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Clinical paper

Optimal timing to measure optic nerve sheath diameter as a prognostic predictor in post-cardiac arrest patients treated with targeted temperature management

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Abstract

Aim: We evaluated the optimal timing of optic nerve sheath diameter (ONSD) measurement to predict neurologic outcome in post-cardiac arrest patients treated with target temperature management (TTM).

Methods: This was a prospective single-centre observational study from April 2018 to March 2019. Good outcome was defined as the Glasgow-Pittsburgh cerebral performance categories (CPC) 1 or 2, and poor outcome as a CPC between 3 and 5. ONSD was measured initially after return of spontaneous circulation (ROSC) ($ONSD_{initial}$), at 24 h ($ONSD_{24}$), 48 h ($ONSD_{48}$), and 72 h ($ONSD_{72}$) using ultrasonography. The receiver operating characteristic (ROC) curves and DeLong method were used to compare the values for predicting neurologic outcomes.

Results: Out of the 36 patients enrolled, 18 had a good outcome. $ONSD_{24}$, $ONSD_{48}$, and $ONSD_{72}$ were higher in the poor outcome group. The area under ROC curve of $ONSD_{24}$ was 0.91 (95% confidence interval 0.77–0.98) in predicting poor neurologic outcomes. With a cut off value of 4.90 mm, $ONSD_{24}$ had a sensitivity of 83.3% and a specificity of 94.4% in predicting poor neurologic outcomes.

Conclusion: Our findings demonstrate $ONSD_{24}$ as a valuable tool to predict the neurologic outcome in post-cardiac arrest patients treated with TTM. Therefore, we recommend performing ONSD measurement using ultrasonography at 24 h after ROSC, rather than immediately after ROSC, to predict neurologic outcome in post-cardiac arrest patients treated with TTM.

Keywords: Cardiac arrest, Prognostication, Optic nerve

Abbreviations: ONSD, optic nerve sheath diameter; TTM, targeted temperature management; CPC, cerebral performance categories; ROSC, restoration of spontaneous circulation; ECMO, extracorporeal membrane oxygenation; CA, cardiac arrest; ICP, intracranial pressure; BBB, blood-brain barrier; GCS, Glasgow coma scale; LP, lumbar puncture; CT, computed tomography; INR, international normalized ratio; GWR, gray-to-white matter ratio; GWR, gray-to-white matter ratio; CPR, cardiopulmonary resuscitation; SOFA, sequential organ failure assessment; MI, myocardial infarction; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia; ROC, receiver operating characteristic; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predict value; NPV, negative predict value.

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Introduction

Ischemia-reperfusion cerebral injury after cardiac arrest (CA) significantly contributes to mortality and may reduce the quality of life in many survivors.[1–3] Brain oedema and loss of pressure reactivity are among the most serious complications following ischaemia-reperfusion cerebral injury, and are associated with poor neurologic outcome and death.[4–6] Brain oedema and increased intracranial blood volume from loss of pressure reactivity can result in a harmful increase in intracranial pressure (ICP). Previous studies have shown that a higher ICP follows global cerebral ischaemia after return of spontaneous circulation (ROSC); severe blood-brain barrier (BBB) disruption began at 24 h after ROSC in the poor neurologic outcome group treated with target temperature management (TTM). In these previous studies, a higher ICP was strongly associated with and was apparently predictive of a poor outcome.[7,8]

However, measuring ICP directly in CA patients is difficult and invasive; therefore, this has limited the number of studies using the direct measurement technique.[9] Instead, previous studies have applied indirect methods such as the measurement of the optic nerve sheath diameter (ONSD). Some studies have examined the relationship between ONSD and ICP in patients with non-traumatic causes of elevated ICP. Good sensitivity has been reported for ONSD measurements in cases of idiopathic intracranial hypertension.[10] Another study reported that ONSD demonstrated the best agreement to assess ICP non-invasively in patients with hypoxic brain injury after cardiac arrest and that it may help in detecting or ruling out of ICP.[11] Conversely, another study reported that ONSD after ROSC was not correlated with neurological outcome at 6 months in patients who underwent TTM.[12] A study that performed a meta-analysis to evaluate the diagnostic performance of ONSD in predicting neurologic outcome in post-cardiac arrest patients reported that one of the significant sources of sensitivity heterogeneity was the time of ONSD measurement after ROSC.[13]

However, to the best of our knowledge, no study has assessed the optimal timing for ONSD measurements for predicting neurologic outcomes. Therefore, in this study, we evaluated the optimal timing for ONSD measurement to predict neurologic outcomes in post-CA patients treated with TTM.

