The Relevance of Pupillometry for Evaluation of Analgesia Before Noxious Procedures in the Intensive Care Unit

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BACKGROUND: Many patients in the intensive care unit are unable to communicate verbally. Accurately predicting whether such patients will exhibit painful behaviors during noxious procedures and assessing the adequacy of analgesia before those procedures is a challenge. In addition to observational pain assessment tools such as the Behavioral Pain Scale, physiologic indicators such as the pupillary response have been proposed. The pupil is innervated by both divisions of the autonomic nervous system and is affected by pain and analgesic medications. We evaluated the pupillary response to a light stimulus before noxious procedures as a method to predict pain during the procedure.

METHODS: We correlated different aspects of the pupillary light reflex with established strategies for pain assessment to evaluate the adequacy of analgesia before surgical dressing changes performed in the intensive care unit in patients with cellulitis associated with mediastinitis or not.

RESULTS: We found that a percentage of variation in pupil size >19% predicted the presence of pain as assessed by a Behavioral Pain Scale score of >3 with a sensitivity of 100% (95% confidence interval, 100%–100%) and a specificity of 77% (95% confidence interval, 54%–100%).

CONCLUSIONS: In patients unable to communicate verbally, pupillometry may potentially guide caregivers to adjust analgesia before noxious procedures. (Anesth Analg 2015;XXX:00–00)

PROCEDURE-RELATED PAIN IN THE INTENSIVE CARE UNIT (ICU) IS AN IMPORTANT CONCERN FOR CAREGIVERS. ALTHOUGH EXCESSIVE USE OF SEDATIVES AND ANALGESICS TO CONTROL PAIN MAY RESULT IN OVERSEDATION AND WORSE OUTCOMES, INADEQUATE PAIN THERAPY MAY INDUCE HYPERALGIESIA AND PSYCHOLOGICAL DISORDERS. PHYSIOLOGICAL REFLEXES RELATED TO PAIN AND NOCICEPTION IMPLY ACTIVATION OF SYMPATHETIC NERVOUS SYSTEM AND INCLUDE INCREASED HEART RATE (HR), POLYPNEA, AND PUPIL DILATION. BECAUSE PUPIL DIAMETER AND MOTILITY DEPEND ON THE BALANCE BETWEEN SYMPATHETIC AND PARASYMPATHETIC RESPONSES, PUPILLARY RESPONSES HAVE BEEN STUDIED FOR THEIR USEFULNESS TO DETECT THE PRESENCE OF PAIN. THE RECENT DEVELOPMENT OF PRACTICAL PUPIL MEASUREMENT TOOLS HAS MADE THIS APPROACH SUITABLE FOR CLINICAL PRACTICE, AND PUPILOMETRY HAS BEEN PROPOSED AS AN ALTERNATIVE METHOD FOR ASSESSING PAIN DURING ANESTHESIA FOR SURGERY OR OUT OF THE OPERATING ROOM.

Because sympathetic responses are affected by anesthetic drugs, pupil size and variation may reflect the extent of analgesia. The goal of the present study was to examine the sensitivity, specificity, and accuracy of pupillary responses to a calibrated light source to assess the adequacy of analgesia before a dressing change in the ICU. Pupillometry was assessed before the dressing change and evaluated as a predictor of pain behavior during the dressing change as measured by the Behavior Pain Scale (BPS). As a secondary objective, variations in vital signs (i.e., HR and arterial blood pressure [BP]) were compared before and during the nociceptive procedure.

METHODS

The protocol was approved by the IRB (Société de Réanimation de Langue Française CE-13-35), and the requirement for written informed consent was waived by the IRB. Accordingly, all patients were verbally informed and consented to participate in the study. We prospectively enrolled patients presenting with severe cervical necrotizing cellulitis, which was associated in some cases with mediastinitis. Study patients required 3 surgical dressing changes per day, each lasting 15 to 30 minutes. The dressing change consisted of debridement of necrotic tissue, cleaning with antiseptic solutions, and positioning of superficial and deep drainage systems. As we have described previously, patients’ lungs were mechanically ventilated during the procedure, and patients were sedated with a continuous infusion of IV flunitrazepam and fentanyl for analgesia. All patients had a Richmond Agitation Sedation Scale score of −5 before beginning the dressing change. The design of the study started with the measurements of pupil and hemodynamic variables (HR, BP, and noninvasive or arterial catheter), followed immediately by the dressing change procedure. The BPS was recorded during the procedure.

Pupillometry was assessed using the Neurolight™ (ID MED™, Marseille, France). This device generates a 1-second 150 Lux flash of light and detects pupillary changes using an infrared camera. Pupillary measurements were performed under sterile drapes just before beginning the dressing change to limit the influence of surgical light or daylight on the measurements. The opposite eye was closed and protected. The Neurolight device allows automatic measurement of maximal and minimal pupil diameter.
(before and after the flash of light, respectively), the percentage of pupil variation ((maximal diameter – minimal diameter)/maximal diameter), the velocity at which the diameter is reduced, and the latency of such variation (between the light flash and the beginning of pupil variation). The measurements were performed twice in each patient, and the mean of both measurements was recorded.

