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Research paper

Nociception assessment with videopupillometry in deeply sedated intensive care patients: Discriminative and criterion validations

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ABSTRACT

Background: Nociceptive assessment in deeply sedated patients is challenging. Validated instruments are lacking for this unresponsive population. Videopupillometry is a promising tool but has not been established in intensive care settings.

Aim/Objective: To test the discriminate validity of pupillary dilation reflex (PDR) between non-noxious and noxious procedures for assessing nociception in non-neurological intensive care unit (ICU) patients and to test the criterion validity of pupil dilation using recommended PDR cut-off points to determine nociception.

Methods: A single-centre prospective observational study was conducted in medical–surgical ICU patients. Two independent investigators performed videopupillometer measurements during a non-noxious and a noxious procedure, once a day (up to 7 days), when the patient remained deeply sedated (Richmond Agitation–Sedation Scale score: −5 or −4). The non-noxious procedures consisted of a gentle touch on each shoulder and the noxious procedures were endotracheal suctioning or turning onto the side. Bivariable and multivariable general linear mixed models were used to account for multiple measurements in same patients. Sensitivity and specificity, and areas under the curve of the receiver operating characteristic curve were calculated.

Results: Sixty patients were included, and 305 sets of 3 measurements (before, during, and after), were performed. PDR was higher during noxious procedures than before (mean difference between noxious and non-noxious procedures = 31.66%). After testing all variables of patient and stimulation characteristics in bivariable models, age and noxious procedures were kept in the multivariable model. Adjusting for age, noxious procedures (coefficient = −15.14 (95% confidence interval = −20.17 to −15.52, $p < 0.001$) remained the only predictive factor for higher pupil change. Testing recommended cut-offs, a PDR of >12% showed a sensitivity of 65%, and a specificity of 94% for nociception prediction, with an area under the receiver operating curve of 0.828 (95% confidence interval = 0.779–0.877).

Conclusions: In conclusion, PDR is a potentially appropriate measure to assess nociception in deeply sedated ICU patients, and we suggest considering its utility in daily practices.

Registration: This study was not preregistered in a clinical registry.

Tweetable abstract: Pupillometry may help clinicians to assess nociception in deeply sedated ICU patients.

1. Introduction

Pain assessment is key to pain management decision-making.[1,2] Despite recent advances in pain research and recommendations for best practice in the intensive care unit (ICU), critically ill patients remain particularly at risk of experiencing pain during their ICU

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stay.[3] Patients with severe pain are at high risk to have serious adverse events, including delirium.[4] Undertreated pain also causes unnecessary suffering and can lead to persistent pain after intensive care. The individual and social consequences of persistent pain can severely affect the ICU survivors' quality of life in their daily life activities.[5,6]

Self-report of pain remains the gold standard in ICU adult patients who are able to communicate. For those who are unable to communicate, observation of pain behaviour using validated tools (e.g., the Critical-care Pain Observation Tool or the Behavioural Pain Scale) is recommended.[7] However, these commonly used observational measures are not suitable for patients who are deeply sedated or paralyzed with neuromuscular blockade because they are unresponsive; no other valid measures are currently available to assess pain in these patients.[8]

One of the potential measures to consider in this specific ICU population is the pupillary dilation reflex (PDR).[9] Pupil dilation is an autonomic response, observed at the brain stem level, which provides information about the nociceptive response (i.e., reflex to a noxious stimulus).[10,11] The PDR can be an objective measure of nociception without needing behavioural clues, which are absent in deeply sedated patients.[12] Nociception is an instinctive response. It does not take into consideration the lived experience, which is a response elaborated at the cortical level.

Initially, pupillometry had been developed in anaesthesiology to assess nociception.[13] This technology has recently been evaluated in ICU patients whose critical illness and drugs administered may alter pupil response in a different way than that of patients treated in the operating room. Measuring pupillary reflex with a pupillometer has the advantage of providing objective and reliable measurements, whereas the clinician's observations are subjective and poorly reproducible.[14] A PDR between 13% and 19% was found to be a significant response to a noxious procedure in deeply sedated ICU patients.[15–18] While the manufacturer-suggested cut-offs are of 12% and 20%, there is no evidence to show which one should be used to detect for routine procedures in ICU-sedated patients. Although patients were deeply sedated at baseline measurements, they were able to demonstrate some pain behaviour during the noxious procedure. Despite these promising results, there is no current evidence of the utility of PDR for patients who are not able to express their pain through behaviour or verbal report even during noxious procedures, due to very deep sedation requirement or need of neuromuscular blockade.