Methods

This study was approved by the Institutional Review Board of Chungnam National University Medical Centre (CNUH IRB 2017-10-027). We obtained approval and consent from the next of kin before enrolment.

Study design and patients

This was a prospective single-centre observational cohort study of patients who had been treated with TTM following CA from April 2018 to March 2019. The primary endpoint was the optimal timing to measure ONSD for predicting neurologic outcome after ROSC. The patients' neurologic status was obtained by directly following up the patients at 3 months after CA.[7] Neurological outcome was assessed using the Glasgow-Pittsburgh cerebral performance categories (CPC) scale. The good outcome group was defined as a CPC 1 or 2, and the poor outcome group as a CPC between 3 and 5. Resuscitated CA patients whose Glasgow coma scale (GCS) was 8 or less after ROSC were included in the study. The exclusion criteria for this study were as follows: (1) under 18 years of age, (2) traumatic CA or interrupted TTM (due to haemodynamic instability), (3) ineligible for TTM (i.e., intracranial haemorrhage, active bleeding, known terminal illness, or poor pre-arrest neurological status), (4) ineligible for lumbar puncture (LP) (i.e., brain computed tomography (CT) showed severe cerebral oedema, obliteration of the basal cisterns, occult intracranial mass lesion, or coagulopathy: platelet count $< 40 \times 10^3/\mu L$ or international normalized ratio (INR) > 1.5),[14] (5) on extracorporeal membrane oxygenation, (6) apparent brain parenchymal disease or ophthalmic disease that could affect ONSD measurement, (7) unable to consent to LP, and (8) refusal of further treatment by the next of kin.

Target temperature management protocol

TTM was applied using cooling devices (Arctic Sun® Energy Transfer Pads TM, Medivance Corp., Louisle, USA). A target temperature of 33 °C was maintained for 24 h with rewarming to 37 °C at the rate of 0.25 °C/h and was monitored using an oesophageal and bladder temperature probe. Sedatives and analgesics were used during TTM and patients received standard care according to a previously described protocol.[15,16] Anti-epileptic medications were administered as soon as a seizure was either suspected clinically or based on electroencephalography. We used ADMS™ (Anesthetic Depth Monitor for Sedation, Unimedics CO., LTD., Seoul, Korea) to monitor anaesthesia depth. All patients received standard intensive care according to our institutional intensive care unit protocol.

Data collection

The following data were collected from the database: age, gender, presence of a witness at the time of the collapse, bystander cardiopulmonary resuscitation (CPR), first monitored rhythm, aetiology of cardiac arrest, time from collapse to CPR (no flow time), time from CPR to ROSC (low flow time), time from ROSC to obtaining ICP via LP (ICP time), time from ROSC to measuring ONSD via ultrasonography (ONSD time), time from ROSC to achieving the target temperature (33 °C) (induction time), sequential organ failure assessment (SOFA) score and GCS after ROSC, and CPC at 3 months after ROSC.

Measurement of optic nerve sheath diameter

ONSD was measured by one investigator using the MyLab™ Seven (Esaote, Inc., Genoa, Italy) at a distance of 3 mm behind the retina of both the left and right eyes using a 10-Hz linear probe prior to ICP measurement, independent of the researcher who performed ICP measurement.[17] ONSD was calculated by averaging the ONSD of both eyes. ONSD was measured initially after ROSC ($ONSD_{initial}$), at 24 h ($ONSD_{24}$), 48 h ($ONSD_{48}$), and 72 h ($ONSD_{72}$).

Measurement of intracranial pressure via a lumbar catheter

The procedure was performed with the patient lying in the lateral decubitus position with hips and knees flexed. A lumbar catheter was inserted using a Hermetic™ lumbar accessory kit (Integra Neurosciences, Plainsboro, NJ, USA) on the level of the lumbar spine between L3 and L4, and ICP measured in the patients while down without any irritation and in a completely relaxed condition induced by a muscle relaxant. The unit of ICP was converted from mmH_2O to mmHg after measurement using a manometer via the lumbar catheter. ICP was measured initially after ROSC ($ICP_{initial}$), at 24 h (ICP_{24}), 48 h (ICP_{48}), and 72 h (ICP_{72}).

