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Clinical paper

Relationship between optic nerve sheath diameter measured by magnetic resonance imaging, intracranial pressure, and neurological outcome in cardiac arrest survivors who underwent targeted temperature management

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Abstract

Aim: Studies on the prognostic performance of optic nerve sheath diameter (ONSD) in out-of-hospital cardiac arrest survivors (OHCA) have reported conflicting results. We aimed to investigate the usefulness of ONSD measured using magnetic resonance imaging (MRI) to estimate its association with intracranial pressure (ICP) and 6-month neurological outcomes in CA survivors treated with targeted temperature management (TTM).

Method: This retrospective study included 37 CA survivors who underwent TTM from January 2018 to December 2018. ICP was measured by lumbar catheter during TTM on Days 0, 1, 2, and 3. ONSD was measured using MRI on Days 0 and 3. The primary outcome was the correlation between ONSD and ICP associated with neurological outcomes obtained after 6 months.

Results: The median (interquartile range [IQR]) ONSD was not significantly different between the good and poor neurological outcome group on Day 0 (5.2 mm [4.8−5.8] vs 5.2 mm [4.8−5.6]; $p = 0.948$) and Day 3 (5.0 mm [4.8−5.2] vs 5.5 mm [4.4−5.9]; $p = 0.105$). ONSD and ICP had excellent correlation on Day 3 ($r = 0.90$, $p < 0.001$). ONSD showed excellent correlation with increased ICP (IICP) defined as ICP above 20 mmHg ($r = 0.89$, $p < 0.001$). ONSD cut-off of 5.99 mm was used with a sensitivity of 90.0% and specificity of 98.0% to identify IICP.

Conclusion: The ONSD on Days 0 or 3 did not show differences in neurological outcomes in OHCA patients treated with TTM. However, ONSD had an excellent correlation with ICP on Day 3 and with IICP. Further studies are required to confirm our results.

Keywords: Out-of-hospital cardiac arrest, Prognosis, Optic nerve, Intracranial pressure, Magnetic resonance image

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Introduction

Interrupted blood flow to the brain even for a few minutes causes significant brain damage via cytotoxic and vasogenic mechanisms.[1] Therefore, cerebral oedema in hypoxic-reperfusion brain injury inevitably occurs after cardiac arrest (CA) with successful return of spontaneous circulation (ROSC).[2] High mortality and poor neurological outcomes are still major problems for CA patients, despite aggressive resuscitation and critical care.[3]

Increased intracranial pressure (ICP) due to cerebral oedema has contributed to the decreasing cerebral blood flow as well as poor neurological outcomes.[4,5] Meanwhile, targeted temperature management (TTM) has been proven in stabilising ICP and improving neurological outcomes for CA survivors.[6,7] At the same time, various factors for predicting neurological outcome have been investigated in several studies to provide information supporting appropriate treatment and communication between physicians and families.

Among these various factors, the optic nerve sheath diameter (ONSD) has been reported as a useful prognostic factor in CA survivors, because ONSD is a known parameter to reflect ICP.[8–10] A meta-analysis has revealed the usefulness of ONSD in predicting neurological outcomes in CA survivors.[11] On the contrary, Lee et al. have reported that ONSD has no correlation with neurological outcomes in CA survivors who underwent TTM.[12] Many studies investigating the value of ONSD as a prognostic factor have reported conflicting results due to methodological difference, type of imaging modality, and timing of measuring ONSD.

Sonography is considered an easy tool to measure ONSD, as it is simple, effective, and a real-time modality.[13] However, sonography has some methodological limitations, such as variability of image quality and measurement techniques.[14] Meanwhile, magnetic resonance imaging (MRI) is reported to be statistically superior to sonography in the measurement of ONSD to reflect increased ICP because MRI has greater accuracy, reliability, objectivity, and lower observer-dependent variation.[15–17] Furthermore, Kimberly and Noble presented MRI as a potential reference standard tool for ONSD measurement in certain settings.[18] We aimed to investigate the usefulness of serial ONSD on MRI to estimate its association with time-sequential values of ICP measured by lumbar catheter and 6-month neurological outcomes in CA survivors treated with TTM.