Objective and quantitative pain measures are therefore needed for patients, who are deeply sedated. This study aimed to validate the use of pupillometer for assessing nociception in patients who are deeply sedated and behaviourally unresponsive to noxious stimulation. The specific objectives were to (i) test the discriminant validity of pupillary dilation reflex between non-noxious and noxious procedures for assessing nociception in patients and (ii) test the criterion validity of pupil dilation by measuring the diagnostic performance of pupil dilation using recommended PDR cut-off points to determine nociception.

2. Methods

2.1. Study population and ethics

This study was conducted from February to August 2021 at the medical–surgical ICU of a tertiary referral hospital in Switzerland. The study was approved by the human research ethics committee (project ID 2020-02210). Written informed consents from legal representatives and, whenever possible, *a posteriori* patients' consent was sought.

The population of the study included adult patients, expected to stay mechanically ventilated for at least 48 h and deeply sedated. Deep sedation was defined with a Richmond Agitation–Sedation Scale (RASS) of −5 (unarousable, no response to voice or physical stimulation) or −4 (deep sedation, no response to voice but any movement to physical stimulation).[19] Patients were excluded if they had one or more condition(s) that could interfere with pupil responses, including primary acute brain injury, cardiac arrest, known severe drug or alcohol abuse, known cognitive impairment, previous known ophthalmologic conditions, and opioid treatment for more than 3 months.

2.2. Design and study procedures

This prospective observational study assessed PDR before, during, and after non-noxious and noxious procedures.

Two investigators (EF, JPM) performed a 30-s video pupillometer measurement during a non-noxious and noxious procedure, once a day during a maximum of 7 days as long as the patient remained deeply sedated (RASS score: -5 or −4). Recordings started 10 s after the pupillometer was in place to avoid the bias induced by pupillary dilation that occurs immediately after eye opening. Each day, pupil measurements were performed at three time points, before, during, and 5 min after each procedure. The same procedures were repeated for non-noxious and noxious procedures. For each measurement, intense light over the patient's head was avoided. An opaque silicone eyecup was placed on the orbit, ensuring optimal device position and environmental darkness. In addition, the opposite eye was closed to decrease the consensual light response. The measurements were arbitrarily obtained from the left eye. The right eye was used in case of ophthalmic disorder in the left eye or if inaccessible in the prone position.

The non-noxious procedure was a gentle touch on each patient's shoulder and was performed when the patient had no stimulation for at least 20 min.[20] The non-noxious procedure started on the pupil measurement side, on the left, for half the measurement time (15 s), and the gentle touch continued for the other half of the measurement time on the other side. The noxious procedures were either an endotracheal tube (ETT) suctioning or turning the patient onto the side. Both procedures were part of frequent routine ICU care and are standardised according to an internal protocol based on good practice.[21,22] The timing and the type of procedure were determined by the bedside nurse according to the patient's clinical needs and care-delivery organisation.

2.3. Management of analgesia and sedation

Analgesia and sedation remained unchanged and were prescribed and administered according to the local nurse–led pain and sedation management protocol in line with current best practice recommendations.[23,24] Prescribed drug doses were tailored to targeted level of sedation (RASS score: −5 and −4). Analgesia was provided using continuous infusion of fentanyl at a standard dose of 1–1.5 μg/kg/h. In addition, and as required, 50–100 μg intravenous boluses of fentanyl could be administered to prevent pain before painful procedures. Patients were primarily sedated with propofol (2–4 mg/kg/h) and as a second-line treatment with midazolam (0.05–0.15 mg/kg/h). When clinically required (e.g., hemodynamic instability, difficulty in ventilating), a non-depolarizing neuromuscular blocking agent (cisatracurium: 3 μg/

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kg/min or rocuronium: 12 μg/kg/min) was administrated in addition to analgesia and sedation.