During the dressing change, behavioral responses were evaluated using the BPS for noncommunicative patients.1,12 In this study, our threshold BPS was 3 for absence of pain behavior during the dressing procedure. For analysis purposes, patients were separated into 2 groups: those expressing pain behavior (BPS >3) or not (BPS = 3) during the procedure.

Statistical Analysis
In this preliminary study, no data were available to make assumptions for the sample size calculation. Quantitative variables were expressed as the median (interquartile range). Because some variables were unlikely to be normally distributed in our population (especially percentage and velocity of pupil size variation), comparisons between groups were performed using nonparametric Mann-Whitney U tests.

The diagnostic accuracy of pupillometry variables was evaluated using receiver operating characteristic curves. Calculation of the area under the curve (AUC) was used to predict a change of >1 unit on the BPS scale before and during the surgery. The 95% confidence intervals of the AUCs, sensitivities, and specificities were estimated using bootstrap operations. All bootstrap operations for confidence interval computation were performed with nonparametric resampling and using the percentile method. For each estimate, 2000 duplicates were computed.

Sensitivity, specificity, negative predictive value, positive predictive value, and best cutoff values were estimated according to the Youden index (defined as the sum of sensitivity + specificity – 1). Statistical analyses were performed using R-statistical software (http://www.r-project.org/), The R Foundation for Statistical Computing, Vienna, Austria). A 3-sided P value < 0.05 was considered statistically significant.

RESULTS
A total of 37 patients with cellulitis were included. Among these patients, 8 also presented with mediastinitis, 22 were male (59.5%), the median age was 54 years (range, 39–63), and the median Simplified Acute Physiology Score II score was 36 (range, 26–42). The test was performed at the onset of the disease at day 2 (range, 1–2) after ICU admission.

All patients had a BPS = 3 before the surgical dressing and for pupillary tests, and 24 (65%) demonstrated pain behavior (BPS >3) during the dressing. Before the dressing change, hemodynamic and pupillary variables were different in patients who did not express pain behaviors (BPS = 3) compared with those who did (BPS >3, median BPS = 5 [range, 4–6.2]). Specifically, HR was slower in patients who did not demonstrate pain (85 [76.8–95.8] vs 100 [85–102] beats/min; P = 0.014); the median minimal diameters were lower (1.8 [1.8–2] vs 2.5 [2–2.8] mm; P = 0.0018); the median maximal diameters were lower (2.2 [2.1–2.3] and 4.1 [3–4.5] mm; P < 0.001); the median percentage variation was lower (13% [11–18] and 34.5% [25.2–38.5]; P < 0.001); and the median velocities were greater (1.1 [1–1.5] and 3.7 [2.4–3.9] mm/s; P < 0.001), respectively. Mean BP and latency did not differ between patients who demonstrated pain by BPS and those who did not.

Receiver operating characteristic curves were built to assess the ability of each parameter of interest to predict the presence of pain (Fig. 1). According to AUC calculations, the percentage of pupil variation was 0.938 (0.849–0.942), the velocity was 0.95 (0.872–0.955), the minimal and maximal diameters were 0.814 (0.655–0.817) and 0.938 (0.833–0.942), respectively, latency was 0.607 (0.412–0.606), and HR was 0.655 (0.436–0.853). The best thresholds for each parameter of interest for pain prediction are listed in Table 1. Among several pupillary parameters, the percentage of variation was probably associated with the highest sensitivity in predicting the presence of pain in accordance with a BPS score of >3 in our population.

DISCUSSION
We found that the pupillary responses can be valid tools for evaluating the depth of analgesia and predicting the presence of pain when standardized complex surgical dressing procedures for cellulitis are performed in the ICU.

Because hemodynamic changes are not valid correlates of pain in critically ill patients,11,12 current guidelines recommend that caregivers of patients unable to self-report should use pain behavior assessment tools such as the BPS in patients with intact motor function. Pupillary reflex dilation in response to pain stimulus has been reported in adults and children and in patients under general anesthesia14,15 or deeply sedated in the ICU.9 Pupil size and variation (light reflex) results from the sympathetic/parasympathetic balance that can be tested with a flash of light.