Sample size

Based on previous studies,[18,19] that reported an ONSD of 5.6 ± 0.6 mm in patients with good outcomes and of 6.3 ± 0.6 mm in patients with poor outcomes, 36 patients were needed to achieve a power of 0.90 at a significance level of 0.05 (two-sided test) by applying a 10% missing rate.

Statistical analysis

Depending on the normal distribution, we reported continuous variables as the median with interquartile ranges, or as the mean and standard deviations. Categorical variables were reported as frequencies and percentages. Comparisons between the two groups were made using the chi-square, Fisher's exact, Mann–Whitney U, and two-tailed *t*-tests. We used Pearson's test to assess the correlation between ONSD and ICP. The receiver operating characteristic (ROC) curves and DeLong method were used to compare the values for predicting neurologic outcomes. All statistical analyses were performed using the PASW/SPSSTM software, version 18 (IBM Inc., Chicago, USA) and MedCalc 15.2.2 (MedCalc software, Mariakerke, Belgium). Results were considered significant at $P < 0.05$.

Results

Characteristics of study subjects

Among the 48 post-CA patients who achieved ROSC, 36 were enrolled in the study and none had abnormal findings in the coagulation test.

A total of 18 and 18 patients were in the good and poor outcome groups, respectively (Fig. 1). The mean age, no flow time, SOFA score, and ONSD time were not significantly different between the two groups. In the 36 enrolled patients, 18 (50.00%), 0 (0.00%), 0 (0.00%), 7 (19.44%), and 11 (30.56%) patients had CPC 1, 2, 3, 4, and 5, respectively (Table 1).

Comparison of ONSD between the poor and good outcome groups

The values of $ONSD_{initial}$ in the poor and good outcome groups were 4.88 ± 1.11 and 4.23 ± 0.85 mm, respectively ($p = 0.06$). The corresponding values of $ONSD_{24}$ were 5.24 ± 0.56 and 3.78 ± 0.83 mm ($p < 0.001$). The respective $ONSD_{48}$ values were 5.31 ± 0.54 and 4.43 ± 0.63 mm ($p < 0.001$), and the corresponding $ONSD_{72}$ values were 5.24 ± 0.59 and 4.18 ± 0.63 mm ($p < 0.001$) (Table 2).

