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ORIGINAL WORK

Neurological Pupil Index as an Indicator of Neurological Worsening in Large Hemispheric Strokes

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Abstract

Background/Objective: Cerebral herniation due to brain edema is the major cause of neurological worsening in patients suffering large hemispheric strokes. In this study, we investigated whether quantitative pupillary response could help identify the neurological worsening due to brain swelling in patients with large hemispheric strokes.

Methods: Quantitative pupillary assessment using an automated pupillometer (NPi-100) was performed between April 2017 and August 2019 for patients suffering large hemispheric strokes. Consecutive pupillary responses were measured every 2 or 4 h as a part of routine clinical care. We compared the mean neurological pupil index (NPi) values, NPi value at the time of neurological deterioration, and percentage change in NPi from the immediate previous value between patients with and without neurological worsening.

Results: In this study, 2442 quantitative pupillary assessments were performed ($n = 30$; mean age, 67.9 years; males, 60.0%). Among the included patients, 10 (33.3%) experienced neurological worsening. Patients with neurological worsening had a significantly lower mean value of NPi and a sudden decrease in the NPi value as compared to those without neurological worsening during the whole monitoring period (3.88 ± 0.65 vs. 4.45 ± 0.46, $P < 0.001$; and 29.5% vs. 11.1%, $P = 0.006$, respectively). All patients with NPi values below 2.8 showed neurological deterioration.

Conclusions: Quantitative monitoring of the pupillary response using an automated pupillometer could be a useful and noninvasive tool for detecting neurological deterioration due to cerebral edema in large hemispheric stroke patients.

Keywords: Neurological pupil index, Neurological worsening, Large hemispheric stroke

Introduction

Patients suffering a large hemispheric stroke are prone to neurological deterioration that often leads to poor neurological outcomes [1, 2]. The main causes of neurological worsening in these patients are brain edema and concomitant intracranial hypertension, regardless of the ischemic or hemorrhagic origin [1–4]. Pupillary light reflex (PLR) is an important neurological examination that reflects subtle changes in intracranial pressure (ICP) due to brain swelling [5–7]. Therefore, serial assessment of PLR has been routinely performed in the neurological intensive care unit (NICU) for the early detection and possible mitigation of secondary brain injury from the ICP crisis [6, 8–10]. Recent studies showed that quantitative assessment of the PLR using an automated pupillometer provided accurate information for managing patients with an elevated ICP [10–13]. There was an inverse correlation between the neurological pupillary index (NPi)

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and midline shift or transtentorial herniation observed on brain imaging in patients with traumatic brain injury, cardiac arrest, and ischemic stroke [8, 10, 13–16]. However, most comparisons were made between the NPi and radiological or ICP values, regardless of the clinical information on neurological deterioration. Therefore, we aimed to investigate the association between changes in PLR using pupillometer and neurological worsening in large hemispheric stroke patients.

Methods

Study Population

Between April 2017 and August 2019, we retrospectively screened 51 patients admitted to our NICU for the diagnosis of ischemic or hemorrhagic stroke, who were evaluated using the pupillometer. Patients were excluded for the following reasons: (1) posterior circulation stroke ($n=3$) and (2) any missing values in serial PLR data ($n=18$). Finally, 30 patients with anterior circulation stroke were included for the analyses (Fig. 1). The present-study protocol was approved by the institutional review board (IRB no. H-1009-062-332).

Assessment of Pupillary Reflex Using an Automated Quantitative Pupillometer

Bilateral pupillary examinations were performed using an automated pupillometer (NPi-100 Pupillometer, NeurOptics Inc., Irvine, CA, USA) every 2 h by the ICU nurses or neurointensivists on service depending on the neurological severity of the patients. When the patients were neurologically stable, pupillary examinations were repeated every 4 h. The NPi value was automatically standardized on a scale of 0–5. Generally, the NPi value below 3 indicates an abnormal PLR and greater value suggests better PLR [13–16]. The NPi values and percentage change of NPi calculated from the immediate previous values were collected for the analysis [17–19]. In patients with neurological worsening, the percentage change of NPi was obtained at the time of neurological deterioration, whereas in those without neurological worsening, the highest percentage change value was calculated from the whole monitoring data. For sensitivity analysis, we also measured conventional pupillary reactivity and classified it into three categories: prompt (brisk, normal), sluggish (abnormal), and fixed (non-reactive), and compared it with the NPi values at the timing of neurological deterioration. While monitoring the NPi values and the conventional pupillary reactivity, we used those values for clinical decision making in included patients during the NICU care.