Because we were looking for a way to detect the risk of pain in patients during daily surgical dressing changes, we studied pupillary reflex constriction to a flash of light before the start of the surgical dressing. This approach allowed us to avoid causing patients any additional pain. The light reflex response has been thoroughly described and may be altered by sedation16–18 or sympathetic activity.29 Specifically higher levels of sympathetic activity result in the larger pupil size or variation. Accordingly, the percentage of pupil variation thus appeared particularly interesting because it is a functional test for pupil motility, and it evaluates the effect of sedative and analgesic drugs on sympathetic/parasympathetic balance. In our study, the

![Figure 1. Receiver operating characteristics (ROC) curves for minimal diameter, maximal diameter, percentage of variation of pupil, and velocity associated with feeling pain during the procedure.](image-url)
Correlation between pupil maximal diameter and percentage of variation.

Table 1. Estimates of Specificity, Sensitivity, Accuracy, Negative Predictive Value, and Positive Predicted Value Using the Selected Threshold for Each Variable of Interest

<table>
<thead>
<tr>
<th>Minimal diameter, mm</th>
<th>Maximal diameter, mm</th>
<th>% Variation</th>
<th>Velocity, mm/s</th>
<th>Heart rate, beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1.8–2.7)</td>
<td>2.9 (2.2–4.3)</td>
<td>26 (18–37)</td>
<td>2.5 (1.5–3.7)</td>
<td>86 (82–98)</td>
</tr>
<tr>
<td>2.20</td>
<td>2.60</td>
<td>19.00</td>
<td>1.55</td>
<td>97</td>
</tr>
<tr>
<td>100% (100–100)</td>
<td>100% (100–100)</td>
<td>77% (54–100)</td>
<td>77% (54–100)</td>
<td>62% (39–85)</td>
</tr>
<tr>
<td>71% (50–88)</td>
<td>83% (67–96)</td>
<td>100% (100–100)</td>
<td>96% (88–100)</td>
<td>88% (75–100)</td>
</tr>
<tr>
<td>0.85</td>
<td>0.92</td>
<td>0.88</td>
<td>0.86</td>
<td>0.78</td>
</tr>
<tr>
<td>0.65</td>
<td>0.76</td>
<td>1.00</td>
<td>0.91</td>
<td>0.73</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>0.89</td>
<td>0.88</td>
<td>0.81</td>
</tr>
</tbody>
</table>

To be more generalizable, alternative thresholds were tested. Instead of 19% ± 0.2 SD as the % variation, a threshold of 16.85% was associated with a sensitivity of 92% and a specificity of 77%.

DISCLOSURES

Name: Anne-Claire Lukaszewicz, MD, PhD.

Contribution: This author designed and conducted the study, and prepared the manuscript.

Attestation: Anne-Claire Lukaszewicz has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: Domitille Dereu, MD.

Contribution: This author helped conduct the study, and collect the data.

Attestation: Domitille Dereu has seen the original study data, and approved the final manuscript.

Name: Etienne Gayat, MD, PhD.

Contribution: This author helped analyze the data as statistician.

Attestation: Etienne Gayat has seen the original study data, and approved the final manuscript.

Name: Didier Payen, MD, PhD.

Contribution: This author helped design the study, and prepare the manuscript.

Attestation: Didier Payen has seen the original study data, and approved the final manuscript.

This manuscript was handled by: Avery Tung, MD.

REFERENCES

4. Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F; Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. Anesthesiology 1997;87:849–35
7. Aissou M, Snauwlaert A, Dupuis C, Achatbahan A, Aubrun E, Beausser M. Objective assessment of the immediate decrease in percentage of pupil variation in patients who exhibited no pain behaviors (BPS = 3 during the procedure) may have resulted from a small maximal diameter (Fig. 2) related to sympathetic inhibition (limited pupil dilation) and analgesia-related inhibition of pupil constriction. However, the patients with the largest pupil diameter and greatest variation were those who presented pain behavior during the subsequent procedure, possibly because of insufficient analgesia. These observations may reflect a higher basal level of sympathetic activity before dressing changes even in apparently sedated patients (Richmond Agitation Sedation Scale = −5 and BPS = 3) and predict insufficient analgesia for the subsequent noxious procedure.

Based on our findings, we showed that a threshold of 19% pupil variation was probably associated with a high level of discrimination for the presence of pain (BPS > 3) during the procedure in our population. The findings are encouraging, and future work is needed to study the sensitivity of these values to the threshold.

Our results suggest that pupillometry is a valid method that may guide caregivers in the ICU to proactively identify patients at risk for insufficient analgesia before noxious procedures. Because of the simplicity of measurement, this variable can be translated easily into clinical practice for nurses and nonmedical caregivers. This preliminary study should be considered hypothesis generating only, and we recommend that the threshold of 19% pupil variation should be used cautiously in patients with severe comorbidities or in elderly patients with altered pupil motility. In this preliminary study, no sample size calculation was performed, which may limit the precision of our estimates. Additional prospective studies in larger populations should be performed before wider use of pupillometry for titrating analgesic drugs for noxious surgical procedures in the ICU.
postoperative analgesia using pupillary reflex measurement: a prospective and observational study. Anesthesiology 2012;116:1006–12