Methods

Study design and population

This was a retrospective observational study using prospectively collected data of comatose out-of-hospital cardiac arrest (OHCA) survivors treated with TTM at the Chungnam National University Hospital (CNUH) in Daejeon, Korea, from January to December in 2018. This study was approved by CNUH Institutional Review Board (CNUH 2019-04-003). This study was conducted partly concurrent to a previous study which was approved by the IRB of CNUH (CNUH 2017-10-027).[13] Hence, 17 patients overlapped with those in that study. However, these studies were independently designed with different groups of patients, since the methodological approach and criteria applied were different for both studies.

OHCA patients >18 years old who had undergone TTM were included in this study. Patients were subsequently excluded if they (2) had pre-arrest cognitive impairment, (3) had experienced CA due to trauma, (4) had TTM interrupted due to transfer to another hospital or unstable haemodynamics, (5) were ineligible for TTM (i.e. brain haemorrhage, active bleeding, known terminal illness, or poor pre-arrest neurological status), (6) were ineligible for lumbar catheter placement (e.g. observed severe brain oedema in imaging study such as pseudo-subarachnoid haemorrhage, visible intracranial mass, no consent from the family), and (7) were ineligible for brain MRI (e.g. extracorporeal membrane oxygenation, metal device implanted in the body, unable to provide consent).

TTM protocol

Patients were managed according to a previously published TTM protocol.[19] TTM was induced with ice packs, intravenous cold saline, and TTM devices, namely, Arctic Sun® and Energy Transfer Pads™ (Medivance Corp, Louisville, CO, USA). A target temperature of 33 °C or 36 °C was maintained for 24 h and monitored with a bladder probe. After completion of the TTM maintenance phase, patients were rewarmed at a rate of 0.25 °C per hour following normothermia until 72 h after ROSC. Midazolam (0.05 mg/kg intravenous bolus, followed with a titrated intravenous continuous infusion between 0.05 and 0.2 mg/kg/h) and cisatracurium (0.15 mg/kg intravenous bolus, followed with an infusion up to 0.3 mg/kg/h) were administered for sedation and control of shivering. All patients received standard intensive care according to our institutional intensive care unit protocol.

Measurement of ICP and ONSD

The procedure was performed with the patient lying in the lateral decubitus position with the neck, hips, and knees flexed. The lumbar catheter was inserted using a Hermetic™ lumbar accessory kit (Integra Neurosciences, Plainsboro, NJ, USA) under aseptically guided sonography by an expert physician, and ICP was continuously measured using LiquoGuard® pump system (Möller-Medical, Fulda, Germany) and recorded on Days 0, 1, 2, and 3. In all patients, ICP was measured in millimetres of mercury (mmHg). In this study, the ICP on Day 0 was measured immediately after ROSC, and ICP on Days 1, 2, and 3 was measured after 24, 48, and 72 h from Day 0, respectively. We defined increased ICP (IICP) when ICP had been above 20 mmHg at any time of measurement (Days 0–3).

In all patients, MRI was performed using a 3T whole-body scanner (Ingenia, Philips Healthcare, Netherlands) at two points, that is, before the cooling stage and once normothermia was maintained on Days 0 and 3. The axial proton density/T2-weighted turbo spin-echo fat-suppressed sequence was used. Scanning parameters were as follows: repetition time, 3000 ms; echo time, 80 ms; slice thickness, 3 mm; and spacing between slices, 4 mm. The optic nerve sheath appeared as a high signal surrounding a region of low signal corresponding to the optic nerve (Fig. 1). Measurements were carried out by a neuro-radiologist who was well informed of the protocol and blinded to the patient's prognosis and ICP value. The retrobulbar area was zoomed 7.5 times enough to visualise the optic nerve sheath clearly, and the ONSD was then measured at 3 mm behind the globe.[17]