Baseline Characteristics and Clinical Information

Baseline characteristics, including demographics (age and sex) and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, history of stroke/transient ischemic attack, coronary artery disease, atrial fibrillation, and smoking), were obtained. Furthermore, we assessed the diagnoses of patients at the time of NICU admission and thrombolytic therapy (intravenous thrombolysis, with or without endovascular recanalization therapy). We also evaluated other patient management protocols, such as targeted temperature management and craniectomy/craniotomy, and the sedative agents (midazolam, remifentanil, dexmedetomidine, and propofol) administered during the NICU care. Midline shift was assessed using brain computerized tomography (CT) with axial slices of 3 mm thickness and was determined

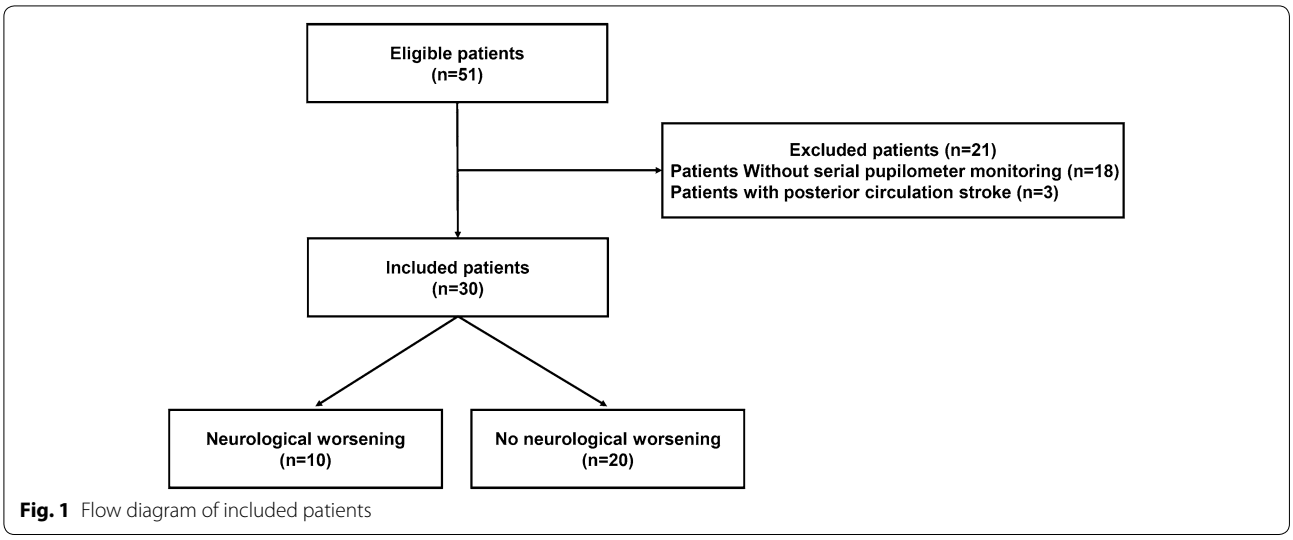

Fig. 1 Flow diagram of included patients

by measuring the distance from the midline to the septum pellucidum, as previously described [20, 21].

Neurological assessment was performed using the National Institute of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS) during the NICU hospitalization. All patients were examined for the severity of neurological symptoms based on the NIHSS and the GCS by specialized nurses or neurointensivists, every 4 h in the NICU at least. Neurological worsening was defined as a worsening of total NIHSS ≥ 4 points while admitted in the NICU [22, 23]. The patients were categorized into two groups based on the presence or absence of neurological worsening.

