Diagnostic accuracy test of quantitative pupillary light reflex as an indicator of increased intracranial pressure in traumatic brain injury patients: a cross-sectional study

Dhania A. Santosa1*, Edward Kusuma1, Nancy Margarita Rehatta1

ABSTRACT

Introduction: The gold standard of intracranial pressure (ICP) measurement is an invasive procedure of inserting ICP monitor and one of the limitations of its surrogate, ultrasonography-based (US) optic nerve sheath diameter (ONSD) measurement is operator-dependent. Quantitative pupillary light reflex (PLR) measurement provides objective data promisingly able to predict ICP elevation. The aim of this study was to evaluate diagnostic accuracy of PLR as an indicator of ICP elevation in traumatic brain injury (TBI) patients compared to US-ONSD measurement.

Methods: This was a cross-sectional study involving moderate and severe TBI patients aged 18-65 years without any eye lesion, nor medication and illness that may influence PLR. Healthy volunteers were recruited as control group. ONSD and quantitative PLR measurements (baseline diameter, maximum constriction, constriction velocity, latency and amplitude) were assessed to both groups. The Student t-test or Mann-Whitney U-test was used to compare the ONSD and PLR between case and control group. Further analyses were done to determine the sensitivity, specificity and cut-off value of PLR compared to ONSD in case group.

Result: ONSD measurements or parameters were significantly different between case and control group (p<0.001), while all PLR parameters were significantly different (p<0.005) except for right eye constriction latency. The baseline diameter of the right eye had the highest accuracy with cut-off value of >3.9 mm (specificity of 100%, sensitivity of 50%). Other PLR components had variable in accuracy.

Conclusion: The baseline diameter of the right eye was the most accurate PLR component as an indicator of ICP elevation, represented by ONSD.

Keywords: Pupillary light reflex, optic nerve sheath diameter, ONSD, intracranial pressure, traumatic brain injury.


INTRODUCTION

The Monro-Kellie doctrine described the skull as a rigid structure with constant volume containing brain, blood and cerebrospinal fluid.1,2 Any reason for increased intracranial volume will increase intracranial pressure (ICP), cause secondary brain injury and brain herniation which subsequently leads to worse outcomes and even death.3 ICP measurement is therefore the cornerstone in management of patients with intracranial lesions.

Traumatic brain injury (TBI) is one of the major health problems globally with 60 million patients per year around the world.4 Management on critically-ill TBI patients is ideally based on patient’s ICP, as stated in the Guidelines for the Management of Severe Traumatic Brain Injury by Brain Trauma Foundation.5 An invasive procedure of inserting catheter (ICP monitor) intracranially is the gold standard of ICP measurement.5 Nevertheless, only 30.6% of severe TBI patients received such treatment which signifies most severe TBI patients were not treated by the highest standard available. The arguments behind the low rate of ICP insertion include the risk of infection and bleeding6, moreover it poses higher risk for the patients who are already in severe condition.6,7

Optic nerve sheath diameter (ONSD) measurement using ultrasonography (USG) is a less-invasive method used to estimate ICP elevation. Previous study and systematic reviews stated that ONSD measurement cut-off value of more than 5 mm has a sensitivity of 94-97% and specificity of 86-88% in diagnosing ICP elevation in TBI patients.6,9 Nonetheless, this technique requires a specific skill and operator-dependent; thus, its applicability is still limited.

Pupillary light responses (PLR) measurement has long been routinely used to determine a patient’s neurological status. PLR measurement using penlight is subjective with wide inter- and intra-observer variability.10 Quantitative pupillometry is a non-invasive, easy-to-use and bedside-available tool to measure pupillary light reflex quantitatively. This
relatively small-sized device is able to measure baseline diameter, constriction velocity, constriction latency, maximum constriction and constriction amplitude. These objective data from quantitative pupillary light reflex measurement can hopefully be used to estimate ICP elevation towards better patient care. This study aimed to test the diagnostic accuracy of quantitative PLR as an indicator of elevated intracranial pressure in patients with TBI, as compared to using ONSD measurement as a standard reference.