2.4. Measures

2.4.1. Pupillary dilation reflex

To measure PDR, we performed video pupillometry using the AlgiScan® (IdMed, Marseille, France). AlgiScan® is an automated portable pupillometer device designed to assess sensitivity to nociception in unresponsive patients. PDR is regulated by the sympathetic and parasympathetic pathways. Sympathetic innervation contracts the iris dilator muscle, and the parasympathetic innervation decreases or even inhibits constriction of the sphincter muscle. Both result in pupil dilation (mydriasis).[25] The tool records dynamic pupil measurements through an infrared camera, with a 0.1 mm precision. In the PDR mode, the pupil-size change is video-recorded, with a capture of 47 images per second, without any light stimulation and during 1 min maximum.[26] The automated pupillometer provides reliable measures to detect pupil-size change.[14]

Pupillary dilation reflex was evaluated using the percentage of pupil change (the absolute pupil change [mm] divided by the pupil base diameter [mm] multiplied by 100). Positive value shows pupil dilation, and negative value shows pupil constriction. It is recommended by the manufacturer that a <12% change shows no or mild sensitivity, between 12% and 20% high sensitivity, and >20% very high sensitivity to nociception.[26] These cut-off points were congruent with ICU literature[15–18] and were used to define the nociception thresholds in the analysis of the diagnostic performance.

2.4.2. Patient characteristics

Patient demographics and clinical characteristics were extracted from the patient electronic health records. Demographics included age (years) and gender (male/female). Clinical characteristics included body mass index (kg/m^2), admission diagnosis at ICU admission, medical or surgical condition, the Sequential Organ Failure Assessment score on admission (score range: 0–24; 0–1 is associated with a ICU mortality risk of 0%; 2–3, of 6%; 4–5, of 20%; 6–7, of 22%; 8–9, of 33%; 10–11, of 50%; ≥12 of 95%).[27] the Charlson Comorbidity Index, a mortality predictor within 1 year of hospitalisation, based on the presence of comorbid conditions (index range: 0–37; 0 indicates no comorbidity; 1–2 indicates a mortality risk of 26%; 3–4, of 52%; ≥5 of 85%),[28] duration of mechanical ventilation (days), ICU length of stay (days), and ICU mortality (percentage). The investigators performing the video pupillometry measurements assessed the depth of sedation using the RASS during each procedure.

2.5. Statistical analyses

2.5.1. Discriminant validity of PDR: Ability to detect nociception

Mean PDR scores was calculated for before, during, and after each procedure. To test PDR as a valid indicator for nociception diagnosis, a significant increased PDR between before and during the noxious procedures had to be demonstrated. To be discriminant, no PDR change was expected between before and during a non-noxious procedure. Unconditional general linear mixed model was used to calculate intraclass correlation to determine the effect of multiple measurements in one patient on the outcome (i.e., variability). It also shows the percentage of PDR change that is related to differences between patients by dividing the between patients' amplitude change divided by the total amplitude change (i.e., the between subject differences).

Bivariable and multivariable general linear mixed models were used to test what characteristics were associated with the PDR change (i.e., the within subject differences). Variables with a significant level of $p \leq 0.20$ (conservatively) in the bivariable models were kept in the final multivariable model.

2.5.2. Criterion validity: The diagnostic performance of PDR to assess nociception

In the absence of a gold standard, ETT suctioning, and turning onto the side, known to be painful routine cares, were used as reference criterions to assess the diagnostic performance of pupil dilation. Based on the recommended thresholds for PDR, sensitivity and specificity analyses were performed with two cut points of 12% and 20%. As further validation, areas under the curve of the receiver operating characteristic curve were calculated. Based on the recommended PDR threshold of 12% as predictor of high sensitivity to noxious stimuli, the PDR was dichotomised into the following categories: no or mild sensitivity to nociception for a PDR of <12% and high to very high sensitivity to nociception when the PDR was ≥12%. A similar model was analysed using a threshold of PDR >20% as it is the limit suggested to detect very high sensitivity to nociception.