Statistical Analyses

Continuous variables were compared using the Student's *t* tests or Mann–Whitney's *U* test, and proportions of categorical variables were compared using Pearson's χ^2 tests or Fisher's exact test according to the neurological worsening outcome as appropriate. Data were presented as mean ± standard deviation or as median with interquartile range (IQR) according to the data distribution. For all analyses, a two-tailed *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (version 25.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 8, GraphPad Software, San Diego, CA, USA).

Results

In this study, 2442 quantitative pupillary assessments were performed for the included patients ($n = 30$; mean age, 67.9 years; males, 60.0%). The median duration of monitoring was 168.0 h (IQR [114–252.5]), and the median numbers of pupillary assessments were 48 (IQR [13.5–107.0]). Among the included patients, 10 patients (33.3%) experienced neurological worsening in the NICU. There was no statistical difference with respect to age, sex, vascular risk factors, or stroke severity as measured by the NIHSS between the patients with and without neurological worsening (Table 1). Additionally, there was no statistically significant difference between the two groups in terms of the stroke subtypes or the proportion of patients with sedatives (Table 1). During the total monitoring period, the mean value of NPi, regardless of the side of the lesion, was significantly lower in groups with neurological worsening than in those without neurological worsening (3.88 ± 0.65 vs. 4.45 ± 0.46,

Table 1 Clinical characteristics of study population

	Total ($n = 30$)	Neurological worsening ($n = 10$, 33.3%)	No neurological worsening ($n = 20$, 66.7%)	*P* value
Age (mean ± SD), years	67.9 ± 15.6	66.9 ± 13.2	64.5 ± 16.6	0.799
Male, *n* (%)	18 (60.0)	5 (50.0)	13 (65.0)	0.461
Hypertension, *n* (%)	13 (43.3)	4 (40.0)	9 (45.9)	1.000
Diabetes mellitus, *n* (%)	10 (33.3)	5 (50.0)	5 (25.0)	0.231
Hyperlipidemia, *n* (%)	6 (20.0)	2 (20.0)	4 (30.0)	1.000
Coronary artery disease, *n* (%)	5 (16.7)	2 (20.0)	3 (15.0)	1.000
Atrial fibrillation, *n* (%)	12 (40.0)	4 (40.0)	8 (40.0)	1.000
Previous stroke/TIA, *n* (%)	11 (36.7)	2 (20.0)	9 (45.0)	0.246
Smoking, *n* (%)	8 (26.7)	4 (40.0)	4 (20.0)	0.384
Initial NIHSS, median (IQR)	20.5 (13.75–24.25)	16.5 (9.25–23.0)	21.5 (16.75–24.75)	0.131
Initial GCS, median (IQR)	9.5 (7–12)	10.5 (8.0–13.0)	9 (7–11)	0.198
Stoke subtypes, *n* (%)				0.101
Ischemic stroke	20 (66.7)	9 (90.0)	11 (55.0)	
ICH	10 (33.3)	1 (10.0)	9 (45.0)	
Thrombolytic therapy among the ischemic strokes, *n* (%)				0.890
IV thrombolysis	5 (25.0)	3 (33.3)	2 (18.2)	
ERT	2 (10.0)	1 (11.1)	1 (9.1)	
Combined IV thrombolysis with ERT	1 (5.0)	0 (0.0)	1 (9.1)	
Craniotomy/craniectomy, *n* (%)	11 (36.7)	5 (50.0)	6 (33.3)	0.425
Targeted temperature management, *n* (%)	6 (20.0)	3 (30.0)	3 (15.0)	0.372
Sedative drugs, *n* (%)	11 (36.7)	5 (50.0)	6 (30.0)	0.425

ERT endovascular recanalization therapy, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *IV* intravenous, *NIHSS* National Institute of Health Stroke Scale, *SD* standard deviation, *TIA* transient ischemic attack

