Original Article

Prediction of the level of consciousness using pupillometer measurements in patients with impaired consciousness brought to the emergency and critical care center

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Aim: We investigated whether the level of consciousness can be predicted using pupillometer measurements in patients with severe disturbance of consciousness.

Methods: Patients with a Glasgow Coma Scale (GCS) of 3–8, except for those after cardiac arrest, were included. Pupillary contraction rate and contraction velocity were each measured using a pupillometer.

Results: Thirty-five patients were analyzed. At the time of discharge or changing hospitals, 16 patients had a GCS score of 3–13 and 19 patients had a GCS score of 14–15. In the non-sedative group at about the time of arrival at our hospital, average pupillary contraction rates were 18.36% in the GCS 3–13 group and 19.67% in the GCS 14–15 group ($P = 0.739$), and average pupillary contraction velocities were 1.02 and 1.48, respectively ($P = 0.182$). Approximately 48 h after arrival, average pupillary contraction rates were 21.18% and 29.27%, respectively ($P = 0.058$), and average pupillary contraction velocities were 1.37 and 1.91, respectively ($P = 0.172$). Among the sedative group, at about the time of arrival, average pupillary contraction rates were 8.75% in the GCS 3–13 group and 19.75% in the GCS 14–15 group ($P = 0.032$). Average pupillary contraction velocities were 0.34 and 1.48, respectively ($P = 0.001$). Approximately 48 h after arrival, average pupillary contraction rates were 13.50% and 13.50%, respectively ($P = 1.00$), and average pupillary contraction velocities were 0.80 and 0.82, respectively ($P = 0.93$).

Conclusions: Pupillometer measurements could predict level of consciousness of patients with severe consciousness disorder.

Key words: Consciousness disorder, Glasgow Coma Scale, intensive care, neuroptics, pupillometer

INTRODUCTION

MANY PATIENTS WITH severe disturbance of consciousness are transported to an emergency and critical care center. The causes of severe disturbance of consciousness include trauma, stroke, post-cardiac arrest, and other diseases. However, it is difficult to predict the level of consciousness of patients regardless of the cause of disturbance of consciousness in the early stages after transportation, and it is often difficult to explain this to the family. Therefore, electroencephalography (EEG), somatosensory evoked potentials (SSEP), and neuron-specific enolase (NSE) blood levels have been used to predict the level of consciousness of patients after cardiac arrest.[1] However, EEG and SSEP require technical skills for interpretation, and are not quantitative tests. We investigated whether level of consciousness can be predicted using pupillometer measurements in patients with severe disturbance of consciousness, other than after cardiac arrest, expecting that this can readily be used to estimate the prospects of a patient's future consciousness. A previous study by Oddo *et al*.[1] analyzed the use of pupillometry for the prognosis prediction of post-cardiac arrest patients. To our knowledge, our present study is the first report on prognosis prediction using pupillometry in patients other than post-cardiac arrest patients.

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METHODS

Study design, participants, and protocol

THIS WAS A single-center, retrospective observational study. The study protocol was approved by the ethics committee at Tokyo Medical University. Patients with a Glasgow Coma Scale (GCS) score of 3–8, except for those after

cardiac arrest, who were transported to Tokyo Medical University Hospital Emergency and Critical Care Center between November 2017 and November 2019 were analyzed. Specifically, quantitative pupillary contraction rates and contraction velocities at the time of their arrival at our hospital and 48 h thereafter were analyzed regarding their association with GCS score at discharge or at the time of changing hospitals. The patients were divided according to their level of consciousness at the time of discharge or changing hospitals. In general, among patients who have head injuries but with stable respiration and circulation, a GCS score of 14–15 is considered to be a mild degree of consciousness disturbance. Therefore, the patients were divided into two groups, the GCS 3–13 group and the GCS 14–15 group, and their association with the pupillometer parameters was investigated. The patients of each group were further divided into two groups for comparison, to analyze the effects of analgesics and sedatives on the pupillometer measurements. Patients who were treated with midazolam, propofol, fentanyl, and dexmedetomidine were defined as the sedative group, and patients who were not given any of these drugs were defined as the non-sedative group. Patients who died 48 h after their transportation were defined as GCS 3. Patients were also analyzed for the presence of intracranial diseases and extracranial diseases, because intracranial diseases could affect the pupillometer parameters. Intracranial diseases included stroke, psychiatric diseases, epilepsy, and head injury. Furthermore, hospitalization days between the GCS 3–13 group and the GCS 14–15 group were also analyzed, because GCS scores may be affected by the timing of the judgment of consciousness. The research design was a retrospective observational study. The pupillometer used in this study was the NeurOptics NPi-200 Pupillometer System (Laguna Hills, CA, USA). If there was anisocoria, the larger value was recorded.

