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Use of Digital Pupillometry to Measure Sedative Response to Propofol

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Background: Digital pupillometry (DP) accurately and precisely measures pupillary responses. Little is known about using DP to measure the sedative effect of isolated propofol administration.

Methods: We conducted a cross-sectional study of 19 adults undergoing moderate sedation with propofol during which we measured pupillary changes using DP.

Results: Maximum and minimum pupillary diameters decreased significantly with propofol (mean change from baseline to procedural termination −1.24 mm, standard error [SE] 0.25 and −0.79 mm, SE 0.13, respectively; $P \leq 0.001$ for both). Mean constriction velocity decreased by 0.84 mm/s between baseline and procedural termination ($P = 0.001$). Pupillary latency increased significantly between baseline and induction (mean change 0.016 seconds, SE 0.007; $P = 0.04$) but was not significantly different at other time points.

Conclusion: We speculate that DP may be a useful tool to monitor propofol sedation.

Keywords: *Conscious sedation, hypnotics and sedatives, propofol, reflex–pupillary*

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INTRODUCTION

Excessive sedation of critically ill patients is associated with prolonged mechanical ventilation, increased length of stay, and higher mortality.[1] Subjective scoring systems for determining sedation depth, such as the Richmond Agitation-Sedation Scale (RASS), have demonstrated good interrater reliability during validation trials.[2,3] However, data suggest that the routine implementation of these scoring systems into clinical care is not uniform and that the use of scripted scales may be time consuming for bedside providers.[4]

Sedative-hypnotic drugs can significantly attenuate the pupillary light reflex (PLR), a central nervous system sensory-motor reflex.[5] The penlight examination has historically been the primary tool for the measurement of the PLR. Penlight examination, however, is prone to error because of its nonstandardized light source, high interobserver and intraobserver variability, and inability to measure dynamic responses (ie, pupillary latency and constriction velocity).[6,7] Handheld digital pupillometry (DP) is a novel technology that enables inexperienced providers of multiple professions and educational levels to accurately and precisely measure static and dynamic pupillary responses.[5] Consequently, DP may theoretically become a more useful tool for the assessment of sedation appropriateness than a subjective scoring system and penlight examination.[5] In a prior study, investigators used a portable infrared pupilometer to evaluate PLRs under propofol and nitrous oxide anesthesia[8]; however, no studies to date have involved the use of a handheld digital pupillometer to investigate pupillary responses during moderate propofol sedation.

In this initial investigation of the effects of moderate sedation with propofol on DP, we purposely chose to study ambulatory patients undergoing routine esophagogastroduodenoscopy and/or colonoscopy rather than to study critically ill patients because of concerns that we would not be able to confidently attribute changes in pupillary function solely to propofol in a clinically ''noisy'' intensive care unit environment. We hypothesized that the administration of propofol would result in changes in both static measures (minimum and maximum pupillary diameter) and dynamic measures (pupil latency and pupil constriction velocity).

METHODS

The study design was reviewed and approved by both the Louisiana State University and Ochsner Medical Center institutional review boards. Written informed consent was obtained from each study participant prior to enrollment.

Study Design and Subjects

We conducted a cross-sectional study of ambulatory adults undergoing elective outpatient endoscopy under monitored moderate sedation with propofol. A gastroenterology fellow (J.L.B.) assisted with subject identification and recruitment. All subject identification and data collection were performed at Ochsner Medical Center during October 2015. Subjects were screened by electronic medical record review and approached for informed consent in the preoperative holding area prior to their procedures. Exclusion criteria included blindness (unilateral or bilateral), eye surgery, eye trauma, therapeutic eye drop use, glaucoma, symptomatic cataracts, or cerebral injury (stroke, traumatic brain injury, or meningitis). Patients using sedating medications (benzodiazepines or opiates) as part of their home medication regimen were also excluded.

Measurements

Patients received an intravenous propofol bolus induction dose of 0.3-0.7 mg/kg followed by intermittent maintenance doses (range 200-800 mg). The propofol was administered by 1 of 5 certified registered nurse anesthetists under the supervision of a board-certified anesthesiologist and was titrated to a level of moderate sedation per usual practice.

Measurements were performed by one of the investigators using the NeurOptics NPi-100 digital pupillometer. Each measurement took approximately 10 seconds to obtain. All measurements were obtained following at least 2 minutes of low ambient lighting ($<$100 lumens as measured by a digital lux meter [Lux Meter, Pavel Bukhonov]). Low lighting conditions did not impact patient care and were not required for accurate operation of the pupillometer. The investigators chose to standardize lighting conditions to account for any potential confounding by ambient light. Single DP measurements were obtained from each eye at 4 sequential time points: baseline (in the preoperative anesthesia holding area), induction (2 minutes after the initial propofol bolus), termination (upon endoscope withdrawal), and recovery (once the subject awoke and was able to count to 3).