$P < 0.001$) (Table 2). Moreover, the lowest NPi value ipsilateral to the lesion was significantly lower in patients with neurological worsening compared to those without neurological worsening (2.9 [IQR 1.4–3.7] vs. 4.1. [IQR 3.2–4.2], $P = 0.009$). Likewise, contralateral NPi values were lower in patients with neurological worsening compared to those without neurological worsening (3.5 [IQR 1.8–4.2] vs. 4.2 [IQR 3.5–4.5], $P = 0.031$). However, the absolute NPi values were higher on the contralateral side compared to the ipsilateral side in the neurological worsening group. Regarding the percentage changes of NPi, the ipsilateral NPi decreased by 29.5% (median, IQR [20.0–66.1]) at the time of neurological deterioration as compared to the immediate previous measurements in patients with neurological worsening, which was higher compared to those in patients without neurological worsening (29.5% vs. 11.1%, $P = 0.006$). Moreover, the contralateral NPi decreased by 18.7% (median, IQR [5.7–54.0]) in the neurological worsening group as compared to the 8.7% decrease observed in patients without neurological worsening and was not statistically significant (Table 2). Furthermore, all patients with NPi values below 2.8 had neurological worsening regardless of the side of the lesion, whereas no patients in groups without neurological worsening had NPi values below 2.8 (Fig. 2). Moreover, there was a sudden drop in NPi values when neurological deterioration occurred (Supplementary Figure 1). The individual values of NPi at the time of neurological deterioration are summarized in Table 3. Among the patients with neurological worsening, 80% showed significant changes in the NPi values when neurological deterioration occurred (Table 3). Although an automated pupillometer showed that all but one had reactive pupils regardless of the side of the lesion before the neurological

Table 2 The values of neurological pupil index according to neurological worsening

	Neurological worsening ($n = 10$, 33.3%)	No neurological worsening ($n = 20$, 66.7%)	*P* value
Total value of NPi during monitoring (mean ± SD)	3.82 ± 0.52	4.38 ± 0.50	< 0.001
Lowest value of NPi during monitoring on the ipsilateral side, median (IQR)	2.9 (1.4–3.7)	4.1 (3.2–4.2)	0.009
Lowest value of NPi during monitoring on the contralateral side, median (IQR)	3.5 (1.8–4.2)	4.2 (3.5–4.5)	0.031
Percent change of NPi from previous value in the ipsilateral side, median (IQR)	29.5 (20.0–66.1)	11.1 (5.7–25.0)	0.006
Percent change of NPi from previous value in the contralateral side, median (IQR)	18.7 (5.7–54.0)	8.7 (2.3–12.5)	0.050

IQR interquartile ranges; *NPi* neurological pupil index; *SD* standard deviation

