Clinical Utility of an Automated Pupillometer in Patients with Acute Brain Lesion

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Objective: The purpose of this study was to evaluate the clinical utility and validity of using a pupillometer to assess patients with acute brain lesions.

Methods: Pupillary examinations using an automated pupillometer (NeuroOptics® NPi™-100 Pupillometer) were performed every 4 hours and were simultaneously assessed using the Glasgow Coma Scale (GCS) and for intracranial pressure (ICP), from admission to discharge or expire in neuro-intensive care unit (NICU). Manual pupillary examinations were also recorded for comparison. By comparing these data, we evaluated the validity of using automated pupillometers to predict clinical outcomes.

Results: The mean values of the Neurologic Pupillary index (NPi) were different in the groups examined manually. The GCS correlated well with NPi values, especially in severe brain injury patients (GCS below 9). However, the NPi values were weakly correlated with intracranial pressure (ICP) when the ICP was lower than 30 cm H2O. The NPi value was not affected by age or intensity of illumination. In patients with a "poor" prognosis who had a Glasgow Outcome Scale (GOS) of 1 or 2, the mean initial NPi score was 0.88±1.68, whereas the value was 3.89±0.97 in patients with a "favorable" prognosis who had a GOS greater than 2 (p<0.001). For predicting clinical outcomes, the initial NPi value of 3.4 had the highest sensitivity and specificity.

Conclusion: An automated pupillometer can serve as a simple and useful tool for the accurate measurement of pupillary reactivity in patients with acute brain lesions.

Key Words: Pupillometer · Light reflex · Neurologic Pupillary Index.
Assessment of pupillary reflex using an automated pupillometer

Pupillary examinations using an automated pupillometer (NeurOptics® NPitm-100 Pupillometer, Neuroptics Inc., Irvine, CA, USA) were performed every 4 hours. A pupillometer is a handheld optical scanner that stimulates the eye with a flash of light and captures and analyzes a rapid sequence of digital images to obtain a temporal measurement of the diameter of a human pupil (Fig. 1). It analyzes the captured image data and displays a summary of the measurements on the screen. The NPi algorithm was developed to quantify pupillary reactivity and to remove subjectivity from this assessment[9]. Each variable from an individual pupil measurement taken by the pupillometer is compared against the mean of a reference distribution of healthy subjects for the same variable. Finally, the set of all the standardized differences (or z-scores) were combined to fall into a scale between 0 and 5. An NPi value closer to 5 is considered more "prompt" and an NPi value closer to zero denotes a more abnormal PLR. Both eyes were tested in all patients, and inspection time was less than 30 seconds per person.

A GCS estimation and a manual pupillary examination were simultaneously performed with each exam by pupillometer. Infratranial pressure (ICP) was also evaluated in available patients. The results of the manual pupillary examination were classified as "fixed", "sluggish" and "prompt" and the mean NPi value was calculated. Twenty-seven patients were available for the measurement of ICP. Seventeen patients had indwelling extra-ventricular drainage catheters, and 10 patients had ICP monitoring catheters. Classification by ICP grouped patients into 3 categories (lower than 15 cm H₂O, 15 cm H₂O to 30 cm H₂O, and higher than 30 cm H₂O), and the relationship between NPi value and each category was analyzed.

Validity of pupilometer measurements

Statistical analysis was performed using the SPSS 20 (IBM, Armonk, NY, USA). The relationships between NPi and other parameters (GCS, ICP, manual exam, illumination and age) were examined by comparing the mean value of each group. The differences between two groups were verified by t-test, and differences between more than three groups were verified by one-way ANOVA.

The area under the curve (AUC) was used to assess the ability of the pupillometer to predict a patient's outcome. This curve was plotted by MedCalc for Windows, version 11.6.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Validity of pupilometer measurements

The NPi was measured 1522 times on 117 patients using a pupillometer. The characteristics of patient group according to prognosis (poor or favorable) is shown in Table 1. The mean values of NPi in "fixed," "sluggish," and "prompt" pupils were 0.21±0.85, 1.79±1.58, and 3.86±1.10, respectively. The mean values of NPi in the groups categorized by GCS 3 to 5, 6 to 8, 9 to 12, and GCS 13 to 15, and the average NPi value was calculated. Twenty-seven patients were available for the measurement of ICP. Seventeen patients had indwelling extra-ventricular drainage catheters, and 10 patients had ICP monitoring catheters. Classification by ICP grouped patients into 3 categories (lower than 15 cm H₂O, 15 cm H₂O to 30 cm H₂O, and higher than 30 cm H₂O), and the relationship between NPi value and each category was analyzed.

