondary objective was to compare the ability of the pupillary measures to assess pain based on the correlation between the first PLR measure and the first NRS. A second secondary objective was to investigate if pupillometry could be a predictive factor of the presence of moderate to severe pain (NRS ≥4) in patients presenting to the ED. A final secondary objective was to explore the influence of anxiety on the values obtained with pupillometry.

2.6 | Analysis

We calculated the sample size using the program STEP 14.0.7. A sample of 314 patients was needed to estimate with good precision (95% confidence interval [CI] with a small width) the correlation between the pupillometry and NRS values for a correlation coefficient of 0.78 (95% CI: 0.725–0.825). This correlation value is based on a 2019 study, which found that PD fluctuations present a strong correlation with the VAS ($r = 0.78$; $p < 0.0005$) (Charier et al., 2019). To account for patient exclusions due to manipulation errors or missing data, we decided to include 320 patients.

We performed statistical analyses using the software JMP Pro 16.0.0. We set the significance threshold of tests to 5%. We expressed qualitative data as numbers and percentages, and continuous data as medians and ranges.

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We quantified the associations between continuous variables using Pearson correlations. We used univariate logistic regression analysis and AUC to quantify the association between pupillometry parameters, pain and anxiety.

3 | RESULTS

3.1 | Characteristics of study subjects

Between August 2021 and January 2022, we screened 397 consecutive patients of whom 320 were included in the study. We excluded seven patients due to their inability to perform the pupillometry measures ($n=5$) or their refusal to participate in the second measurement ($n=2$). Figure 1 depicts the flow chart of patient screening and inclusion.

Table 1 summarizes the baseline characteristics of the study population. Median patient age was 41 years, and 52% were women ($n=163$). The most common pathologies were trauma ($n=122$, 38%), abdominal pain ($n=91$, 29%) and chest pain ($n=32$, 10%).

Among the 313 included patients, 126 (40%) qualified their pain as absent or mild (NRS <4), 100 (32.3%) as moderate (4≤ NRS <7) and 87 (27.7%) as severe (NRS ≥7). A total of 188 patients (60%) received no analgesics, including 27 patients (8.6%) who refused the pain relief proposed by the triage nurse. For the 187 patients presenting moderate to severe pain (NRS ≥4), 82 (43%) received no analgesics. Five patients (1.5%) were given intravenous morphine. Table 2 summarizes the different analgesics given to patients depending on their level of pain. The evolution of pain after 1 h was very modest (mean difference between NRS1 and NRS2 = 0.78 [95% CI: 0.57–0.98]).

4 | MAIN RESULTS

4.1 | Correlation between pupillometry measures and NRS

Table 3 summarizes the correlations (r, Pearson's coefficient of correlation) between the NRS values and the pupillometry measures and analyses the differences between gender.

4.2 | Receiver operating characteristic analysis

Figure 2 presents the receiver operating characteristic curves that show the ability of each pupillometer measure to discriminate patients with moderate to severe pain (i.e. NRS ≥4). The AUC was 0.500 for PUAL (a), 0.513 for baseline PD (b), 0.513 for decrease in PD (c), 0.509 for PD latency (d) and 0.537 for the slope (e).

Table 4 summarizes the main values obtained for the pupillometry parameters according to the three levels of pain reported in the NRS.

The p-values of the Kruskal–Wallis test compare the three levels of pain based on the NRS.