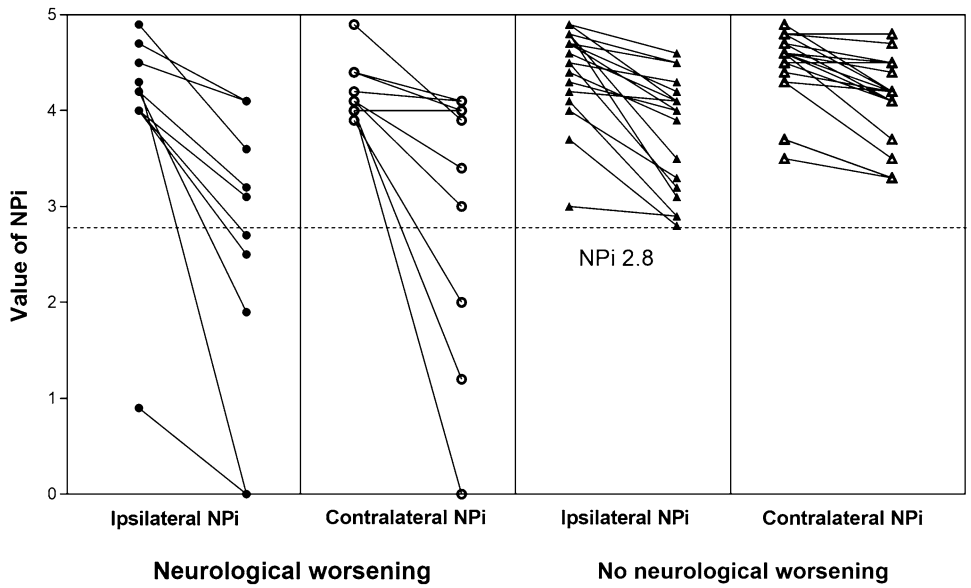

Fig. 2 Distributions of neurological pupil index (NPi) during monitoring periods after stroke onset according to neurological worsening. The scatterplots show individual NPi values during monitoring periods according to neurological worsening. The mean value of NPi, regardless of the side of the lesion, was 3.88 in the neurological worsening group and 4.45 in the group without neurological worsening. There was no patient with NPi values below 2.8 in group without neurological worsening

Table 3 Changes of neurological pupil index values and midline shift among the patients with neurological worsening

No.	Stroke types	Lesion side	NPi before neurological worsening (right/left)	NPi after neurological worsening (right/left)	Change of midline shift (mm)
1	Ischemic stroke	Right	4.3/4.4	0.0/4.0	12.7 → 17.5
2	Ischemic stroke	Right	4.2/4.0	1.9/1.2	10.7 → 14.5
3	Ischemic stroke	Right	4.9/4.9	3.6/3.6	4.2 → 8.2
4	Ischemic stroke	Left	4.5/4.7	4.4/4.1	2.1 → 13.3
5	Ischemic stroke	Bilateral	4.1/4.2	3.4/3.2	3.4 → 9.0
6	Hemorrhagic stroke	Left	3.9/4.0	2.0/2.7	0 → 1.9
7	Ischemic stroke	Right	4.0/4.1	2.5/3.0	0 → 9.0
8	Ischemic stroke	Right	4.5/4.2	4.1/4.1	4.5 → 11.7
9	Ischemic stroke	Bilateral	4.0/4.0	3.1/4.0	16.2 → 17.6
10	Ischemic stroke	Right	0.9/4.1	0/0	5.4 → 6.5

*Midline shift was assessed by measuring the distance from the midline to the septum pellucidum using brain CT

NPi neurological pupil index

deterioration, a conventional pupil examination using a penlight showed that seven patients were regarded as having reactive pupils on the ipsilateral to the lesions (Supplementary Table 1 and Figure 2). At the time of neurological deterioration, conventional light reflex could not accurately identify the changes in pupillary reactivity. Although an automated pupillometer identified one additional patient with an ipsilateral blown pupil, the patient was regarded as having a sluggish pupil on a penlight examination. Moreover, conventional examinations described that seven patients had still reactive pupils and two had sluggish responses. However, an automated pupillometer showed that only five patients had reactive pupils (Supplementary Table 1).

In patients without neurological worsening ($n=20$), three patients (15%) experienced with a sudden drop in the NPi values (ipsilateral side: mean ± SD, 28.4 ± 0.8%; contralateral side: mean ± SD, 16.3 ± 3.4%) without aggravation of neurological examinations and recovered to the baseline on the next evaluation. Moreover, the NPi values were not influenced by the uses of sedatives and TTM (Supplementary Table 2 and Supplementary Table 3). It took about 10 min (median, IQR [5–14.25]) from a sudden drop in NPi to the detection of neurological deterioration in the neurological worsening group (the representative case in Supplementary Figure 2). Moreover, the time difference from neurological worsening to performing imaging studies (brain CT/magnetic resonance imaging) was 1.85 h (median, IQR [0.88–2.9]).

Discussion

This study showed that a sudden drop in NPi value below 2.8 was always associated with neurological worsening, regardless of the side of the lesion. Moreover, a percentage decrease in NPi by 30% as compared to the immediate previous assessment was associated with neurological worsening in patients suffering large hemispheric strokes.