We also evaluated the influence of illumination and age on NPi as an aspect of the validity analysis. We compared the mean NPi value measured during the daytime (8 a.m. to 20 p.m.) with the value measured at night. We analyzed the difference in NPi between an older patient group (65 years old or older) and a younger group (below 65 years old). These two analyses were performed in patients with a GCS of 9 or higher.

To determine the predictive value of NPi in terms of clinical outcomes, we used the Glasgow Outcome Scale (GOS) at 1 month after the onset of event. The clinical outcome was classified as "favorable" if the GOS 1 month after the event was equal to or greater than 3 and "poor" if the GOS was below 3. We compared initial NPi values in these two groups. The area under the receiver operating characteristic (ROC) curve was used to assess the cut-off value for predicting clinical outcomes. True positive was defined as a group with an NPi lower than the cut-off value and a "poor" outcome. False positive was defined as a group having an NPi lower than the cut-off value and a "favorable" outcome.

Statistical analysis

Statistical analysis was performed using the SPSS 20 (IBM, Armonk, NY, USA). The relationships between NPi and other parameters (GCS, ICP, manual exam, illumination and age) were examined by comparing the mean value of each group. The differences between two groups were verified by t-test, and differences between more than three groups were verified by one-way ANOVA.

The area under the curve (AUC) was used to assess the ability of the pupillometer to predict a patient's outcome. This curve was plotted by MedCalc for Windows, version 11.6.0 (MedCalc Software, Mariakerke, Belgium).
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12, and 13 to 15 were 1.36±1.78, 2.68±1.64, 3.65±1.27, and 4.06±1.76, respectively (p<0.001). The GCS can be said to have a directly proportional relationship with the NPi (Fig. 2). The mean NPi in the group with ICP higher than 30 cm H$_2$O was 1.02±1.35, which was lower than that in the group with ICP lower than 30 cm H$_2$O (3.26±0.64) (Fig. 3). In the one-way ANOVA analysis, NPi and ICP showed less of a relationship when ICP was lower than 30 cm H$_2$O, but when ICP was higher than 30 cm H$_2$O, NPi was significantly decreased.

The mean NPi value during the daytime was 4.03±1.02, whereas the value was 3.83±1.17 at night (p=0.123). The mean NPi value in the young age group was 3.92±1.10, whereas in the older age group it was 4.09±0.96 (p=0.078). These values were not statistically different, and it can be said that the NPi value was not influenced by age or the intensity of illumination.

### Predicting the value of NPi in terms of patient outcome

The mean initial NPi value of the “poor” prognosis group was 0.88±1.68, whereas that of the “favorable” prognosis group was 3.89±0.97. This difference was statistically significant (p=0.001). To evaluate the cut-off value of the NPi in terms of predicting clinical outcomes, we used the ROC curve (Fig. 4) and made a cross-tabulation table by changing the presumed cut-off value from 2.5 to 4.0 (Table 2). In our study, an NPi value showed the AUC of 0.92, and the initial NPi value of the automated pupillometer had a sensitivity of 86.0% and a specificity of 84.6% in predicting the clinical outcome at 1 month after the event when cut-off value was 3.4.

### DISCUSSION

PLR, estimated manually by inspectors using a light source, is
used for the evaluation of patients in various clinical situations. However, results from this procedure include a number of inconsistencies and inaccuracies due to its inherently subjective nature. According to Larson and Muhiudeen, a routine clinical examination, performed with a traditional penlight, is unable to detect the PLR when the amplitude is less than 0.3 mm. In several reports comparing manual exams to the use of automated pupillometers, automated pupillometers have been reported to reduce these inaccuracies. Meeker et al. reported that inter-examiner disagreement regarding the pupillary reactions was 39% for manual examinations compared with 1% for automated pupillometers. Hence, studies to define the relationship between clinical manifestations and PLR determined by automated pupillometer have been conducted in various fields.