METHODS

This analytic, cross-sectional study was conducted at an academic national referral hospital in Indonesia. Twenty-seven traumatic brain injury patients were enrolled from June 2022 to September 2022 and written informed consent was taken. Inclusion criteria were adult patients aged 18-65 years old with moderate and severe traumatic brain injury with Glasgow coma scale (GCS) ranged from 3 to 12. Exclusion criteria were patients with eye lesions, subsequently known subarachnoidal hemorrhage from CT scan and patients with history of diabetes mellitus, Alzheimer and Parkinson, as well as those with certain therapies: opioid, barbiturate, metoclopramide, droperidol and sulfas atropine. Twenty-nine healthy volunteers were also included in this study as control group. Data collected were as follows: patient age, GCS at arrival, ONSD measurement result and quantitative pupillary light reflex consists of: basal diameter, constriction amplitude, constriction velocity, constriction latency and maximum constriction.

After secondary survey were done, ONSD measurement was done by an experienced consultant of neuroanesthesia using Vivid-q GE ultrasonography (USG) to both eyes, three times per eye and average values were obtained. Subsequently, quantitative pupillary light reflex was measured using NeuroLight® quantitative pupillometry for both eyes. Twenty-nine healthy volunteers were also included in this study as control group. ONSD and quantitative PLR measurement were done to control group by the same operator with the same device.

Data collected were written in the form of its mean and standard deviation. Shapiro-Wilk test was used to check the normality of quantitative data. For normally-distributed data, a Student t-test was performed, while for skewed data a nonparametric Mann-Whitney U-test was used for statistical analysis. Furthermore, sensitivity, specificity, positive predictive value, negative predictive value analysis of quantitative pupillary light reflex was done using ONSD as a reference test with a cut-off value of more than 5 mm indicating elevated ICP. Cut-off values of each pupillary light reflex element were obtained from area under curve (AUC) of receiver operating characteristic (ROC) curve. All the statistical tests were performed at a significance level of a < 0.05.

RESULTS

Twenty-seven patients with moderate and severe traumatic brain injury (as case group) and 29 healthy volunteers (as control group) were included in this study with demographic characteristics shown in Table 1 and the characteristics of case group described in Table 2.

ICP monitor catheter insertion was performed in 6 out of 21 (28.57%) patients

Table 1. Age and sex distribution of case and control group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case group (n=27)</th>
<th>Control group (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (66.7%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (33.3%)</td>
<td>19 (67.9%)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>41.22 ± 15.91</td>
<td>34.38 ± 11.27</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of case group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>Severity (GCS at arrival)</td>
<td></td>
</tr>
<tr>
<td>Moderate traumatic brain injury (GCS 9-12)</td>
<td>6 (22.22%)</td>
</tr>
<tr>
<td>Severe traumatic brain injury (GCS 3-8)</td>
<td>21 (77.78%)</td>
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<tr>
<td>CT head scan findings</td>
<td></td>
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<tr>
<td>Hematoma</td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>6 (21.43%)</td>
</tr>
<tr>
<td>Subdural</td>
<td>10 (35.71%)</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>10 (35.71%)</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>2 (7.14%)</td>
</tr>
<tr>
<td>Bilateral hematoma</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>9 (47.37%)</td>
</tr>
<tr>
<td>Not present</td>
<td>10 (52.63%)</td>
</tr>
<tr>
<td>Midline shift</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (51.85%)</td>
</tr>
<tr>
<td>Present, less than 5 mm</td>
<td>2 (7.41%)</td>
</tr>
<tr>
<td>Present, 5 mm or more</td>
<td>11 (20.74%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>17 (62.96%)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (37.04%)</td>
</tr>
</tbody>
</table>

Figure 1. NeuroLight® quantitative pupillometer.