2.5.3. Data presentation

Distributions and frequencies were performed to check for errors and missing values. No data were missing from the measured events. There were several outliers in the outcome variable; thus data analyses were performed with and without them. The results of the data analyses did not change with or without outliers; therefore, the final analyses were conducted with the complete dataset (including outliers). Descriptive analysis including frequency, mean, standard deviation, median, and range were used to show the characteristics at patient and pupil measurement levels.

All analyses were performed using the Statistical Package for Social Science software version 27 (SPSS Inc, Chicago, IL).

3. Results

Out of the 249 screened patients, 60 patients were included in the study; the rest of patients were mostly excluded owing to comorbidities that could affect PDR. A total of 305 sets of 3 pupil

Table 1
Description of patient characteristics and pupil measurement levels in Study.

Variables	Patients (N = 60)
Age, years	64.5 (19–83)
Female gender, n (%)	18 (30.0)
Body mass index	27.5 (18–60)
Charlson score	3.0 (0–9)
SOFA on admission	7.0 (1–13)
SOFA on day 1 of sedation	8.0 (1–17)
Principal diagnosis, n (%)	
Respiratory failure	30 (50.0)
Cardiac failure	20 (33.3)
Others	10 (16.6)
Medical admission	35 (58.3)
COVID-19 diagnosis, n (%)	24 (40.0)
Drug dose[a]	
Propofol, mg/kg/h	4.3 (0–19.7)
Midazolam, mg/kg/h	0.1 (0–0.5)
Fentanyl, μg/kg/h	1.5 (0–10.0)
Continuous infusion of a neuromuscular blockade, n (%)	36 (60)
Length of mechanical ventilation, days	7.5 (2–135)
Tracheostomy, n (%)	6 (10.0)
Length of intensive care unit stay, days	11 (2–135)
Intensive care unit mortality, n (%)	13 (22.0)

Data are presented as median (range), or number (percentage).
Abbreviation: *SOFA* Sequential Organ Failure Assessment.
[a] Median dose received during the first 7 days of sedation.

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measurements (before, during, and after) were performed. Table 1 summarises patient characteristics. Pupil measurements were more often performed in nonsurgical patients with respiratory failure. This finding is consistent with the fact that these patients had severe acute respiratory distress syndrome with significant and prolonged ventilation support, requiring deep sedation and mechanical ventilation.[29]

Table 2 presents pupil measurements characteristics. On average, each patient had between 2 and 3 sets of pupil measurements for each procedure resulting in 164 sets of non-noxious procedures and 141 sets of noxious procedures. Two-thirds (67%) of the noxious procedures were ETT suctioning, and the rest were changing positions of the patients. Bolus administration of analgesics or sedation before a noxious procedure was given in 11% of cases. The majority of patients (86%) had a RASS score of −5 during pupil measurements. Analgesic and sedative doses were administered according to the unit protocol, in line with current recommendations. The eye used for pupil measurement was the left one in 93% of cases.

3.1. Discriminant validity: PDR for nociception diagnosis

Fig. 1 illustrates PDR at the three time-point measurements for the non-noxious (n = 164 at each time-point) and noxious (n = 141 at each time-point) procedures. Pupil variation did not change throughout the non-noxious procedures but importantly increased in response to noxious procedures compared to before the procedure (mean difference = 31.66%). The intraclass correlation showed that 1.7% of the variance in pupil-size change was due to differences between patients and the different numbers of measurements by patient. We included age, gender, body mass index, medical versus surgical admission, tracheotomy, non-noxious versus noxious stimulations, and type of noxious stimulation (ETT suctioning or turning onto the side) in a bivariable analysis to investigate associated factors with PDR change. Out of the collected variables, age ($p = 0.14$) and noxious procedures ($p < 0.001$) were significant and remained in the multivariable analyses (Table 3). After adjusting for age, noxious procedures (n = 141) remained the only predictive factors for higher PDR (coefficient = −15.14 (95% confidence interval [CI]: −20.17 to −15.52, $p < 0.001$). Type of noxious stimulation cannot be included in the final analysis due to its high correlation with the nociceptive variable. The pseudo R^2 test showed that 23% of the PDR change was explained by this multivariable model.