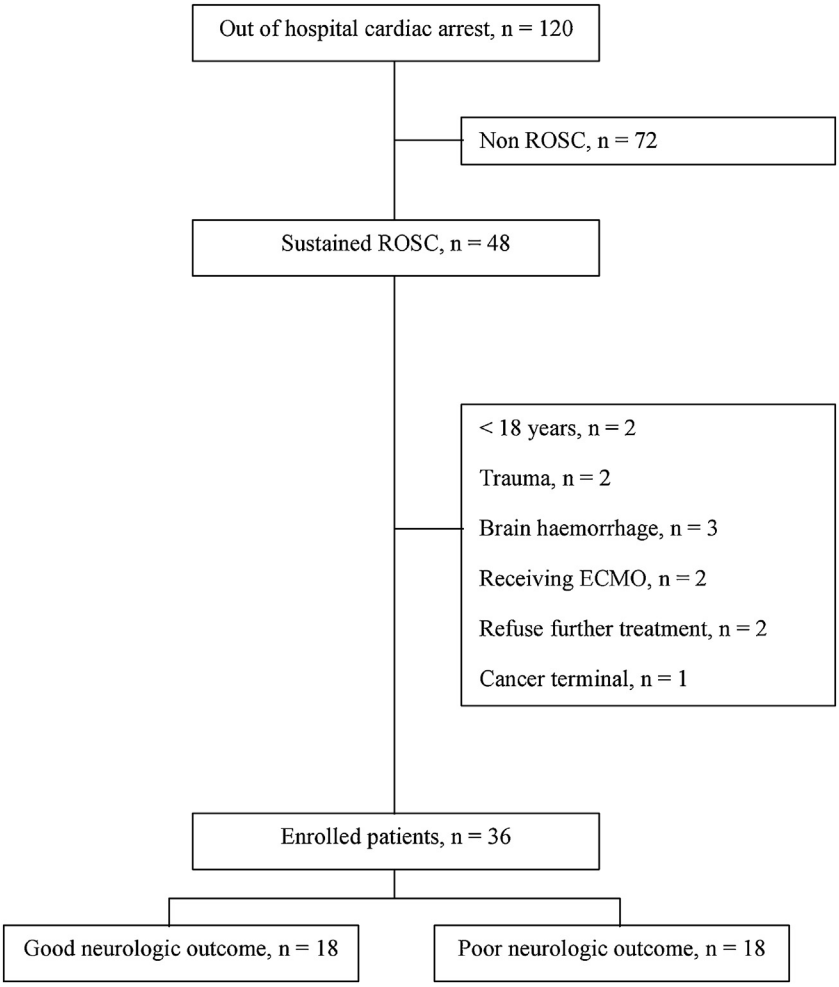

Fig. 1 – Flowchart of the study (ROSC: return of spontaneous circulation; ECMO: extracorporeal membrane oxygenation).

Table 1 – General characteristics and comparison of the study population between the outcome groups.

Characteristics		Total	Good outcome	Poor outcome	P value
Age (years)		51.83 ± 15.53	50.67 ± 15.49	53.00 ± 15.93	0.66
Sex, n (%)	Male	26(72.22)	15(83.33)	11(61.11)	0.26
	Female	10(27.78)	3(16.67)	7(38.89)	
Witness, n (%)	Yes	22(61.11)	13(72.22)	9(50.00)	0.31
	No	14(38.89)	5(27.78)	9(50.00)	
Bystander CPR, n (%)	Yes	27(75.00)	16(88.89)	11(61.11)	0.11
	No	9(25.00)	2(11.11)	7(38.89)	
Initial rhythm, n (%)	Asystole	7(19.44)	1(5.56)	6(33.33)	0.004
	PEA	15(41.67)	5(27.78)	10(55.56)	
	VF	12(33.33)	11(61.11)	1(5.56)	
	Pulseless VT	1(2.78)	0(0.00)	1(5.56)	
	Unknown	1(2.78)	1(5.56)	0(0.00)	
Causes, n (%)	Hypoxia	22(61.11)	8(44.44)	14(77.78)	0.09
	MI	5(13.89)	4(22.22)	1(5.56)	
	Arrhythmia	6(16.67)	5(27.78)	1(5.56)	
	Unknown	3(8.33)	1(5.56)	2(11.11)	
GCS, n (%)	3	27(75.00)	11(61.11)	16(88.89)	0.12
	4	3(8.33)	1(5.56)	2(11.11)	
	5	2(5.56)	2(11.11)	0(0.00)	
	6	3(8.33)	3(16.67)	0(0.00)	
	7	1(2.78)	1(5.56)	0(0.00)	
No flow time (min)		2.00(0.00–12.75)	0.50(0.00–5.00)	3.50(0.75–16.25)	0.08
Low flow time (min)		20.08 ± 13.68	12.67 ± 9.05	27.50 ± 13.68	0.001
ONSD time (h)		4.82 ± 1.61	4.90 ± 1.88	4.74 ± 1.34	0.76
ICP time (h)		5.04 ± 1.58	5.16 ± 1.85	4.93 ± 1.30	0.66
Induction time (h)		6.52 ± 2.28	6.90 ± 2.51	6.14 ± 2.03	0.32
SOFA score		9.00(8.00–11.00)	8.50(7.25–11.75)	10.00(8.00–11.00)	0.28

Continuous variables expressed as the median with interquartile ranges, or as mean and standard deviations, depending on the normal distribution. CPR, cardiopulmonary resuscitation; MI, myocardial infarction; GCS, Glasgow coma scale; ONSD, optic nerve sheath diameter; ICP, intracranial pressure; SOFA, sequential organ failure assessment; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

Correlation analysis of ONSD and ICP

$ONSD_{initial}$ was not significantly correlated with $ICP_{initial}$ (correlation coefficient, 0.18; p = 0.30), while $ONSD_{24}$ was correlated with ICP_{24} (correlation coefficient, 0.38; p = 0.02). $ONSD_{48}$ was not significantly correlated with ICP_{48} (correlation coefficient, 0.25; p = 0.14), and $ONSD_{72}$ was not significantly correlated with ICP_{72} (correlation coefficient, 0.29; p = 0.09) (Fig. 2).