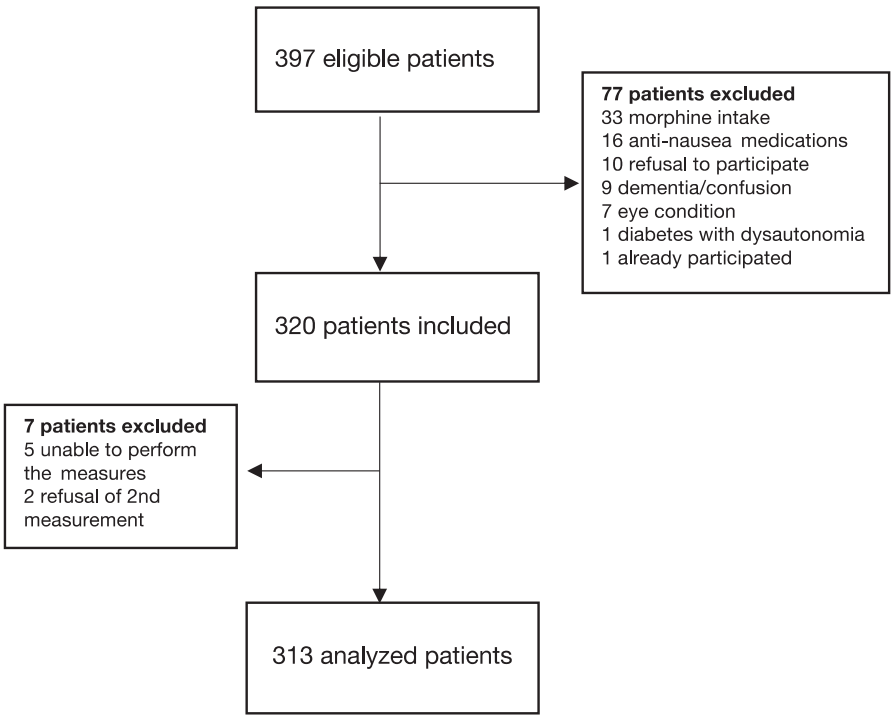


FIGURE 1 Study selection flow chart.

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4.3 | Influence of anxiety

Table 5 summarizes the main values obtained for the pupillometry parameters according to the three levels of anxiety reported in the NRS (NRS-A).

We performed univariate logistic regression to determine whether the pupillometry parameters could predict NRS ≥4 when excluding either highly anxious patients (NRS-A ≥8) or minimally anxious patients (NRS-A ≤2).

TABLE 1 Baseline characteristics of analysed patients.

Cohort characteristics	*n* = 313
Median age	41[a] (18–86)
Sex ratio (F/M)	0.52
Heart rate (beats/min)	85[a] (44–140)
Systolic blood pressure (mmHg)	136[a] (101–188)
Diastolic blood pressure (mmHg)	81[a] (46–130)
Numerical rating scale 1[b]	5[a] (0–10)
Numerical rating scale 2[c]	4[a] (0–10)
Anxiety	3[a] (0–10)

[a]Median (range).

[b]Numerical rating scale at triage.

[c]Numerical rating scale 1 h after triage.

TABLE 2 Analgesics given to patients according to their pain level based on the numeric rating scale (NRS).

	NRS <4 (*n* = 126)	NRS ≥4 (*n* = 187)	Total (*n* = 313)
None	106 (33.8%)	82 (26.2%)	188 (60%)
Paracetamol (1 g)	8 (2.5%)	31 (9.9%)	39 (12.4%)
Tramadol[a]	3 (0.9%)	33 (10.5%)	36 (11.4%)
Anti-inflammatory[a]	2 (0.6%)	14 (4.4%)	16 (5%)
Morphine[a]	0	5 (1.5%)	5 (1.5%)
Other	0	2 (0.6%)	2 (0.6%)
Analgesic refusal	7 (2.2%)	20 (6.4%)	27 (8.6%)

[a]±paracetamol.

After removing highly anxious patients from our sample, the pupillometry parameters were unable to discriminate NRS ≥4. The AUC was 0.547 for baseline PD, 0.494 for PD decrease, 0.565 for latency, 0.552 for slope and 0.519 for PUAL. Similarly, we were unable to identify any pupillometry parameters able to predict NRS ≥4 after excluding minimally anxious patients from our sample. No pupillometry parameter was significant, with the AUC being 0.526 for baseline PD, 0.502 for PD decrease, 0.576 for latency, 0.485 for slope and 0.491 for PUAL.

Finally, we did not observe any correlations between the NRS and heart rate ($r = 0.0498$), the NRS and systolic blood pressure ($r = 0.0749$) and the NRS and diastolic blood pressure ($r = 0.0950$).

5 | DISCUSSION

This prospective study analysed the use of pupillometry as a pain assessment tool in the ED. Although its beneficial use has been shown in anaesthesiology, our findings did not reveal statistically significant correlations between the NRS, PUAL and PLR. Moreover, in an ED setting, pupillometry cannot discriminate patients with moderate to severe pain (i.e. NRS ≥4).

Although an initial study from 2013 on 26 women in labour demonstrated the excellent ability of PLR to discriminate patients with NRS ≥4 (AUC = 0.80 [0.7–0.89]) (Guglielminotti et al., 2013), our results are in accordance with another study from 2014 conducted on 145 conscious patients in the recovery room in the context of postoperative pain, which did not show any significant correlation between the NRS and PLR ($r = 0.03$ [95% CI: 0.13–0.19], $p = 0.72$) (Kantor et al., 2014). Likewise, a third study from 2019 on 345 patients in the early postoperative period did not reveal a statistically significant correlation between the VAS and PLR (Charier et al., 2019). Several hypotheses may be put forward to explain these contradictory results. The difference observed with the Guglielminotti et al.'s study may be due to the continuity of pain in the postoperative setting contrary to the irregular uterine contractions

TABLE 3 Correlations between the first numeric rating scale (NRS 1) and the first pupillometry measures.