Table 2
Pupil measurements.

Variables	Pupil measurement sets
Stimulus, n (%)	
Non-noxious	164 (53.8)
Noxious	141 (46.2)
Type of noxious procedure, n (%)	
Endotracheal tube suctioning	94 (66.6)
Turning onto the side	47 (33.4)
RASS, n (%)	
−5	265 (85.6)
−4	44 (14.4)
Eye for measurement, n (%)	
Left	283 (92.8)
Right	22 (7.2)
Bolus administration of sedative or opioid before measurement, n (%)	15 (5)

Data are presented as number (percentage).
Abbreviation: RASS: Richmond Agitation−Sedation Scale.

3.2. Criterion validity: The diagnostic performance of PDR to assess nociception

Using 12% threshold for nociception (n = 141), the area under the curve was 0.828 (95%CI = 0.779−0.877) (Fig. 2). This cut-off value showed a sensitivity of 65% and a specificity of 94%. By increasing the cut-off point to 20%, area under the curve was 0.826 (95% CI = 0.778−0.875), with a sensitivity of 55% and a specificity of 97%.

4. Discussion

Our study suggests that PDR is an acceptable measurement tool to assess nociception in deeply sedated critically ill patients as it could simply distinguish between non-noxious and noxious procedures and was not affected by covariates, such as age. Our simple model notably was able to explain a quarter of the variance in PDR change. A previous study reported the PDR ability to discriminate between non-noxious and noxious stimulations in sedated ICU cardiac surgery patients (RASS score: ≤ -3).[16]

We found that a PDR cut-off of >12% was better at detecting nociception during an ETT suctioning or turning onto the side than a PDR cut-off of >20. The very high specificity found in this study could help clinicians to ensure that patients receive sufficient analgesics and not overdose them. The pertinence of this cut-off value is supported by other studies. Recently, in a sample of brain-injured and non-brain-injured ICU patients, a PDR of >12% was able to predict Behavioural Pain Scale response during ETT suctioning with a specificity of 79%, a sensitivity of 88%, and an area under the receiver operating curve of 0.862 (95%CI: 0.714−0.954).[15] A PDR of >12% after a 40-mA tetanic stimulation was found to be predictive of insufficient analgesia before an ETT suctioning in 34 deeply sedated (RASS score: ≤ -4) surgical ICU patients with a sensitivity of 85% and a specificity of 78%.[18] Two other studies reported slightly higher PDR cut-off values. The study by Li et al. involving 48 sedated (RASS score: ≤ -3) and mechanically ventilated cardiac surgery ICU patients showed that the pupil size significantly increased by 16% during an ETT suctioning or repositioning.[16] A study with severe cortical necrotising cellulitis ICU patients showed that a PDR of >19% was predictive of nociception before a dressing change.[17] Attention needs to be paid on the fact that these studies had different goals. The studies by Lukaszewicz et al. and Paulus et al. aimed to obtain a nociception prediction instrument and therefore, performed the measurements before noxious care, while studies by Li et al. and Vinclair et al., similar to ours, investigated the ability of PDR to detect nociception when it was occurring. Therefore, pupil measurements were performed during noxious care. In this context, it remains challenging to define a PDR cut-off at which the diagnosis of nociception could be established, and more evidence is required before it can be identified. Because the patients in our sample received high and continuous doses of analgesics, we hypothesised, and our results confirmed that patients present low PDR when unstimulated. Thus, we tested the PDR as a tool able to detect nociception during noxious stimulation.

