ORIGINAL RESEARCH

The Presence of Cataract Does Not Influence Assessment of The Pupillary Light Reflex Using Automated Pupillometry

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Abstract

Background: Advanced Pupillary Light Reflex (PLR) assessment with an automated infrared pupillometer (AIP) is becoming standard. Although cataract prevalence and risk for neurologic illness both increase with age there is no literature on the influence of cataract when assessing PLR using AIP.

Objective: Our aim is to explore the effect of cataract on pupillary response to light.

Methods and Materials: Mixed model analyses were performed by enrolling 3,650 patients with PLR readings from AIP. The Neurological Pupil Index (NPi), and each component of the PLR was examined separately.

Results: 3,207 patients did not have cataract, 59 had unilateral, and 271 bilateral cataract. Generalized linear mixed effect model of 87,290 right eye, and 76,587 left eye AIP measurements found no effect of cataract on any PLR measures: NPi (p=0.221 and p=0.655); latency (p=0.483 and p=0.865); initial pupil size (p=0.661 and 0.712); minimum pupil size (p=0.708 and p=0.720); constriction velocity (p=0.646 and 0.347); nor dilation velocity (p=0.716 and 0.194) for the right and left eye groups respectively. Paired t-test found no difference in NPi (p=0.146). Among those with unilateral cataract (n=59).

Conclusion: The presence of cataract does not alter the PLR findings assessed with a pupillometer.

Keywords: *Cataract, Pupil, Pupillary light reflex, Automated Pupillometer, Neurological Pupillary Index, Assessment*

Introduction

Neurologic disorders are the leading cause of global disability adjusted life years.[(GBD 2015 Neurological Disorders Collaborator Group, 2017)] Neurologic assessment relies on multiple parameters, including a reliable assessment of the PLR which is a biomarker of injury.[(Aoun et al., 2019; Mader et al., 2020; Ortega-Perez et al., 2019)] As clinicians more towards increased specialization there is a need for multimodal neurologic monitoring.[(Kim et al., 2019; Olson & Ortega-Perez, 2018; Vespa et al., 2020)] Unfortunately, the subjective assessment of the PLR by human evaluation is unreliable.[(Olson et al., 2016)] However, hand-held AIP can reliably assess PLR when used by various types of healthcare personnel.[(Zhao et al., 2016) (Couret et al., 2016; Park et al., 2015)] Modern AIP quantifies elements of the PLR including pupil size at baseline, size when fully constricted, the percent change in size, the latency between light stimulus and initial constriction, the constriction velocity (CV), and the dilation velocity (DV).[(Lussier, Stutzman, et al., 2019)] The most commonly available commercial device provides a derived parameter called the Neurological Pupil index™ (NPi™), which is a proprietary summary score that includes all PLR indices.[(Lussier, Olson, et al., 2019)]

It is already established that eye color does not affect the PLR assessed with AIP.(Al-Obaidi et al., 2019) However, cataract, which is cloudiness in the eye lens of the, is a significant cause of blindness. Its prevalence is higher in individuals with advanced age, with more than half of all Americans age 80 or older either have cataracts or have had surgery to remove cataracts. In a review of eight United States (US) studies published between 1992 and 2013, the overall cataract prevalence ranges from 2.8% to 29.5%. [(Dougherty et al.)] Another study recorded a 43.6% ten-year cumulative incidence among participants aged 55-80 years.[(Koo et al., 2013)]

Although the robustness of the AIP measures have been explored under a variety of conditions and diagnoses most studies, to date, have excluded patients with cataract.[(Jahns et al., 2019; Riker et al., 2019; Shoyombo et al., 2018; Tamura et al., 2020)] Various patient factors and bedside conditions can affect PLR measurements, for example, the rate of change of pupil diameter is inversely related to age, and the pupillary reaction is affected by the luminance level.[(Winn et al., 1994)] However, pupil size is independent of gender, refractive error, or iris color.[(Winn et al., 1994)] Other factors that can affect the PLR include: the robustness of circadian rhythm [(Bonmati-Carrion et al., 2016)], classical conditioning [(Kakigi, 1964)], anxiety [(Nagai et al., 2002)], and depression[(Bär et al., 2004)]. Certain medications such as narcotics, psychotropics, and anesthetic drugs have an effect on pupillary function.[(Knaggs et al., 2004), (Larson et al., 1993)] Ascertaining the proportional distribution of significant demographic and clinical characteristics in the comparison groups based on patient cataract status is relevant to study, as it could affect the subsequent outcome of patients.[(Song et al., 2014)]