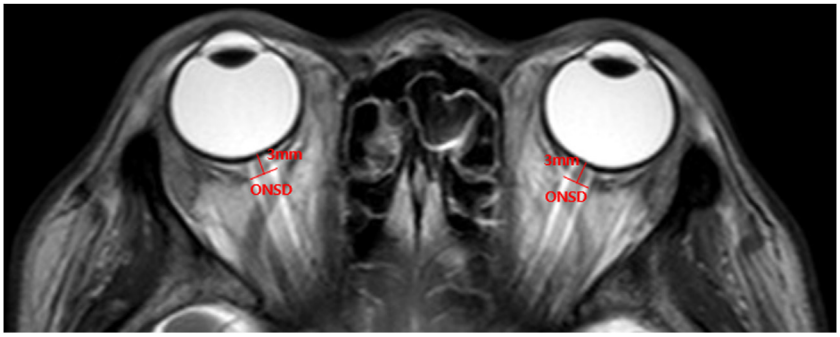

Fig. 1 – Magnetic resonance imaging (MRI)-measured ONSD 3 mm posterior to the inner scleral surface.

Neurological outcomes

The neurological status was obtained by assessing the hospital records of patients or interviewing the patients or patients' family on telephone. Neurological outcome was assessed using the Glasgow–Pittsburgh cerebral performance categories (CPC) scale at 6 months post-CA. The CPC scale was classified into CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death). A good neurological outcome was defined as a CPC of 1 or 2, and a poor neurological outcome was defined as a CPC of 3–5.

Data analysis

Categorical variables were presented as frequencies and percentages. Comparisons of categorical variables were performed using chi-squared or Fisher's exact tests. Continuous variables were reported as median and interquartile range (IQR). We used the Mann–Whitney U test to compare ONSD and ICP values between the neurological outcome groups. The correlation between ONSD and ICP was assessed by the Pearson correlation coefficient.

A receiver operating characteristics (ROC) curve analysis including cut-off values for the optimal area under the curve (AUC), sensitivity, and specificity was performed to identify the predictive performance of ONSD and IICP via MRI for CA survivors. An optimal cut-off value was defined as the point at which the value of 'sensitivity + specificity − 1' was at a maximum (Youden's index). Furthermore, intraclass correlation coefficients (ICCs) of 0–0.20 indicated poor correlation, 0.21–0.40 indicated fair correlation, 0.41–0.60 indicated moderate correlation, 0.61–0.80 indicated good correlation, and 0.81–1.00 indicated excellent correlation. Statistical analyses were performed using IBM SPSS statistics ver. 21.0 (IBM Corp., Armonk, NY, USA). ROC curves and sample size were calculated using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium). Results were considered significant at $p < 0.05$.

Results

Patient characteristics

A total of 43 OHCA comatose patients were treated with TTM. Among them, six were excluded from this study (Fig. 2). Patient demographics

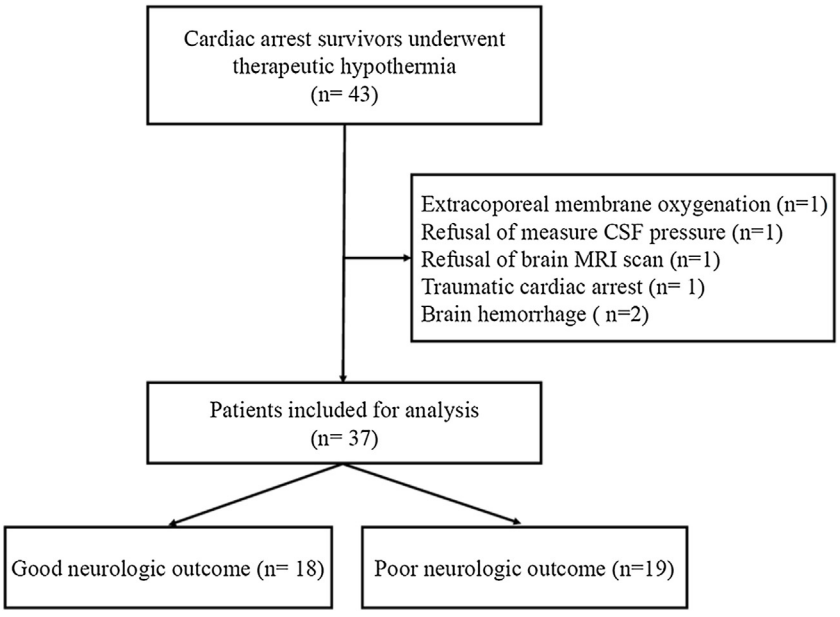

Fig. 2 – Flow diagram of patients included in the present study.