In our study, we observed that nurses administered opioid or sedative boluses before ETT suctioning or turning in only 10% of the cases, while our unit protocol supports administering pre-emptive analgesia before painful procedures. This result is very low, compared to the results of a worldwide online survey, in which, 52% of the respondents working in Europe reported that nurses administer analgesics to prevent painful care.[30] In contrast, it has been shown that nurses make their own interpretations when the patient is asleep[31] or sedated rather than making their clinical judgement based on rating scales.[32] In our study, patients were heavily sedated

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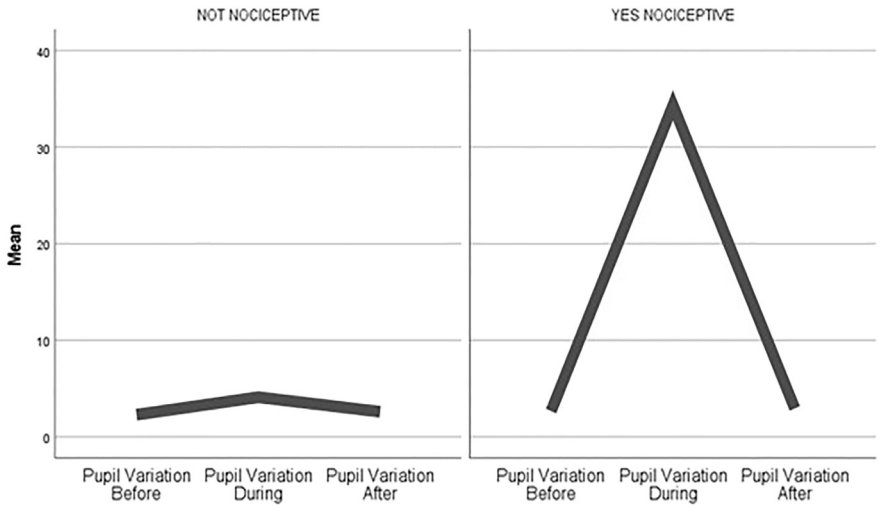

Fig. 1. Mean (standard errors) pupil variation before, during, and 5 min after a non-noxious stimulus versus a noxious stimulus.

and were thus unable to show any behavioural sign of pain, possibly resulting in the false impression that the patient was in no pain during the painful procedure. Another possible explanation of our results is that nurses tend to encourage patients to tolerate pain before giving analgesics.[33] However, according to our results, we can assume that the participants experienced repeated nociception during routine noxious procedures, suggesting the protocolised continuous analgesia and sedation management put in place was insufficient to prevent nociception. This reflects the clinical challenges of pain management in a population where pain assessment is interfered with by (i) health professionals having no objective measures to detect pain; (ii) clinical instability of patients and administration of sedatives that mask pain behaviour; (iii) nurses' attitudes are not always in line with their knowledge.

Pupil dilation was higher during endotracheal tube suctioning than during turning on the side ($p = 0.002$). This association was no longer present in the multivariable model, demonstrating that both noxious procedures are sufficiently nociceptive to be detected by the PDR assessment. These results are consistent with the study by Li et al., where the study sample received either of these two procedures with significant differences in pupil size (+16%) between the noxious and non-noxious procedures.[16]

Table 3
Bivariable and multivariable results of noxious procedure effect on pupil variation.

Variables	Bivariable (*p*-value)	Multivariable (*p*-value)
Age, years	−0.19 (0.18)	−0.18 (0.14)
Gender		
Female	–	–
Male	2.89 (0.45)	–
Body mass index	0.13 (0.55)	–
Type of admission		
Medical	1.67 (0.65)	–
Surgical	–	–
COVID-19 diagnosis		
Yes	–	–
No	−0.93 (0.25)	–
Tracheotomy		
Yes	–	–
No	0.56 (0.91)	–
Stimulus, n (%)		
Noxious	−29.86 (<0.001)	−29.85 (<0.001)
Non-noxious	–	–
Type of nociceptive procedure, n (%)		
Endotracheal suctioning	−13.88 (0.002)	–
Turning onto the side	–	–
RASS		
−5	−0.54 (0.91)	–
−4	–	–

Abbreviation: RASS: Richmond Agitation–Sedation Scale.

5. Limitations

Our study presents several limitations. We may have limited generalisability because the study was conducted in a single centre and with a relatively small sample size. However, the unit of analyses being the pupil measurements and not the patients, enabled to achieve statistical significance and therefore sufficient power.