Statistical Analysis

Prior estimates of the mean difference in pupillary constriction velocity during deep sedation were 1.1-1.4 mm/s with an SD of 20% of the mean.[9] We thereby estimated a sample size of 12 subjects would have 90% power to detect a 20% change in constriction velocity using a significance level of $P \leq 0.05$. To increase precision and ensure data quality, we planned to enroll 20 subjects.

We used descriptive statistics to characterize mean values for continuous normally distributed variables, median values with interquartile ranges (IQR) for skewed distributions, and proportions for categorical variables. The MIXED procedure in v.9.4 of the Statistical Analysis System (SAS) was used to analyze a mixed-effects model for mean change from baseline to procedure termination that included time as a fixed effect and subjects as random effects. Estimates from the mixed-effects model were reported as mean changes with standard errors (SEs). Because no differences were found between eyes, the mean response across eyes was used in mixed-model analyses. All other statistical analyses were performed using STATA v.13.0 (StataCorp LLC). A P value ≤ 0.05 was considered statistically significant.

RESULTS

Twenty subjects were consented for the study. One consented subject was removed from the analysis because of an inability to obtain all the measurements secondary to early procedure termination. Complete measurements were obtained for the remaining 19 subjects.

Most subjects were middle-aged (median 58 years [IQR 47-67 years]), and 68% were women. Most subjects underwent colonoscopy alone (63%), while 37% underwent colonoscopy and esophagogastroduodenoscopy. The median procedure time was 20 minutes (IQR 12-26 minutes), while the median induction and total propofol doses were 100 mg (IQR 100-140 mg) and 250 mg (IQR 220-550 mg), respectively. Mean pupillary measurements with standard deviations collected at each time point are summarized in the Table.

In the mixed-effects model, the maximum pupillary diameter decreased significantly during the course of propofol administration (mean change −1.24 mm, SE 0.25; $P<0.001$) between baseline and procedural termination and returned toward baseline in the recovery period (mean change from baseline to recovery −0.83 mm, SE 0.21; $P=0.001$). Likewise, minimum pupillary diameter decreased significantly between baseline and procedural termination (mean change −0.79 mm, SE 0.13; $P \leq 0.001$) and returned toward baseline in the recovery period (mean change from baseline to recovery −0.45 mm, SE 0.09; $P<0.001$). Mean constriction velocity also decreased by 0.84 mm/s between baseline and procedural termination ($P=0.001$) with a return toward baseline in the recovery period (mean change from baseline to recovery −0.62 mm/s, SE 0.15; $P \leq 0.001$) (Figure). Pupillary latency increased significantly between baseline and induction (mean change 0.016 seconds, SE 0.007; $P=0.04$) but was not significantly different from baseline at the other time points. The correlation between the eyes was significant for the maximum pupillary diameters ($r=0.73$, $P<0.001$) and the constriction velocity ($r=0.81$, $P<0.001$). Total propofol dose was inversely correlated with both the mean constriction velocity (left eye, $r=-0.49$, $P=0.03$; right eye, $r=-0.34$, $P=0.15$) and the maximum pupillary diameter (left eye, $r=-0.43$, $P=0.07$; right eye, $r=-0.39$, $P=0.10$).

DISCUSSION

To our knowledge, our study provides the first data regarding the use of DP for measurement of the sedative response to propofol. In patients undergoing elective outpatient endoscopy, propofol sedation was associated with a significant decrease in maximum and minimum pupillary diameter and in mean constriction velocity. Our findings suggest that pupillary diameter and constriction velocity are the 2 DP variables most impacted by sedation with propofol. We found a significant correlation between propofol sedation and pupil latency between baseline and induction with propofol but not throughout the course of full procedural sedation.