The prognosis of large hemispheric stroke is usually dismal. Regardless of whether it is intracerebral hemorrhage or large ischemic stroke, the chances of favorable outcome at 6 months or 1 year are about 24%, even with the best medical therapy [1, 24]. Early management of brain swelling with decompressive surgery or osmotherapy is the main goal of the treatment protocol [1, 2, 4, 25–28]. PLR is the most important clinical neurological examination reflecting brain swelling and herniation in the NICU [5, 8, 29–33]. However, its poor inter-rater reliability stresses the need for a more objective and quantitative assessment tool [9, 33]. The automated pupillometer allows continuous assessment of various aspects of PLR [9, 11, 17, 30, 34, 35]. Among the variables of quantitative pupillary assessment, the NPi values are the least affected by sedatives. In addition, this study showed that the NPi values were not significantly influenced by the sedative drugs in consistent with previous studies [11–13, 18]. Several studies demonstrated a significant correlation between the NPi values and radiological midline shift or ICP values in patients with acute brain injuries [7–10, 13, 14, 16, 36]. However, they did not show a temporal association between the NPi change and clinical deterioration. Our study showed that there was a sudden drop in NPi values when neurological deterioration occurred (Supplementary Figure 1). Consistent with previous studies, patients with neurological worsening had lower NPi values compared to those without neurological worsening. Moreover, our results demonstrated that a sudden drop in the NPi value (by about

30% as compared to the immediate previous NPi value) was an important clue indicating neurological worsening in patients with hemispheric stroke. Fluctuations of the NPi value are frequently observed in serial monitoring, partly due to the circadian rhythm [37]. Even with biological fluctuations, any abrupt decrease in NPi of more than 30% was mostly always associated with neurological deterioration. Moreover, 15% of patients showed a sudden drop in the NPi values during the monitoring period in patients without neurological worsening. However, those values recovered within a short time (2–4 h) without any changes in neurological examinations.

In this study, 80% of the patients of the neurological worsening group had a significant decrease in the NPi value, accompanied by an aggravation of the midline shift with transtentorial herniation on brain CT. Two patients with neurological deterioration were not accompanied by a change in the NPi values because they developed new lesions mainly in the frontal lobes which did not have a direct effect on pupillary reactivity [13–16]. The sudden drop in NPi preceded neurological worsening, which triggered the brain imaging. Therefore, a quantitative pupillometer could be used in selecting patients who require brain imaging. Given that transportation of the patients out of the ICU is sometimes challenging and often leads to adverse events, a careful selection of the patients who need brain imaging using a pupillometer will have a high clinical impact [38–40]. Therefore, close monitoring of their neurological status, including pupillary response using pupillometer, could be useful for the evaluation of neurological worsening and the need for intervention in patients suffering large hemispheric strokes [9, 29].

Among the several definitions on the neurological deterioration using NIHSS, we defined it as an aggravation of NIHSS $\geq$ 4 points due to high specificity with low chance of false sensitivity. If we change the definition as a deterioration of NIHSS $\geq$ 2, 43.3% of the patients (13 out of 30) were categorized as having the neurological deterioration, and 23.1% (3 out of 13) of patients recovered within hours without permanent neurological damage. Therefore, we defined the neurological deterioration as a worsening of NIHSS $\geq$ 4 in the patients with severe stroke in consistent with previous studies [22, 23].

This study had several limitations. First, this was a single-center study conducted on a small number of patients. Second, we could not adjust the effect of osmotic therapy on the NPi or the midline shift on brain imaging in patients with neurological deterioration. Most osmotic therapies were administered when NIHSS deteriorated $\geq$ 4 points with a concomitant drop in the NPi values. Then, the patients were sent for brain imaging. Therefore, NPi values were measured before the administration of osmotic therapy. Although there is a possibility that the use of osmotic therapy may have reduced the midline shift, the correlation between NPi values and neurological deterioration did not change. Third, several patients were treated with sedatives and this might have affected the pupillary reactivity. However, we chose the NPi values for a comparison, because the NPi values are the least modified by sedatives compared to other parameters including constriction, dilatation velocity, or pupil size. [11–13]. Moreover, the two groups did not differ in terms of the uses of sedatives, and the effect of sedative drugs on the changes of NPi according to neurological worsening was not significant in this study.