Statistical analysis

Data were statistically analyzed using SPSS software (version 26; IBM, Armonk, NY, USA), and P-values <0.05 were considered to indicate a statistically significant difference between two groups. The Shapiro–Wilk test was carried out on two groups to confirm a normal distribution. The Welch test was applied after the Levene test. SPSS software was also used for statistical analysis of the results, by the Pearson χ^2-test.

RESULTS

AMONG THE 52 patients included in the study, 11 were excluded due to the lack of sufficient medical records, 6 were excluded because they died within 48 h after admission, and the remaining 35 patients were analyzed. The flowchart is shown in Fig. 1. Table 1 shows the baseline demographics and outcomes of the patients. At the time of discharge or changing hospitals, 16 patients had a GCS score of 3–13 and 19 patients had a GCS score of 14–15. None of the patients were given any muscle relaxants, analgesics, or sedatives at the time of transfer. Among the non-sedative group, at about the time of arrival at our hospital, average pupillary contraction rates were 18.36% in the GCS 3–13 group and 19.67% in the GCS 14–15 group (P = 0.739), and the cut-off value was 21.50%. Average pupillary contraction velocities were 1.02 in the GCS 3–13 group and 1.48 in the GCS 14–15 group (P = 0.182), and the cut-off value was 1.50. Approximately 48 h after arrival, average pupillary contraction rates were 21.18% in the GCS 3–13 group and 29.27% in the GCS 14–15 group (P = 0.058), and the cut-off value was 24.50%. Average pupillary contraction velocities were 1.37 in the GCS 3–13 group and 1.91 in the GCS 14–15 group (P = 0.172), and the cut-off value was 1.57. Among patients in the sedative group, at about the time of arrival, average pupillary contraction rates were 8.75% in the GCS 3–13 group and 19.75% in the GCS 14–15 group (P = 0.032), and the cut-off value was 19.00%. Average pupillary contraction velocities were 0.34 in the GCS 3–13 group and 1.48 in the GCS 14–15 group (P = 0.001), and the cut-off value was 0.91. Approximately 48 h after arrival, average pupillary contraction rates were 13.5% in the GCS 3–13 group and 13.50% in the GCS 14–15 group (P = 1.00), and the cut-off value was 14.50%. Average pupillary contraction velocities were 0.80 in the GCS 3–13 group and 0.82 in the GCS 14–15 group (P = 0.93), and the cut-off value was 0.88. Overall, regarding the sedative groups in the two GCS groups, the mean pupil contraction rate and mean pupil contraction velocity at the time of transfer showed a statistically significant difference between the two groups, and they were associated with GCS score (Table 2). The results shown in Table 2 are the pupillary contraction velocity and the pupillary contraction rate, using a cut-off value. Table 3 shows the sensitivities and specificities of pupil contraction rates and pupil contraction velocities for the GCS 3–13 and GCS 14–15 groups. There was no statistically significant difference between the number of intracranial diseases and extracranial diseases in the two sedative groups with different GCS scores (P = 0.46; Table 4). In addition, there was no statistically significant difference in hospitalization days between the two sedative groups with different GCS scores (P = 0.21; Table 5).