	N	PUAL	Baseline diameter	Decrease[a]	Latency[b]	Slope[c]
NRS 1 (total)	313	0.007	−0.048	0.024	0.019	−0.051
NRS 1 (men)	163	−0.054	0.007	0.058	0.042	−0.118
NRS 1 (women)	150	0.010	−0.124	0.083	0.024	−0.003

Abbreviation: PUAL, pupillary unrest under ambient light.

[a]Decrease in pupil diameter (PD) during calibrated illumination.

[b]Time between the luminous flash and the contraction of the pupil.

[c]Rate of PD decline.

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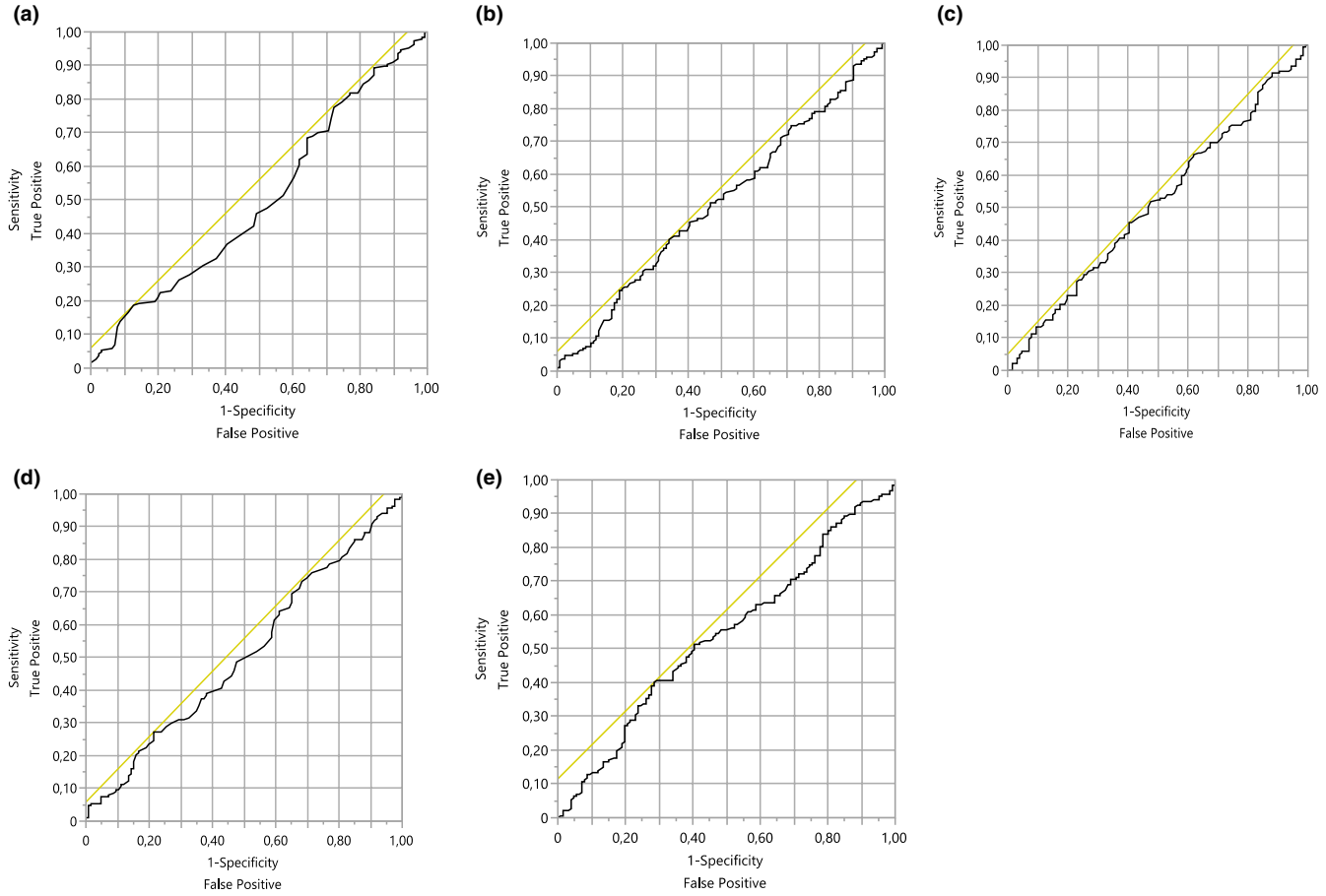