Materials and Methods

The main objective of this retrospective cohort analysis was to evaluate the effect of cataract on PLR assessed by AIP in a hospital setting. Participants were selected from the Institutional Review Board approved END-PANIC registry (NCT02804438), a multisite prospective registry that includes AIP and associated clinical data on over 5,000 patients and over 89,000 AIP readings.[(Olson et al., 2017)] Subjects were considered eligible if they had at least one pupillometer reading using the NPi-200 (NeurOptics, Inc.), demographic data (age, gender, race), and documentation of the presence or absence of cataracts. Additional variables extracted from the registry for this analysis include: admission diagnosis, admission Glasgow Coma Scale (GCS) score, and concurrent use of narcotics, diprovan, or barbiturate during hospitalization. The laterality of cataract was analyzed using a de-identified patient identification number. Admission GCS trichotomized as: mild (13-15), moderate (9-12), or severe (3-8). Primary neurologic diagnoses of patients were broadly grouped depending on the pathologic causes as vascular (e.g., aneurysms), traumatic, tumor or space-occupying lesions, ischemic (e.g., cerebrovascular accident), and those grouped as others which are not included on the categories mentioned above.

Descriptive and inferential statistics were performed using SAS v 9.4 (SAS Institute, Cary NC, USA). Statistical significance was defined as a p-value <0.05. Age was analyzed as a continuous variable; gender was analyzed as a binary predictor with two levels using females as reference. Race was analyzed as a categorical predictor with three levels: Caucasian, African American, and Other using Caucasian as reference. The GCS was analyzed as a categorical predictor with three levels using the mild group set as reference. The PLR measures of: pupil size, pupillary latency, CV, DV, and NPi were all analyzed as continuous variables. Two proportion Z-tests were performed to compare the distribution of categorical and binary variables between patients with and without cataract. To reduce multicollinearity, separate analyses were performed in the right and left eye. Two independent sample t-tests were used to compare the average ages, NPi, size, percent change, latency, CV, and DV between patients with cataract and without cataract, and the 95% confidence intervals were computed. Binary variables, which include sex and in-hospital medication use (narcotics, propofol, and barbiturate), distribution according to cataract status, were statistically analyzed by using Z-statistic for comparing proportions. Finally, generalized linear mixed models were employed to understand the relationship between the presence of cataract on the various pupillometry variables. Each of the models adjusted for age, sex, race, GCS levels, and the use of narcotics, diprovan, and barbiturates. The generalized mixed model is vital because the model will efficiently use the longitudinal data, and will accommodate attrition that is ignorable (essentially, missing at random (MAR)).[(Cao & Mukhopadhyay, 2020; Daniels & Hogan, 2008)]

Results

The analysis included 3,650 patients. Table 1 summarizes baseline characteristics as separately analyzed for right and left eyes. The majority of participants were Caucasian (77.7%) and female (51.1%). The proportion of Caucasians was statistically different for those with cataract in the left eye and those without (82.5% vs 77.3%; p=0.043 respectively); and the proportion of patients with severe brain injury with and without cataract in the left eye is (4.3% vs 2.6%, p=0.026 respectively). The mean (sd) age of patients with cataract in the right eye was 56.2 (17.3), and for those without was 71.9 (11.9; p <0.001). Similarly, the mean age of those with cataract in the left eye was 72.1 (11.7), and for those without was 56.2 (17.3; p <0.001). Of these, 304 had a cataract in the right eye, and 297 had a cataract in the left eye, and 3,235 were without cataract (bilateral cataract was present in 271 patients).