Another limitation is that drugs were not included in the statistical models. Measuring accurately the effect of drugs on pupil dilation was not possible because the course of critical illness and patient differences affect the pharmacokinetic and

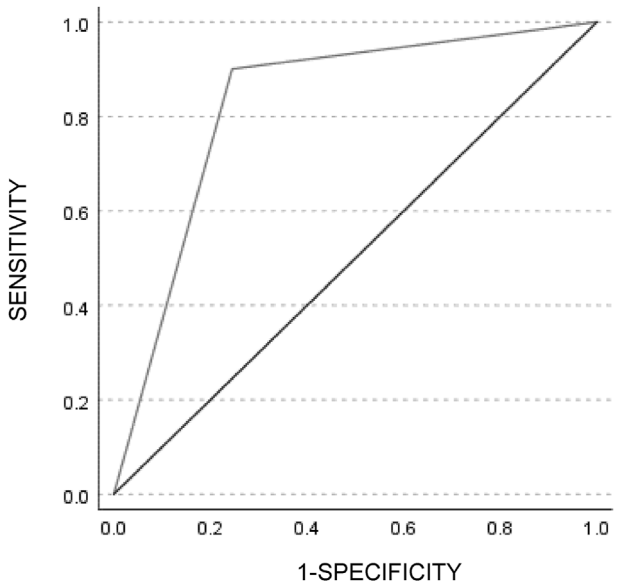

Fig. 2. Receiver operating characteristic curve of the pupil variation when nociception is defined as a percentage of pupil variation above 12. AUC indicates Area under the curve.

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pharmacodynamics of the drugs, and no pharmacokinetic testing was performed.[34] However, patients in our study received standardised doses of analgesia sedation based on the department protocol. The median doses of fentanyl and propofol were at the higher end of recommended doses, and depth of sedation was confirmed by repeated RASS assessments providing reliable and valid sedation measures of the clinical sedative effect of the drugs administered. Moreover, pupil change was significantly higher during than before a noxious procedure, which shows that despite all the limitation, this procedure still could be a valid measure of nociception. Pupillary reflex was not shown not to be affected by neuromuscular blocking agents in healthy volunteers under anaesthesia as well.[35]

Pupillometry has its own limitations. The feasibility of pupil measurements is complex in daily practice. A dedicated person is needed if the measurement is to be performed during care in order to hold the device still and obtain data with no artefacts. In addition, in the awakening phase, patients may tend to force their eyes closed or move their heads making the measurement uninterpretable or impossible to perform. However, it is important to note that no assessment is currently available in this specific population and that ICU teams are becoming familiar with pupillometry for neurological assessments in neurocritical patients.[36] This novel routine could facilitate its adoption to assess nociception in this specific population. A study showed that nurses working in a neurotrauma ICU found pupillometry acceptable and that it could improve clinical decision-making.[37] The handling of the device is simple and intuitive and requires a quick training on the different modes available. It is mainly the interpretation that follows from the measurements that need to be protocolised and evaluated. Very recently, Chanques and Gélinas have proposed an algorithm that includes the monitoring of nociception with an electrophysiology device in paralyzed patients.[38] These combined findings are promising for a population, where commonly available clinical signs, such as vital signs, are not specific to pain.[39]

6. Conclusion(s)

Our findings consider the use of pupil measurement to assess nociception in deeply sedated ICU patients. A PDR of >12% showed good specificity but low sensitivity to detect nociception related to patient usual care. In conclusion, PDR appears to be an acceptable measure to assess nociception in deeply sedated ICU patients, and we suggest considering its utility in daily practices. Further research is warranted to confirm these results in this vulnerable population.

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CRediT authorship contribution statement

Eva Favre: Conceptualisation, design of methodology, data collection, application of statistical analyses, writing—original draft, conducting a research process

Zahra Rahmaty: Conducting statistical analyses—review

Nawfel Ben Hamouda data collection—review

John-Paul Miroz: data collection—review

Samia Abed Maillard ethical protocol development, submission, regulatory aspects—project administration, review

Marco Rusca: data collection—review revised the manuscript.

Mauro Oddo review and editing—supervision, funding acquisition

Anne−Sylvie Ramelet: Conceptualisation, methodology, validation, writing—original draft, supervision

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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