Table 1 – Baseline demographics and clinical characteristics.

	Total (n = 37)	Good outcome (n = 18)	Poor outcome (n = 19)	*p*
Age, years, median (IQR)	52.9 (27–83)	50.9 (27–83)	54.7 (31–83)	0.870
Male, n (%)	25 (65.6)	14 (77.8)	11 (57.9)	0.197
Cardiac arrest characteristics				
Witness, n (%),	23 (62.2)	13(72.2)	10(52.6)	0.219
Bystander CPR, n (%)	26 (70.3)	15(83.3)	11(57.9)	0.091
Shockable rhythm, n (%)	13 (35.1)	12(66.7)	1(5.3)	<0.001
Cardiac aetiology, n (%)	13 (35.1)	11(61.1)	2(10.6)	0.01
No flow time, min, median (IQR)	4.6 (0.0–54.0)	5.4 (0.0–30.0)	9.7 (0.0–54.0)	0.290
Low flow time, min, median (IQR)	20.0 (2.0–51.0)	12.4 (2.0–30.0)	27.2 (7.0–51.0)	0.005
GCS immediately after ROSC	3 (3–7)	3 (3–7)	3 (3–4)	0.020
Time to measure ICP on Day 0 from ROSC, hour, median (IQR)	4.9 (2.0–11.6)	4.6 (2.4–7.8)	5.2 (2.1–11.6)	0.331
Time to measure ONSD on Day 0 from ROSC, hour, median (IQR)	3.8 (1.3–3.0)	3.3 (1.3–6.9)	4.2 (1.3–13.0)	0.232

IQR, interquartile range; CPR, cardiopulmonary resuscitation; GCS, Glasgow coma scale; ROSC, restoration of spontaneous circulation; ICP, intracranial pressure; ONSD, optic nerve sheath diameter.

and clinical characteristics are shown in Table 1. Patients with good neurological outcomes have shown significantly higher number of shockable rhythms, cardiac aetiology, initial GCS score after ROSC, and shorter time of low flow.

Serial comparison of ICP and ONSD by neurological outcomes

The median ICP values were 10.5 mmHg (IQR: 9.3–11.6) versus 11.3 mmHg (IQR: 10.0–16.2) on Day 0, 10.5 mmHg (IQR: 9.1–11.3) versus 19.7 mmHg (IQR: 13.3–23.7) on Day 1, 13.5 mmHg (IQR: 11.8–16.6) versus 19.2 mmHg (IQR: 17.0–24.2) on Day 2, and 14.1 mmHg (IQR: 12.4–19.0) versus 17.4 mmHg (IQR: 14.9–21.9) on Day 3, for good versus poor neurological outcomes ($p = 0.144$, $p < 0.001$, $p = 0.004$, $p = 0.141$; Table 1), respectively.

The median ONSD values were 5.2 mm (IQR: 4.8–5.8) versus 5.2 mm (IQR: 4.8–5.6), and 5.0 mm (IQR: 4.8–5.2) versus 5.5 mm (IQR: 4.4–5.9), for good versus poor neurological outcomes on Days 0 and 3, respectively ($p = 0.948$, $p = 0.105$; Fig. 3).

Correlation between ONSD and ICP in each group

The correlation between ONSD and ICP was analysed on Days 0 and 3. Using coefficient of variation, there was excellent correlation between ONSD and ICP only on Day 3 ($r = 0.90$ $p < 0.001$; Fig. 4), but the ONSD has no significant correlation with ICP on Day 0 ($r = 0.13$ $p = 0.47$; Fig. 4).