Conclusion

In conclusion, our study suggests that a significant and sudden drop of NPi can be an indicator of neurological worsening due to brain edema in patients suffering large hemispheric strokes. Furthermore, serial quantitative PLR could be a helpful tool for monitoring using the automated pupillometer in patients at risk of cerebral edema. Further researches should be conducted to confirm the true relationship between changes in NPi values and the outcomes in neurocritically ill patients.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-00936-0) contains supplementary material, which is available to authorized users.

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Authors' Contributions
S-BK contributed to the study concept and design. JEK, H-SK, and WSC contributed to the study concept. TJK, S-HP, H-BJ, and EJH contributed to data collection. TJK, S-HP, and S-BK analyzed the result and drafted the manuscript. All authors read and approved the manuscript.

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Availability of Data and Materials

Data supporting the findings of this study are available from the corresponding author (Pf. Sang-Bae Ko) on reasonable request.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent
This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB no. H-1009-062-332), and we obtained the informed consent from the included patients. The need for informed consent was waived by the IRB.

Consent for Publication
All authors have read and approved the submitted manuscript and publication.

Publisher's Note

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References

1. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6(3):215–22.
2. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant'middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53(4):309–15.
3. Siegler JE, Samai A, Semmes E, Martin-Schild S. Early neurologic deterioration after stroke depends on vascular territory and stroke etiology. J Stroke. 2016;18(2):203–10.
4. Qureshi AI, Suarez JI, Yahia AM, Mohammad Y, Uzun G, Suri MFK, et al. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. Crit Care Med. 2003;31(1):272–7.
5. Choi SC, Narayan RK, Anderson RL, Ward JD. Enhanced specificity of prognosis in severe head injury. J Neurosurg. 1988;69(3):381–5.
6. Hoffmann M, Lefering R, Rueger J, Kolb J, Izbicki J, Ruecker A, et al. Pupil evaluation in addition to Glasgow Coma Scale components in prediction of traumatic brain injury and mortality. Br J Surg. 2012;99(S1):122–30.
7. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. Surg Neurol Int. 2011;2:82.
8. Papangelou A, Zink EK, Chang WW, Frattalone A, Gergen D, Gottschalk A, et al. Automated pupillometry and detection of clinical transtentorial brain herniation: a case series. Mil Med. 2018;183(1–2):e113–21.
9. Park JG, Moon CT, Park DS, Song SW. Clinical utility of an automated pupillometer in patients with acute brain lesion. J Korean Neurosurg Soc. 2015;58(4):363–7.
10. Stevens AR, Su Z, Toman E, Belli A, Davies D. Optical pupillometry in traumatic brain injury: neurological pupil index and its relationship with intracranial pressure through significant event analysis. Brain Inj. 2019;33(8):1032–8.
11. Larson MD, Behrends M. Portable infrared pupillometry: a review. Anesth Analg. 2015;120(6):1242–53.
12. Rollins MD, Feiner JR, Lee JM, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. Anesthesiology. 2014;121(5):1037–44.
13. Tamura T, Namiki J, Sugawara Y, Sekine K, Yo K, Kanaya T, et al. Quantitative assessment of pupillary light reflex for early prediction of outcomes after out-of-hospital cardiac arrest: a multicentre prospective observational study. Resuscitation. 2018;131:108–13.
14. Suys T, Bouzat P, Marques-Vidal P, Sala N, Payen J-F, Rossetti AO, et al. Automated quantitative pupillometry for the prognostication of coma after cardiac arrest. Neurocrit Care. 2014;21(2):300–8.
15. Osman M, Stutzman SE, Atem F, Olson D, Hicks AD, Ortega-Perez S, et al. Correlation of objective pupillometry to midline shift in acute stroke patients. J Stroke Cerebrovasc Dis. 2019;28(7):1902–10.