FIGURE 2 Receiver operating characteristic curves on the ability of pupillometer parameters to predict moderate to severe pain defined as a numeric rating scale score ≥4. The pupillometer parameters relate to PUAL (a), baseline pupil diameter (PD) (b), decrease in PD (c), PD latency (d) and slope (e).

TABLE 4 Median values of the pupillometry parameters according to the three levels of pain based on the numeric rating scale (NRS).

	N	PUAL	Baseline diameter	Decrease[a]	Latency[b]	Slope[c]
NRS <4	126	0.38	5.71	−2.27	240	5.35
4≥ NRS <7	100	0.37	5.66	−2.25	241	5.11
NRS ≥7	87	0.42	5.65	−2.26	238	5.17
		$p=0.271$	$p=0.875$	$p=0.817$	$p=0.235$	$p=0.474$

Abbreviation: PUAL, pupillary unrest under ambient light.

[a]Decrease in pupil diameter (PD) during calibrated illumination.

[b]Time between the luminous flash and the contraction of the pupil.

[c]Rate of PD decline.

experienced during labour (Guglielminotti et al., 2013). Further, the absence of correlation between the self-assessment pain scales and pupillometry observed in the two studies conducted in a postoperative setting could be associated with the residual effect of anaesthetic agents (opioids, volatile agent) administered during surgery and the activation of the sympathetic system following hypoxia or hypercapnia due to the residual effects of the anaesthetic drugs (Rollins et al., 2014). These findings are supported by Connelly et al. (2014) who studied children later in the postoperative course, showing that each 10-point increase in the VAS was associated with increases of 0.4% in PD and 0.11 mm/s in its rate of decline (Connelly et al., 2014). Given that the situation in the ED is more similar to the context of this latter study, we decided to study the PLR despite the mixed results observed in adults to date.

Many factors can interfere with pupillometry measures, as reported in the aforementioned studies. For this reason, we excluded patients with unstable respiratory status to avoid the influence of hypoxia. We also excluded all

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TABLE 5 Correlations between the numeric rating scale for anxiety and the pupillometry measures.

	N	PUAL	Baseline diameter	Decrease[a]	Latency[b]	Slope[c]
Anxiety (total)	313	−0.017	−0.039	0.052	−0.063	−0.045
Anxiety (men)	163	−0.028	−0.049	0.044	0.031	0.047
Anxiety (women)	150	−0.041	−0.075	0.091	−0.099	−0.137

Abbreviation: PUAL, pupillary unrest under ambient light.

[a]Decrease in pupil diameter (PD) during calibrated illumination.

[b]Time between the luminous flash and the contraction of the pupil.

[c]Rate of PD decline.

analgesics (e.g. opioid, clonidine) and non-analgesic drugs (e.g. dopamine antagonist treatment), which could modify the pupillometry measures. Despite this rigorous methodology, our study did not find any correlations between the PLR and NRS in conscious patients. Our findings combined with those of Kantor et al. (2014) demonstrate that the PLR is not an effective tool for measuring continuous pain in conscious patients, as suggested by a study previously conducted in healthy subjects (Eisenach et al., 2017).

Several studies on PD fluctuations measured using the VCPD or PUAL have yielded promising results in adults. One study revealed a strong correlation between the VAS and PD fluctuations in women during labour ($r = 0.81$; $p < 0.001$) in which the ability of PD fluctuations to predict moderate to severe pain (i.e. NSR ≥4) was excellent (AUC 0.96 [95% CI: 0.928–1.0]; $p < 0.05$) (Charier, Zantour, et al., 2017). Another study performed in the immediate postoperative period confirmed these results, with a strong correlation observed between the VAS and PD fluctuations ($r = 0.78$; $p < 0.0005$) (Charier et al., 2019). The ability of PD fluctuations to predict NSR ≥4 in these patients was also excellent (AUC 0.92 [95% CI: 0.89–0.95]; $p < 0.0005$).

In our study, however, we did not identify any correlation between the NRS and PD fluctuations ($r = 0.007$) in conscious patients presenting to the ED. Similarly, pupillometry could not sufficiently identify moderate to severe pain (i.e. NRS ≥4) in an ED setting (The AUC was 0.500 for the PUAL).