Comparison of ONSD by the presence of IICP

IICP was observed in 10 individuals (13.5%), and all these IICP cases were observed on Day 3. The median ICP in the IICP group was 23.2 mmHg (20.9–26.5). The ONSD of individuals with IICP was significantly greater than that of the group without IICP (6.2 mm [5.1–6.5] vs 5.19 mm [4.8–5.6] $p = 0.015$; Fig. 5A). Interestingly, ONSD in cases with IICP showed more significant linear correlation with ICP compared to cases without IICP ($r = 0.89$ $p < 0.001$ vs $r = 0.14$ $p = 0.35$; Fig. 5B). The relative cut-off value of ONSD for identifying IICP (ICP > 20 mmHg) using ROC analysis was 5.99 mm, the AUC was 0.744 (95% confidence interval [CI]: 0.615–0.848), sensitivity was at 60.0% (95% CI: 26.2–87.8), and specificity was at 98.0% (95% CI: 89.4–99.9), as shown in Fig. 5C.

Discussion

This retrospective observational cohort study found that ONSD on MRI and ICP have an excellent correlation on Day 3 and in the group of patients that had IICP. The ICP on Days 1 and 2 was significantly higher in the poor outcome group. However, the ICP and ONSD on Days 0 and 3 did not show significant difference in neurological outcomes.

Since the CSF in the optic nerve sheath can move freely between the subarachnoid space of the intra-cranial and intra-orbital areas, CSF accumulation in the optic nerve sheath allows the ONSD to expand.[20,21] As a result, ONSD has been proven as a parameter for measuring ICP indirectly. However, Hansen and Helmke have

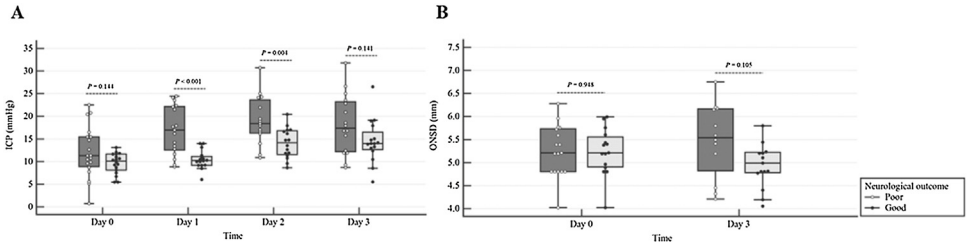

Fig. 3 – Comparison of the ICP (A) and ONSD (B) for different neurological outcomes at each time point. ICP, intracranial pressure; ONSD, optic nerve sheath diameter.

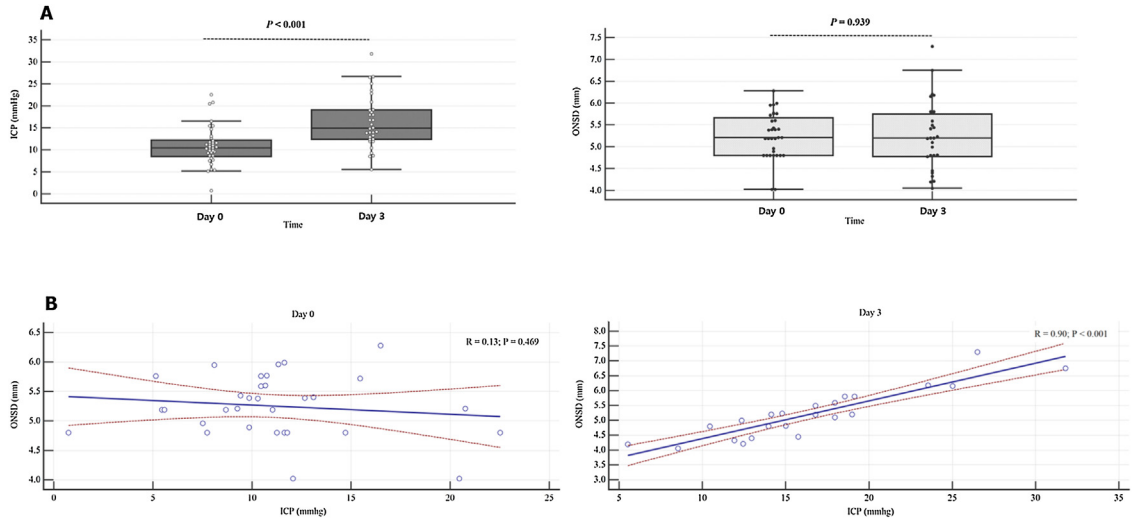

Fig. 4 – (A) Comparison of the ICP and ONSD between Days 0 and 3. (B) Correlation of the ICP and ONSD on Days 0 and 3. ICP, intracranial pressure; ONSD, optic nerve sheath diameter.