Evaluation of the optimal timing to measure optic nerve sheath diameter

Compared to the area under the ROC curve (AUROC) for $ONSD_{initial}$ of 0.68 in predicting neurological outcomes, that of $ONSD_{24}$, $ONSD_{48}$, and $ONSD_{72}$ were 0.91 (p = 0.006), 0.87 (p = 0.03), and 0.90 (p = 0.02), respectively. In predicting poor neurological outcomes, compared to an AUROC for $ONSD_{24}$ of 0.91, those of $ONSD_{48}$ and $ONSD_{72}$ were 0.87 (p = 0.35) and 0.90 (p = 0.78), respectively. Compared to an AUROC for $ONSD_{48}$ of 0.87 in predicting poor neurological outcomes, that of $ONSD_{72}$ was 0.90 (p = 0.73) (Fig. 3).

The cut-off value of optic nerve sheath diameter to predict the neurologic outcomes

$ONSD_{initial}$ with 100% specificity for predicting poor neurologic outcome had a limited sensitivity of 16.67% and a cut-off value of 5.65 mm. $ONSD_{24}$ with 100% specificity for predicting poor neurologic outcome had a limited sensitivity of 5.56% and a cut-off value of 6.05 mm. $ONSD_{48}$

Table 2 – Comparison of intracranial pressure and optic nerve sheath diameter between the outcome groups.

Values	Total	Good outcome	Poor outcome	P value
$ICP_{initial}$ (mmHg)	10.24 ± 4.43	9.33 ± 2.10	11.16 ± 5.86	0.23
ICP_{24} (mmHg)	13.69 ± 5.49	9.97 ± 2.33	17.42 ± 5.21	<0.001
ICP_{48} (mmHg)	15.90 ± 5.51	13.22 ± 3.99	18.57 ± 5.61	0.002
ICP_{72} (mmHg)	14.99 ± 6.19	13.51 ± 5.25	16.47 ± 6.82	0.15
$ONSD_{initial}$ (mm)	4.56 ± 1.03	4.23 ± 0.85	4.88 ± 1.11	0.06
$ONSD_{24}$ (mm)	4.51 ± 1.02	3.78 ± 0.83	5.24 ± 0.56	<0.001
$ONSD_{48}$ (mm)	4.87 ± 0.73	4.43 ± 0.63	5.31 ± 0.54	<0.001
$ONSD_{72}$ (mm)	4.71 ± 0.81	4.18 ± 0.63	5.24 ± 0.59	<0.001

Continuous variables expressed as mean and standard deviations. ICP, intracranial pressure measured initially ($ICP_{initial}$), at 24 h (ICP_{24}), 48 h (ICP_{48}), and 72 h (ICP_{72}) after return of spontaneous circulation; ONSD, optic nerve sheath diameter ($ONSD_{initial}$), 24 h ($ONSD_{24}$), 48 h ($ONSD_{48}$), and 72 h ($ONSD_{72}$).

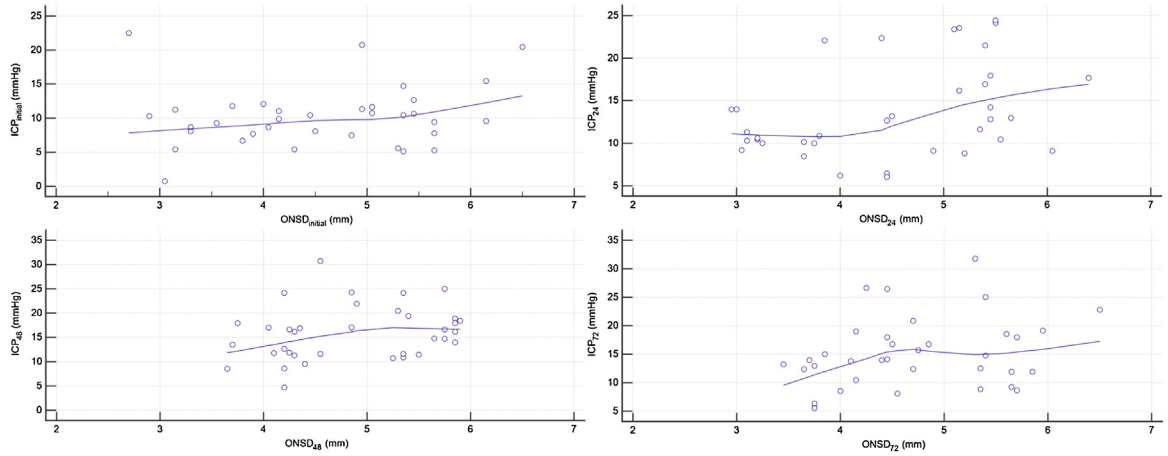

Fig. 2 – Scatter diagram showed that ONSD$_{24}$ had a positive correlation with ICP$_{24}$; ONSD, optic nerve sheath diameter; ICP, intracranial pressure.