There are several possible explanations for these negative results. First, our context differs from that of women in labour in whom intense pain caused by uterine contractions alternates with less painful phases. This allows the physician to measure the PD fluctuations during a baseline state and then compare the results to the painful peaks. Second, the pain assessment environment is different in the ED and the postoperative setting. Pain affects the balance of the autonomic nervous system through sympathetic activation and/or parasympathetic inhibition, thus impacting pupil fluctuations. However, other factors that influence the balance of the autonomic nervous system—and thus pupil fluctuations—are controllable in the postoperative setting but not in the ED (e.g. full bladder, hypothermia and blood glucose disorders).

In addition, numerous psychological phenomena (Ferencová et al., 2021; Steinhauer et al., 2022) can impact pupillometry measurements such as the anticipation of pain (Bitsios et al., 2004), emotional reactions (Henderson et al., 2014) or cognitive tasks (Hess & Polt, 1964). These phenomena are particularly difficult to control in the ED environment.

Finally, with the current technology, pupillometry is difficult to use in emergency medicine. When performing PUAL, patients have to make an effort to keep their eye open with as few blinks as possible for around 10 s. This constraint thus prevents using the tool with certain patients, notably those with cognitive disorders, attention disorders, or difficulties in following instructions (e.g. hearing loss, language barriers).

Our study has several limitations. Our decision to measure pupil fluctuations using the PUAL instead of the VCPD should be discussed. Although both measures are used to quantify pupil fluctuations, their calculation methods differ. The PUAL is calculated using the AUC of the Fourier transform for the PD fluctuations (Neice et al., 2017). The VCPD is the ratio of the average of the sum of the absolute values of the PD median deviations to the median (Charier, Bertheaux, et al., 2017). In both cases, greater pupil fluctuations lead to a higher result. The PUAL is a highly specific indicator of central opioid effect (Bokoch et al., 2015; McKay & Larson, 2021). In postoperative settings, a significant correlation exists between the PUAL and a reduction in the pain score following the administration of opioids (Neice et al., 2017). By contrast, the relation between the PUAL and the pain score in the absence of opioids is yet to be demonstrated. Despite this limitation, we chose to use the PUAL because of the technical difficulties associated with the VCPD, which is strongly influenced by low- and high-frequency artefacts. In our view, the addition of a band-pass filter to the VCPD, as in the PUAL, would not have added value. In the light of our results, we believe that the VCPD would not have provided a better response than the PUAL, as too many parameters infer with the

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balance of the sympathetic and parasympathetic systems during ED admissions.

The recent study by Neice's team observed a standard deviation of around 20% between repeated measures of the PUAL (Neice et al., 2022). The authors therefore suggested performing several PUAL measurements and determining their average. In our study, however, we only measured the PUAL on patient admission and after 1 h, which may have contributed to the lack of an objective correlation between the NRS score and the PUAL.

Even though our pupillometer had an opaque eyecup that completely covered the eye under evaluation, with patients closing and covering the contralateral eye with their hand, we cannot exclude the possible influence of ambient light.

All the measures used a single type of video pupillometer, namely the NeuroLight (iDmed) video pupillometer, which was previously used in preliminary studies to calculate statistical power. No study to date has compared the performances of different models of portable pupillometers.

The NRS score is a subjective measure influenced by many factors. In our study, the patients provided the NRS scores to the nurse. The presence of the nurse and/or patient–nurse interactions may have therefore influenced the NRS scores, which could have contributed to the lack of correlation between NRS scores and pupillometry measures.

In conclusion, given the negative results observed in our cohort of more than 300 conscious and communicating adult patients, pupillometry does not appear to be a feasible method to evaluate pain in the ED environment.

AUTHOR CONTRIBUTIONS

Charles Gregoire, David Charier, André Mouraux, Patricia Lavand'homme, Andrea Penaloza and Gisele Pickering conceived and designed the study and analysis. Charles Gregoire is the principal investigator. Charles Gregoire, Romane de Bergeyck, Floor Van Ouytsel, Romain Lambert and Nicole Zhou collected the data. Celine Bugli consultant in Statistical Methodology and Computing Service (UCLouvain) performed statistical analyses. Charles Gregoire, David Charier, André Mouraux, Patricia Lavand'homme, Andrea Penaloza and Gisele Pickering discussed the results. Charles Gregoire wrote the article. All authors critically reviewed and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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