In the field of ophthalmology, the automated pupillometer has been applied to evaluate the feasibility of differentiating diabetic neuropathies, optic neuritis, relative afferent papillary defects or glaucoma. Some studies have shown that pupillometers detect decreased optic nerve function in experimental optic neuritis, even in the absence of histological detection. In emergency medicine, research revealed that the presence of PLR, determined by automated pupillometer in patients with “fixed” pupils according to manual examinations, could be associated with early survival and a favorable neurological status in the recovery period. Automated pupillometers were also used to assess the prognosis of patients receiving a liver transplantation. Some anesthesiologists and pharmacologists have shown that automated pupillometers could be used to quantify the PLR, which can be affected by drugs and hence can provide proper information about the responses to these drugs. Some reported that there was an association between total opioid dose (expressed as morphine equivalents) and pupil diameter. These previous studies in various fields confirm that the automated pupillometer has the advantages of being non-invasive and objective compared to manual pupillary examinations.

PLR is a very important factor that is used to assess neurological patients. Because pupillomotor fibers and parasympathetic oculomotor nuclei in the midbrain are sensitive to brainstem compression by mass-occupying lesions or ischemia, changes in the PLR can indicate an expanding supratentorial mass lesion with transmission of the associated pressure and subsequent onset of herniation. Previous reports have provided a large amount of evidence showing that alterations in the pupil light reflex, the size of the pupil, or anisocoria are all closely correlated with outcomes following an acute brain injury. Therefore, PLR may serve as a guide for neurosurgeons in determining the need for a further, aggressive work-up or a prompt surgical intervention. This was observed in patients with dilated pupils and is of clinical importance because most urgent decisions regarding the management of patients with abnormal pupils are made when the pupils are dilated and are therefore the most susceptible to error in a manual examination. Many reports have shown that automated pupillometers can detect PLR in pupils that were regarded as “fixed” in a manual exam. In particular, some studies using pupillometers present NPI as an objective index that reflects the pupillary light reflex. Some dynamic studies have reported that changes in the NPI reflect increases in intracranial pressure approximately 16 hours in advance. Decreased PLR velocity was recovered after surgical intervention in these patients.

In our study, the GCS correlated well with the NPI value, especially in severe brain injury patients with a GCS 8 or lower. Low NPI values represented increased ICP when ICP was higher than 30 cm H₂O, but NPI values did not correlate with ICP values lower than 30 cm H₂O. These results are in agreement with a previous study that showed that constriction velocities in the pupil did not fall until ICP increased above 30 mmHg. Pupils assessed as “fixed” or “sluggish” in a manual pupillary exam showed variable NPI values, whereas a “prompt” assessment in a manual pupillary exam almost always had an NPI value above 3.

Table 2. Sensitivity and specificity of pupillometer according to different NPI cut-off value

| NPI cut-off value | Sensitivity (%) | Specificity (%) |
|------------------|----------------|----------------|
| 2.5              | 76.0           | 90.4           |
| 3.0              | 80.0           | 88.2           |
| 3.4              | 84.0           | 86.1           |
| 4.0              | 92.0           | 73.4           |

Sensitivity means the ratio of “poor” predicted outcomes to NPI is lower than the cut-off value, whereas specificity means the ratio of “favorable” predicted outcomes to NPI is higher than the cut-off value. NPI: Neurologic Pupillary index.
This is the first study to evaluate the utility of automated pupillometers in predicting clinical outcomes in patients with acute brain lesions. Our results confirmed a definite difference in the initial NPi values between “poor” and “favorable” groups and indicated that an initial NPi value of 3.4, which has a specificity of 84.2% and a sensitivity of 86.0%, could be used as a cutoff value when predicting clinical outcomes.

Our study has some limitations. First, we did not consider dynamic factors such as delayed clinical deteriorations or neuro-surgical interventions in the evaluation of outcome prediction. These dynamic factors could be postulated to be the cause of less than 90 percent of the sensitivity and specificity of the automated pupillometers used in our study. Future studies will be required to ascertain how dynamic changes in NPi correlate with alterations in clinical conditions. Second, the effects of drug interactions, such as sedatives and other confounding drugs, have not been taken into consideration. However, we observed a tendency towards a slower drop in the NPi value in the pupils of these patients compared to the manual pupillary examination results, which were already recorded as “sluggish” or “fixed” after coma therapy. This suggests that well-designed future studies could reveal a role for NPi values in monitoring patients under sedation or coma therapy.

CONCLUSION

Automated pupillometers can serve as useful tools for the objective and quantitative measurement of pupillary reactivity in patients with acute brain injuries, and could thereby provide prognostic information.

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