with 100% specificity for predicting poor neurologic outcome had a limited sensitivity of 27.78% and a cut-off value of 5.75 mm. ONSD$_{72}$ with 100% specificity for predicting poor neurologic outcome had a limited sensitivity of 5.56% and a cut off value of 5.95 mm (Table 3).

Discussion

The present study found that 24 h after ROSC was the optimal timing for measuring ONSD to predict neurological outcomes in post-CA patients treated with TTM. Of the 16 patients with ONSDs equal to or greater than 5.00 mm at 24 h after ROSC, 15 (93.75%) had a poor neurologic outcome. This indicates that it is important to monitor ONSD in post-CA patients at 24 h after ROSC since it has a sensitivity of 83.3% and a specificity of 94.4% in predicting poor neurologic outcomes as well as a cut-off value of 4.90 mm. Moreover, in this study, ONSD also showed a good performance in predicting poor neurologic outcomes at 24, 48, and 72 h after ROSC. However, prognostic factors of poor neurologic outcome with 100% specificity are needed because withdrawal of life-sustaining therapy has not been widely adopted in South Korea yet. In this study, ONSD$_{24}$ with 100% specificity for predicting poor neurologic outcome had a limited sensitivity of 5.56% and broad confidence intervals with a cut off value of 6.05 mm since one patient, who had an ONSD$_{24}$ greater than 6 mm, had a good prognosis. Therefore, ONSD measurement may be useful as one modality in a multi-modality prognostic assessment, but cannot be used in isolation to predict the outcome.

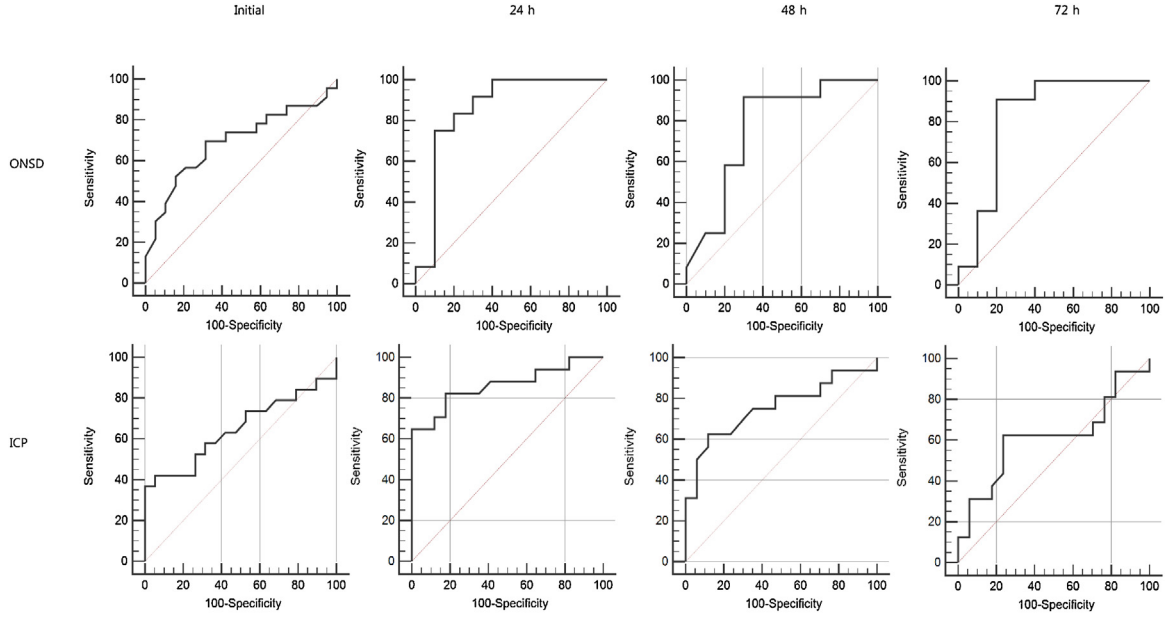

Fig. 3 – The area under the receiver operating characteristic curve showed that ONSD$_{24}$, which was measured at 24 h after return of spontaneous circulation (ROSC), was a valuable tool to predict poor neurologic outcome. (ONSD: optic nerve sheath diameter measured initially, at 24 h, 48 h, and 72 h after ROSC; ICP: intracranial pressure measured initially, at 24 h, 48 h, and 72 h after ROSC).