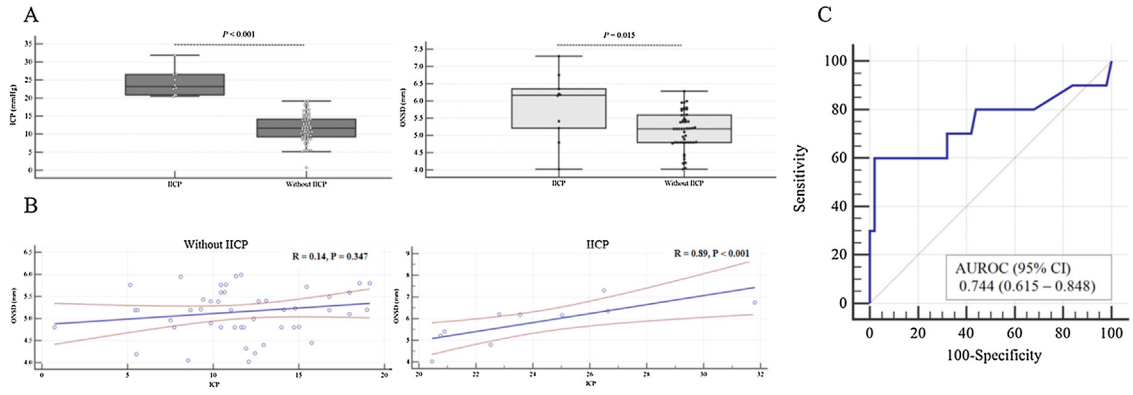

Fig. 5 – (A) Comparison of the ICP and ONSD associated with IICP. (B) Correlation of the ONSD with IICP and without IICP. (C) Receiver operating characteristic (ROC) analysis of the ONSD for expecting IICP.
ICP, Intracranial pressure; ONSD, Optic nerve sheath diameter; IICP, increased intracranial pressure above 20 mmHg.

disclosed that ONSD was not quantitatively associated with ICP.[22] Since the absence or very small changes in the ONSD were observed below the specific CSF pressure by using real-time sonography and CSF infusion test, they suggested that ONSD began to correlate with ICP at a specific value of ICP that might be considered as a threshold.[22] Furthermore, previous studies have reported an increase in ONSD when the ICP is above 13–14 mmHg.[23]

In this study, ONSD on Day 0 was not significantly different between neurological outcomes and poorly correlated with ICP on Day 0. These results suggest that the ICP on Day 0 was too low to affect ONSD and an early time to predict neurological outcomes. The ICP on Days 1 and 2 was different between neurological outcomes (Fig. 3A). If ONSD on Days 1 and 2 was measured, it might have had meaningful results in analysing the relationships between ONSD, ICP, and neurological outcomes. Additionally, the ONSD appeared higher in the poor neurological outcome group on Day 3 but was not significant. There are two possible explanations. First, the limited number of patients might have been a reason for this insignificance. Second, the correlation between ICP and ONSD on Day 3 was significant ($r = 0.90$). However, The ICP on Day 3 did not show significant difference in neurological outcomes. Thus, ONSD on Day 3 could not significantly show difference in neurological outcomes. Fig. 3A shows that ICP continuously increased until Day 2, then decreased at Day 3, and could not been associated with neurological outcomes. We suggest that 72 h after ROSC may be too late to predict neurological outcomes by any parameter of ICP. Therefore, 72 h might have been beyond the optimal time of the valuable prognostic performance of ICP.

Our study published recently has shown that ONSDs measured using ultrasound both immediately and after 72 h of ROSC have a significant difference between poor and good outcome groups ($p = 0.06$, $p < 0.001$).[13] However, even in previous studies, the ICPs measured immediately after ROSC and 72 h later were not associated with neurological outcomes. The association of ONSD with neurological outcomes in the previous study was contrary to the findings in the present study. The reasons for the difference between our findings and those of the previous studies remain unclear. However, there are several possible explanations. First, in both studies, ONSD was

measured by only one investigator. Therefore, it is estimated that the result may differ depending on the skills of the person who measured the ONSD. Second, ONSD is an inspection method that indirectly reflects the ICP. In our study, unlike the previous study, ONSD measured on Days 0 and 3 was not associated with neurological outcomes as did ICP measurements. Thus, ONSD measured using MRI can be assumed to have better predictive performance for ICP than measurements using ultrasound.