DISCUSSION

THE COMBINATION OF EEG, SSEP, and NSE blood levels has been considered to be effective for predicting level of consciousness of patients after cardiac arrest.[2] They

are not tests that can are readily available globally[3] and are difficult to carry out.[4] Instead, in recent years, studies have shown that pupillometer measurements are useful for predicting the level of consciousness after cardiac arrest.[5–8] Serum NSE level is considered to reflect brain axonal damage.[9] Background EEG reactivity to pain is considered to be a strong predictor of prognosis of consciousness after cardiac arrest.[10–13] The bilateral absence of N20 waves on SSEP is known to be a poor consciousness prognostic factor. However, as mentioned above, these are not quantitative tests but require skills for interpretation, and are not tests that can be easily carried out worldwide. It is also difficult to determine an appropriate cut-off value for NSE levels. Based on a study showing that pupillometer measurements were effective for evaluating prognosis of consciousness in patients after cardiac arrest,[14] we investigated whether pupillometer measurements are also effective for evaluating GCS scores in patients with severe consciousness disorder, other than those caused by cardiac arrest. In this study, the mean pupil contraction velocity at the time of arrival at our hospital and the mean pupil contraction rate 48 h after arrival were useful to distinguish the GCS 3–13 group from the GCS 14–15 group, as the values were significantly different between the two groups. Pupillometer measurements were found to be effective for predicting GCS scores, also in patients other than those after cardiac arrest. There was a statistically significant difference between the sedative groups of the two GCS groups regarding pupil contraction rates and velocities at arrival, but there was no significant difference between the non-sedative groups, possibly due to the small number of patients. Pupillary contraction velocity at arrival was measured before sedation, and the value after 48 h might have been affected by sedation. There are reports that sedation reduces pupillary velocity.[15] Although there was no significant difference in pupillary contraction rates and velocities between the two GCS groups, pupillary contraction rates 48 h after arrival at hospital tended to be higher in the GCS 14–15 group. Intracranial diseases could directly affect pupillary contraction rate and pupillary contraction velocity. As shown in Table 3, patients with intracranial and extracranial diseases were analyzed separately, and there were no statistically significant differences between the two GCS groups in the number of patients with intracranial diseases and extracranial diseases. Patients were also analyzed regarding hospitalization days between the

Table 1. Baseline demographic characteristics and outcomes of patients with impaired consciousness brought to the emergency department, grouped according to Glasgow Coma Scale (GCS) score

Variable	GCS 3–13 group	GCS 14–15 group	*P*-value
Patients	16	19	–
Age, years; median (IQR)	75.19 (45–91)	63.74 (27–86)	0.041
Female sex, *n* (%)	7 (47.6)	12 (63.1)	–
Stroke patients	7	3	–
Psychiatric patients	0	1	–
Epilepsy patients	2	3	–
Drug abuse patients	1	2	–
COPD patients	1	0	–
Hypothermia patients	1	0	–
Aortic dissection patients	1	0	–
Head injury patients	0	6	–
Sepsis patients	3	2	–
Hemorrhagic shock patients	0	2	–

Values are shown as *n*, unless otherwise specified
–, not significant; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

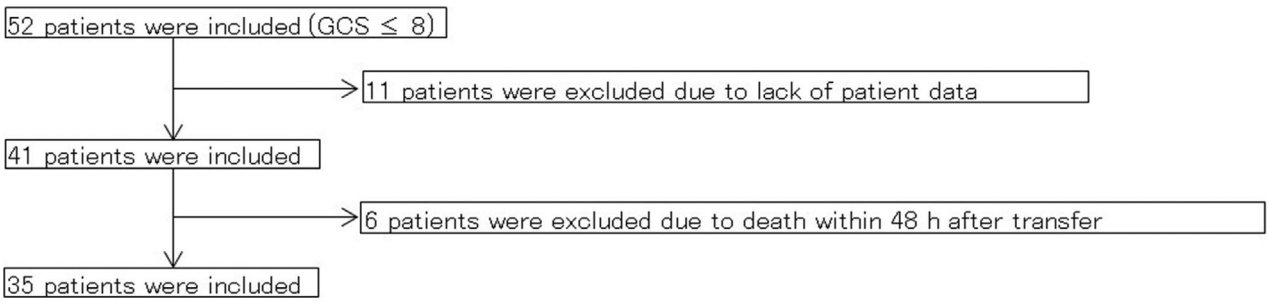

Fig. 1. Flowchart of patients with impaired consciousness brought to the emergency department, selected for this study. Eleven patients were excluded due to lack of sufficient data, and six patients were excluded due to death within 48 h after arrival at our hospital. The data of 35 patients were analyzed. GCS, Glasgow Coma Scale.