Table 1. Distribution of study subjects according to demographic and clinical variables

		Right Eye			Left Eye		
		Cataract	No Cataract	p-value	Cataract	No Cataract	p-value
Age (*years*)		56.19	71.9441	**<0.001**	56.22	72.11	**<0.001**
Sex	Female	163 (53.6)	1650 (51)	0.386	159 (53.5)	1655 (51)	0.418
	Male	141 (46.4)	1584 (49)		138 (46.5)	1585 (49)	
Race	Caucasians	240 (81.4)	2416 (77.4)	0.117	240 (82.5)	2416 (77.3)	**0.043**
	African American	35 (11.9)	433 (13.9)	0.338	32 (11)	435 (13.9)	0.165
	Asians	9 (3.1)	102 (3.3)	0.841	10 (3.4)	101 (3.2)	0.851
	Others	11 (3.7)	171 (5.5)	0.201	9 (3.1)	173 (5.5)	0.076
Glasgow Coma Score	13-15 (mild)	224 (74.2)	2274 (70.5)	0.183	220 (74.6)	2278 (70.5)	0.143
	9 -12 (moderate)	38 (12.6)	396 (12.3)	0.879	39 (13.2)	394 (12.2)	0.609
	3-8 (severe)	40 (13.2)	554 (17.2)	0.08	36 (12.2)	558 (17.3)	**0.026**
Primary Neurologic Diagnosis	Vascular	71 (23.5)	806 (25)	0.555	66 (22.4)	811 (25.2)	0.29
	Traumatic	8 (2.6)	117 (3.6)	0.376	10 (3.4)	115 (3.6)	0.875
	Tumor	79 (26.2)	830 (25.8)	0.889	82 (27.8)	827 (25.7)	0.42

	Right Eye			Left Eye		
	Cataract	No Cataract	p-value	Cataract	No Cataract	p-value
Ischemic	55 (18.2)	584 (18.1)	0.978	54 (18.3)	584 (18.1)	0.935
Other	89 (29.5)	881 (27.4)	0.436	83 (28.1)	887 (27.5)	0.819

Except age, which is shown in years, all values show n (%); statistically significant results indicated by ***bold font***

Separate analyses were performed for the right and left eye. In the study cohort, 9.0% of females and 8.2% of male patients had a right eye cataract, 8.7% of females and 8.0% of males had a left eye cataract, and among all study participants, 4.1% of females and 3.5% of males had bilateral cataract. The 3,650 patients had 87,290 right eye and 76,587 left eye AIP measurements performed during their hospital stay. There were no univariate differences in any of the AIP measures (NPi, size, change in size, CV, DV, and latency) when compared with or without cataract for each eye (Table 2).

Table 2. Comparison of mean PLR values of the right and left eye with and without cataract using t-test

Pupillometry variables	Units	Right Eye: Cataract	Right Eye: No Cataract	Right Eye: p-value	Left Eye: Cataract	Left Eye: No Cataract	Left Eye: p-value
NPi	n/a	4.162	4.130	0.830	4.11	3.96	0.66
Initial Size	mm	3.122	3.653	0.007	3.199	3.605	0.039
Minimum Size	mm	2.395	2.586	0.116	2.467	2.557	0.457
Percent change	%	22.297	27.213	0.006	21.600	26.992	0.004
Constriction Velocity	mm/sec	1.339	1.879	0.001	1.273	1.873	<0.001
Dilation Velocity	mm/sec	0.616	0.816	0.006	0.547	0.814	<0.001
Latency	sec	0.26	0.26	0.48	0.26	0.26	0.87

Furthermore, statistical inference based on a generalized linear mixed effect model analysis (Table 3) found no significance of cataract (right eye and left eye) with respect to NPi (p=0.221 and p=0.655), PLR latency (p=0.483 and p=0.865), initial pupil size (p=0.661 and 0.712), minimum size (p=0.708 and p=0.720), CV(p=0.646 and 0.347), or DV (p=0.716 and 0.194) for the right and left eye groups respectively. Among the 59 patients who had only a unilateral cataract, the paired t-test found no significant difference comparing the NPi of the left and right eye (μ= 3.921 vs 4.143, respectively, p=0.146).