A previous study revealed that ONSD measured by brain CT within 2 h after ROSC has been reported to have no correlation with neurological outcomes in CA survivors (5.61 ± 0.59 mm vs 5.69 ± 0.79 mm; $p = 0.275$).[12] On the contrary, the ONSD measured by sonography within 24 h after ROSC has significant correlation with survival (survivors: 5.36 mm $\pm$ 0.43 vs non-survivors: 5.88 mm $\pm$ 0.44; $p = 0.001$).[24] These conflicting results are possibly due to different timing of measurement and imaging modalities. Among these factors, we suggest that the time of measuring ONSD essentially contributes to the conflicting results of the prognostic performance of ONSD. In detail, each study mentioned above had different times to measure ONSD, for example, within 2 and 24 h after ROSC is similar to Days 0 and 1 of this study, respectively (Table 1). In this study, the width of increasing ICP in the poor outcome group was the largest after 5 to 29 h from ROSC (Table 1). It can be assumed that the ICP change per hour is the greatest during the first 24 h after ROSC, especially in patients with poor neurological outcomes. Hence, we suggest that the time of measuring ONSD is essential considering the reliability of ONSD as a neurological prognostic factor. Therefore, we recommend that measuring ONSD could help predict neurological prognosis between 24 and 48 h after ROSC, because ONSD measured at this time is considered the most reliable in cases with relatively higher ICP during TTM.[23] A recently published study had reported that ONSD measured after 24 h from ROSC is the most valuable tool to evaluate prognosis in CA survivors as it has an AUC value of 0.91 (95% CI: 0.77–0.98) with a sensitivity of 83.3% (95% CI: 58.6–96.4) and a specificity of 94.4 (95% CI: 72.7–99.9).[13]

Increased ICP has been reported to contribute to poor outcomes in patients with brain damage, such as CA and traumatic brain injury. You et al. reported that ICP above 200 mmH_2O measured by lumbar puncture prior to TTM has 87.3% sensitivity and 100.0% specificity in predicting poor outcomes in CA survivors.[25] Moreover, Ziai et al. reported that ICP below 18 mmHg measured by external ventricular drainage is associated with good neurological outcomes in patients with traumatic brain injury.[26] In the present study, 9 of 10 cases with IICP have poor neurological outcomes, and we analysed the usefulness of ONSD for detecting IICP. As a result, ONSD of 5.99 mm is the optimal cut-off value to identify IICP defined as above 20 mmHg in this study.

This study has several limitations. First, this was a retrospective study performed at a single centre with a small number of patients. The inclusion of patients receiving lumbar catheter and MRI at two points during TTM may have led to selection bias. Second, the ONSD on Days 1 and 2, when the ICP has significant relationship with neurological outcomes, was not measured as it was not included in the TTM protocol, given the limited availability, high cost, and patient safety. Third, MR scan was proven to have high scan–rescan reproducibility and low inter-observer variability. However, inter-observer variation is not available in this study because all MR scans were reviewed by a single expert, neuro-radiologist. Fourth, the knowledge of MR scans in comatose survivors after OHCA is sparse; thus, this study adds some information to this scientific area. However, the clinical value may be limited as MR scans are not always used or available in daily clinical practice. Finally, MRI with half-Fourier acquisition single-shot turbo spin-echo sequences was proven as the ideal method to measure ONSD because it is an objective method that acquires high-resolution image and provides good reproducibility, and but this was not performed in this study.[17]

Conclusion

The ONSD measured using brain MRI on Days 0 and 3 after ROSC did not show difference in neurological outcomes at 6 months in post-OHCA patients treated with TTM. However, the correlation between ICP and ONSD was excellent on Day 3, especially in patients in the IICP group. Further prospective multicentre studies are required to confirm our results.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgment

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