Table 1. Age and sex distribution of case and control group

Table 2. Characteristics of case group
with severe traumatic brain injury and the initial ICP readings were 9, 11, 15, 18, 21 and 22 mmHg, respectively. This would imply that 5 out of these 6 patients had increased intracranial pressure. All of these 6 patients were among the survivors. The mortality rate in case group is 10 out of 27 patients (37.04%). ONSD measurements in case and control group were described in Table 3. ONSD measurements for both eyes were significantly different between case and control group. Quantitative pupillary light reflexes for both eyes were significantly different between case and control group except for constriction latency of the left eye. Diagnostic accuracy test of quantitative pupillary light reflex of both eyes as indicator of increased intracranial pressure using ONSD as standard reference.

### DISCUSSION

TBI is one of the health problems with high mortality and burden around the globe including in Indonesia.\(^\text{11-12}\) This study was conducted to assess the accuracy of quantitative PLR to measure elevated intracranial pressure among TBI patients during the coronavirus disease 2019 (COVID-19). Although multiple drugs have been developed,\(^\text{13-14}\) COVID-19 has caused significant changes in multiple aspects.\(^\text{13-18}\) In this present study, 27 TBI patients were included in our study which spanned over 4 months. Out of the patients in case group, subdural and intracerebral hemorrhage were the most frequently found intracranial lesion in our study, meanwhile previous study described that subarachnoid hemorrhage (SAH) and cerebral contusion were more prevalent.\(^\text{17}\) Patients with SAH were excluded from our study due to the fact that SAH may be preceded by a drastic elevation of ICP reaching a level that exceeds the integrity of the optic nerve sheath, leading to inaccurate readings of ONSD measurement.\(^\text{18}\) ONSD measurement between case and control group were significantly different. This strengthened the results of previous studies, systematic reviews and meta-analyses in suggesting the use of ONSD measurement as a modality to assess elevation of ICP in patients with TBI and, very likely, other intracranial lesion. Quantitative PLR measurement between case and control group were significantly different, except for the constriction latency of the right eye. This contradicts previous study which revealed that constriction velocity and latency were the only 2 components of quantitative PLR that were different between TBI and non-TBI patients.\(^\text{19,20}\) In a previous study, patients with mild TBI were included and analysis on pupil dilation characteristics after maximum constriction was done.\(^\text{19}\) This contradiction urges the conduct of further, larger studies involving mild, moderate and severe TBI patients with analysis on re-dilation properties of pupil
and quantitative pupillary light reflex measurement were done during secondary survey, nevertheless sampling time was quite variable, some were done before intubation and others, after intubation, due to patient's condition. In intubated patients, ONSD and quantitative PLR measurements were done with regard to the last time anesthetic agent delivered in order to minimize the possibility of anesthetic agents as confounders. More detailed protocols on sampling time must be arranged in future studies. Information on mechanisms of injury such as direction of impact, location of brain lesion and hematoma, opened or closed fracture as well as dominant brain hemisphere represented by whether patient is right-handed or left-handed need to be recorded in future studies to discover factors influencing the difference of baseline diameter accuracy of both eyes for indicating increased intracranial pressure. Lastly, pupillary light reflex fundamentally is a process which consists of constriction and re-dilation of pupil. Further, larger studies on re-dilation element of pupillary light reflex as well as overall evaluation on all components of quantitative pupillary light reflex as indicator of increased intracranial pressure needs to be done.

CONCLUSION

The baseline diameter of the right eye was shown to be the most accurate element of quantitative pupillary light reflex as an indicator of increased intracranial pressure, using ONSD measurement as a standard reference comparison. Further, larger studies on overall components of quantitative pupillary light reflex, including re-dilation component needs to be done with more detailed study protocol.

ETHICAL APPROVAL

Ethical clearance was obtained from Committee of Health Research Ethics at Dr. Soetomo Academic General Hospital (0423/KEPK/V/2022) dated May 31, 2022. All patients provided their signed informed consent prior to the study.

COMPETING INTERESTS

The authors declare no conflict of interest.

GRANT INFORMATION

This study received no external funding.

AUTHORS CONTRIBUTION

DAA contributed in concepting and designing the study, literature search, data collection, data analysis, manuscript preparation and editing. EK and NMR were responsible in concepting and designing the study, contributed in intellectual content, manuscript editing and final editing.

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REFERENCES