Table 3. Fixed effect estimates of cataract and p-value of the generalized mixed linear model for pupillometer measurement parameters

Pupillometry variables	Right Eye: Estimates (s.e)	Right Eye: p-value	Left Eye: Estimates (s.e)	Left Eye: p-value
NPi	0.103(0.084)	0.221	0.040(0.085)	0.655
Initial Size	0.037(0.84)	0.661	-0.031(0.084)	0.712

Pupillometry variables	Right Eye		Left Eye	
	Estimates (s.e)	p-value	Estimates (s.e)	p-value
Minimum Size	0.022(0.058)	0.708	0.022(0.061)	0.72
Percent change	0.452(0.788)	0.566	-0.657(0.806)	0.415
Constriction Velocity	0.03(0.065)	0.646	-0.063(0.067)	0.347
Dilation Velocity	0.011(0.029)	0.716	-0.039(0.03)	0.194
Latency	-0.003(0.004)	0.483	0.001(0.004)	0.865

Discussion

This study demonstrates that no significant association exists between the presence of cataract and any of the PLR parameters measured by AIP. Age-related cataract is caused by the progressive opacification of the lens of the eye.[(Gali et al., 2019)] The lens of the eye anatomically lies just behind the pupillary opening. The luminance reaching the retina is believed to diminish with cataract and potentially affect the strength of afferent stimulus in the light reflex pathway and alter how the pupil behaves in reaction to light stimulus. Neural reflex latency is presumed to be influenced by the length and conductivity of the nerve fibers and synapses involved in reflex pathways.[(Sadeghi et al., 2004; Stanley, 1981)] Because cataract is not believed to affect these neural factors, it makes sense that pupillary reflex latency was not associated with cataract, and no delay of pupillary contraction to the light stimulus was observed.

During the eye examination procedure, the initial pupillary size measurement is taken before the eye is subjected to a light stimulus emitted from the pupillometer device. The initial pupillary size was not affected by cataract at baseline nor following constriction. The finding suggests that the resting pupillary sphincter tone is similar despite the presence of cataract on ambient light conditions where the examinations are performed in neurocritical patient care.[(Steinhauer et al., 2004)] The minimum pupillary size measured during the light reflex physiologically indicates the smallest pupillary diameter that the constrictor muscles attain during maximum contraction. Lens opacification did not alter the pupillary size under normal luminance levels in hospital settings.[(Tsujimura et al., 2010)] Similarly, the percent change in pupil size, which conveys the amplitude of pupillary contraction undergone in reaction to the light stimulus was not affected by the presence of cataract. These two aspects of pupillary constriction were not associated with the presence of cataracts.

Neither changes in CV, nor changes in DV were related to the presence of cataract. It is difficult to determine what distinct mechanisms are involved that determine the dynamics of pupillary sphincter muscle contraction and relaxation in the presence of cataract.[(Heller et al., 1990)] Although a study in a small number of healthy subjects showed that the intensity of light stimulus affects constriction and dilatation rates,[(Ellis, 1981)] the circular constrictor muscle, as well as the radial dilator muscle functional dynamics as measured by CV and DV in this study, were found to have no significant difference based on the cataract status of the eye.[(Song et al., 2014)]

The specialty of neurointensive care is expanding, and the need to understand the benefits and limitation of advanced monitoring is inherent.[(Jo et al., 2020)] The study has a large sample size. Relevant patient-related demographic and clinical factors were controlled in the generalized mixed model regression analysis. The use of AIP devices has made the study possible by allowing precise measurements of the PLR in real time for a light stimulus. As the PLR measurements in the study were done in routine hospital settings, the results generated from this study would reflect the findings in an everyday clinical practice setting and make it more relevant for patient care.

Limitations

The primary limitation is that the data were accessed from a registry. The AIP data were prospectively collected through automated download, however patient data such as gender, age, and presence of cataract were abstracted from the electronic medical record. Data collection could not actively be monitored for quality control at the patient level. History of cataract status was most often documented by nurses on admission and collected from a patient self-report. Individuals had a varying number of pupillometry measurements performed as directed by the clinical condition of the patients. Besides, only one-time GCS assessment records and binary medication administration were used. Determining the effect of controlling for single level variables obtained on admission in the face of multiple pupillometry tests and how it influenced the analytic results with certainty is difficult.

Conclusion

The presence of cataracts does not independently affect PLR readings obtained with AIP. We found that a significant proportion (9.3%) of hospital patients with a neurologic diagnosis have a concomitant cataract. The large sample size used, and the consistent results from generalized mixed model regression analysis for the right and left eyes support that PLR readings from patients with cataract may be interpreted in a similar fashion to other PLR assessments. These findings extend the utility of AIP to assess the PLR both clinically and as a research variable. Future research investigating PLR should not exclude AIP readings simply based on the presence of cataracts.

Conflict of Interest

Dr. Olson is the Editor for the Journal of Neuroscience Nursing

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