16. McNett M, Moran C, Janki C, Gianakis A. Correlations between hourly pupillometer readings and intracranial pressure values. J Neurosci Nurs. 2017;49(4):229–34.
17. Zhao W, Stutzman S, DaiWai O, Saju C, Wilson M, Aiyagari V. Inter-device reliability of the NPi-100 pupillometer. J Clin Neurosci. 2016;33:79–82.
18. Oddo M, Sandroni C, Citerio G, Miroz JP, Horn J, Rundgren M, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med. 2018;44(12):2102–11.
19. Couret D, Boumaza D, Grisotto C, Triglia T, Pellegrini L, Ocquidant P, et al. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. Crit Care. 2016;20(1):99.
20. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. N Engl J Med. 1986;314(15):953–8.
21. Quattrocchi KB, Prasad P, Willits NH, Wagner FC Jr. Quantification of midline shift as a predictor of poor outcome following head injury. Surg Neurol. 1991;35(3):183–8.
22. Lord AS, Gilmore E, Choi HA, Mayer SA, VISTA-ICH Collaboration. Time course and predictors of neurological deterioration after intracerebral hemorrhage. Stroke. 2015;46(3):647–52.
23. Siegler JE, Martin-Schild S. Early Neurological Deterioration (END) after stroke: the END depends on the definition. Int J Stroke. 2011;6:211–2.
24. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97.
25. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY) a randomized, controlled trial. Stroke. 2007;38(9):2518–25.
26. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(4):1222–38.
27. Koenig M, Bryan M, Lewin J, Mirski MA, Geocadin R, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70(13):1023–9.
28. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, HAMLET investigators. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre open randomised trial. Lancet Neurol. 2009;8(4):326–33.
29. Yamamoto H, Bogousslavsky J, van Melle G. Different predictors of neurological worsening in different causes of stroke. Arch Neurol. 1998;55(4):481–6.
30. Kim TJ, Ko S-B. Implication of neurological pupil index for monitoring of brain edema. Acute Crit Care. 2018;33(1):57–60.
31. Kernohan JW, Woltman HW. Incisura of the crus due to contralateral brain tumor. Arch NeurPsych. 1929;21(2):274–87.
32. Skoglund T, Nellgård B. Long-time outcome after transient transtentorial herniation in patients with traumatic brain injury. Acta Anaesthesiol Scand. 2005;49(3):337–40.
33. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater reliability of pupillary assessments. Neurocrit Care. 2016;24(2):251–7.
34. Chen JW, Vakil-Gilani K, Williamson KL, Cecil S. Infrared pupillometry, the Neurological Pupil index and unilateral pupillary dilation after traumatic brain injury: implications for treatment paradigms. Springerplus. 2014;3(1):548.
35. Heimburger D, Durand M, Gaide-Chevronnay L, Dessertaine G, Moury P-H, Bouzat P, et al. Quantitative pupillometry and transcranial Doppler measurements in patients treated with hypothermia after cardiac arrest. Resuscitation. 2016;103:88–93.
36. Shoyombo I, Aiyagari V, Stutzman SE, Atem F, Hill M, Figueroa SA, et al. Understanding the relationship between the neurologic pupil index and constriction velocity values. Sci Rep. 2018;8(1):6992.
37. Natzeder S, Mack DJ, Maissen G, Strässle C, Keller E, Muroi C. Portable infrared pupillometer in patients with subarachnoid hemorrhage: prognostic value and circadian rhythm of the neurological pupil index (NPi). J Neurosurg Anesthesiol. 2019;31(4):428–33.
38. Fan J-S, Chen Y-C, Huang H-H, Yen DH-T, How C-K, Huang M-S. Interhospital transfer neurological deterioration in patients with spontaneous intracerebral haemorrhage: incidence and risk factors. Postgrad Med J. 2017;93:349–53.
39. Jia L, Wang H, Gao Y, Liu H, Yu K. High incidence of adverse events during intra-hospital transport of critically ill patients and new related risk factors: a prospective, multicenter study in China. Crit Care. 2016;20(1):12.
40. Knight P, Maheshwari N, Hussain J, Scholl M, Hughes M, Papadimos T, et al. Complications during intrahospital transport of critically ill patients: focus on risk identification and prevention. Int J Crit Illn Inj Sci. 2015;5(4):256–64.