Table 2. Comparison of pupillometry test results between patients with impaired consciousness brought to the emergency department, grouped according to Glasgow Coma Scale (GCS) score

Variable	GCS 3–13	GCS 14–15	*P*-value	Cut-off value
Non-sedative group (*n* = 27)				
On arrival at hospital				
Contraction rate, %	18.36	19.67	0.739	21.5
Contraction velocity, mm/s	1.02	1.48	0.182	1.50
48 h after arrival at hospital				
Contraction rate, %	21.18	29.27	0.058	24.5
Contraction velocity, mm/s	1.37	1.91	0.172	1.57
Sedative group (*n* = 8)				
On arrival at hospital				
Contraction rate, %	8.75	19.75	0.032	19.0
Contraction velocity, mm/s	0.34	1.48	0.001	0.91
48 h after arrival at hospital				
Contraction rate, %	13.5	13.5	1.00	14.5
Contraction velocity, mm/s	0.80	0.82	0.93	0.88

two GCS groups, because GCS scores could change depending on the timing of consciousness judgment. As shown in Table 4, there was no statistically significant difference regarding hospitalization days between the two GCS groups. In addition, as the number of patients analyzed was small in this study, it is necessary to analyze more patients in the future. Our results indicate that pupillometer measurements are useful for predicting the level of consciousness of patients in emergency and critical care centers. The pupillometer is a non-invasive device for patients that can be easily used by anyone, hence we believe that it will be used more widely in the future.

LIMITATIONS

IN THIS STUDY, we analyzed GCS scores of patients with severe consciousness disorder due to various causes other than cardiac arrest using pupillometer measurements, although surgery could change a patient's GCS score. As shown in Table 1, there was a statistically significant difference in age between the two GCS groups, so age might

Table 3. Sensitivities and specificities of each parameter for predicting the level of consciousness

Variable	Sensitivity (%)	Specificity (%)
Non-sedative group (*n* = 27)		
On arrival at hospital		
Constriction rate, %	46.7	70.0
Constriction velocity, mm/s	57.1	72.7
48 h after arrival at hospital		
Constriction rate, %	66.7	60.0
Constriction velocity, mm/s	60.0	60.0
Sedative group (*n* = 8)		
On arrival at hospital		
Constriction rate, %	50.0	100
Constriction velocity, mm/s	100	100
48 h after arrival at hospital		
Constriction rate, %	50.0	50.0
Constriction velocity, mm/s	75.0	75.0

Table 4. Comparison of the number of patients with intracranial diseases and extracranial diseases among patients with impaired consciousness brought to the emergency department, grouped according to Glasgow Coma Scale (GCS) score

	GCS 3–13 (*n*)	GCS 14–15 (*n*)	Total (*n*)
Patients with intracranial diseases	9	13	22
Patients with extracranial diseases	7	6	13
Test of difference in hospitalization days *P*-value = 0.458			

Table 5. Comparison of hospitalization days between patients with impaired consciousness brought to the emergency department, grouped according to Glasgow Coma Scale (GCS) score

	GCS 3–13	GCS 14–15	*P*-value
Hospitalization days	32.81	20.50	0.21

affect the GCS scores. As the number of patients analyzed in this study was small, it is necessary to consider increasing the number of patients in the future.

CONCLUSIONS

THE PUPILLARY CONTRACTION rate and pupillary velocity measured using a pupillometer might be useful for predicting the level of consciousness of patients with severe consciousness disorder, even those other than after cardiac arrest. Furthermore, additional cases need to be collected and analyzed to confirm our results.

DISCLOSURE

APPROVAL OF THE research protocol: The study protocol was approved by the ethics committee of Tokyo Medical University (study approval no. T2019-0247).

Informed consent: Informed consent was obtained from all individual participants included in the study. We obtained comprehensive consent in writing from all patients, and revealed the information of this study.

Registry and registration no. of the study/trial: This study was registered in the UMIN Clinical Trial Registry (UMIN000040000).

Animal studies: N/A.

Conflict of interest: None.

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