We purposefully did not use a control group in this experiment because performing colonoscopy on patients without sedation would not be ethical. Although the

Table. Mean (SD) Digital Pupillary Measurements at Sequential Sedation Time Points

	Baseline		Induction		Termination		Recovery	
Measurement	**Left Eye**	**Right Eye**	**Left Eye**	**Right Eye**	**Left Eye**	**Right Eye**	**Left Eye**	**Right Eye**
Maximum pupillary diameter, mm	4.05 (1.1)	4.13 (1.2)	4.21 (1.4)	4.17 (1.3)	2.73 (0.7)	2.97 (1.2)	3.22 (1.0)	3.28 (1.0)
Minimum pupillary diameter, mm	2.73 (0.6)	2.80 (0.7)	2.81 (0.8)	2.86 (1.0)	1.89 (0.4)	2.06 (0.7)	2.29 (0.6)	2.35 (0.6)
Pupillary latency, s	0.25 (0.04)	0.26 (0.03)	0.26 (0.04)	0.28 (0.04)	0.25 (0.04)	0.27 (0.05)	0.26 (0.04)	0.26 (0.05)

colonoscopy itself, rather than propofol, could possibly have caused the observed changes in pupillary size and contractility velocity, this seems improbable. The typical pupillary response to pain is pupillary dilation, not constriction. Furthermore, colon stimulation would be unlikely to produce our observed results because transcutaneous nerve stimulation of the vagus nerve either has no impact on PLR[10] or it increases resting pupillary diameter.[11]

Our findings are consistent with prior DP studies using other sedative agents, including benzodiazepines, thiopental (Pentothal), and sufentanil.[9] Rouche et al showed that the depth of sedation using midazolam correlated with decreased pupillary constriction velocity and diameter.[9] Unlike prior studies, we did not formally assess sedation using a standardized sedation scale. Instead, all patients were sedated to a level of moderate sedation as assessed by certified nurse anesthetists. Results from prior studies suggest a correlation between pupillary reflex dilatation and depth of sedation.[9] Similarly, our study shows that contralateral pupillary responses were correlated.

The current literature regarding DP is limited. Prior studies have evaluated the effects of opioids, barbiturates, neuromuscular agents, and benzodiazepines, but none has examined the use of DP during propofol sedation.[5] These studies suggested that DP had better precision and accuracy than manual light examination[5,12] and was more specific than heart rate or blood pressure for determining the depth of anesthesia.[13] Additional studies are needed to compare DP responses to formal sedation scales and other methods of anesthesia depth assessment, such as bispectral index monitoring, to clarify the utility of DP in the routine administration of anesthesia and conscious sedation in critically ill patients. Our findings suggest, however, that DP can reliably measure pupil responses.

A potential limitation to our findings includes the small cohort size recruited from a single institution, but the baseline characteristics of our patients reflect the general population of patients who undergo outpatient screening endoscopy. While the potential for measurement error exists, the intrasubject correlation between the left and right eyes suggests that error was minimal. Accuracy of the pupillometer is impacted by ocular pathology, and we lack data on device performance in acute cerebral injury, limiting the generalizability of our findings to these patient populations. Finally, we did not perform a standardized sedation scale (such as RASS), so we are unable to correlate our findings with clinical sedation depth. This study was an initial proof-of-concept study to determine the most accurate DP measures of sedative response with the long-term goal of translating this procedure to clinical practice.

CONCLUSION

We conclude that pupillary diameter and constriction velocity measured by DP correlate with the sedative response to propofol in an outpatient setting. The intrasubject correlation between the left and right eye measurements suggests that a single eye measurement may be sufficient for accurate pupillary response assessment in patients without ocular pathology. Our results inform future studies designed to correlate DP values with the depth of sedation as assessed by clinically accepted scoring systems in critically ill patients.

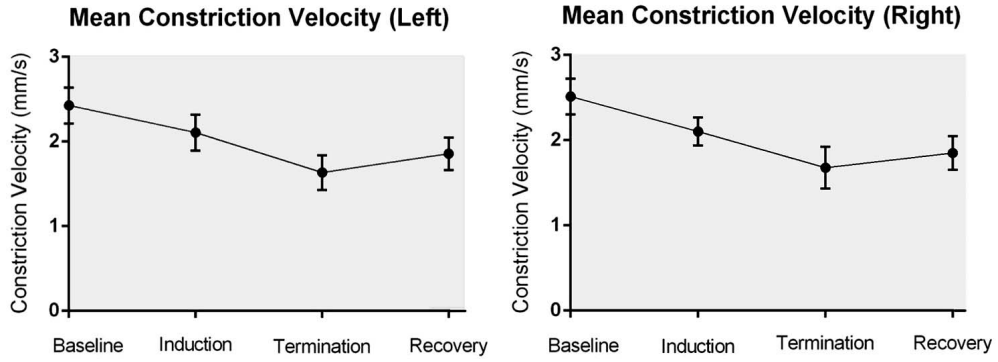

Figure. Constriction velocity trajectory during propofol administration. Mean constriction velocity (± SD) decreased significantly from baseline to recovery ($P<0.001$) with propofol administration.

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