Table 3 – Cut-off and prognostic value of intracranial pressure and optic nerve sheath diameter for poor outcome.

Values	AUC (95% CI)	Cut off	Sensitivity (95% CI)	Specificity(95% CI)	PPV (95% CI)	NPV (95% CI)	FPR (%)	FNR (%)
$ICP_{initial}$ (mmHg)	0.57 (0.40–0.74)	14.71	22.2 (6.4–47.6)	100.0(81.5–100.0)	100.0(39.8–100.0)	56.2(37.7–73.6)	0.0	76.5
ICP_{24} (mmHg)	0.90 (0.75–0.97)	14.20	61.1(35.7–82.7)	100.0(81.5–100.0)	100.0(71.5–100.0)	72.0(50.6–87.9)	0.0	38.9
ICP_{48} (mmHg)	0.77 (0.60–0.90)	16.99	61.1(35.7–82.7)	88.9(65.3–98.6)	84.6(54.6–98.1)	69.6(47.1–86.8)	11.8	38.9
ICP_{72} (mmHg)	0.60 (0.43–0.76)	15.01	55.6(30.8–78.5)	77.8(52.4–93.6)	71.4(41.9–91.6)	63.6(40.7–82.8)	22.2	44.4
$ONSD_{initial}$ (mm)	0.68 (0.50–0.82)	4.95	61.1(35.7–82.7)	72.2(46.5–90.3)	68.7(41.3–89.0)	65.0(40.8–84.6)	27.8	44.4
$ONSD_{24}$ (mm)	0.91 (0.77–0.98)	4.90	83.3(58.6–96.4)	94.4(72.7–99.9)	93.7(69.8–99.8)	85.0(62.1–96.8)	5.6	16.7
$ONSD_{48}$ (mm)	0.87 (0.71–0.96)	4.90	66.7(41.0–86.7)	77.8(52.4–93.6)	75.0(47.6–92.7)	70.0(45.7–88.1)	22.2	33.3
$ONSD_{72}$ (mm)	0.90 (0.76–0.98)	4.85	61.1(35.7–82.7)	88.9(65.3–98.6)	75.0(47.6–92.7)	70.0(45.7–88.1)	11.1	38.9

ICP, intracranial pressure measured initially ($ICP_{initial}$), at 24 h (ICP_{24}), 48 h (ICP_{48}), and 72 h (ICP_{72}) after return of spontaneous circulation; ONSD, optic nerve sheath diameter ($ONSD_{initial}$), 24 h ($ONSD_{24}$), 48 h ($ONSD_{48}$), and 72 h ($ONSD_{72}$); CI, confidence interval; PPV, positive predict value; NPV, negative predict value; FPR, false positive rate; FNR, false negative rate.

The optic nerve sheath is connected to the dura mater surrounding the brain and cerebrospinal fluid, with a fluid-filled cavity between it and the optic nerve. Thus, increased ICP causes the sheath to swell, resulting in an increment of the ONSD.[20–22] A previous study reported that ONSD measured by ultrasonography could be a possible indicator of ICP. This previous study used an intrathecal infusion test to demonstrate that ONSD in humans was elastic enough to allow a detectable dilation in response to ICP and that, within a certain range of ICP, a linear relationship existed between ONSD and ICP. Tamburrelli et al. also reported that the ONSD began to increase when the diastolic ICP increased above 13–14 mmHg, beyond which a linear correlation existed between the two parameters. All these findings suggested that an ophthalmic B-scan ultrasound could detect an enlarged ONSD, and thereby indicate an increase in ICP.[23–25] However, in a study comparing the prognostic performance of ONSD with that of gray-to-white matter ratio (GWR) on brain CT, both ONSD and GWR showed limited performance in the prognostication of post-CA patients, especially in terms of sensitivity.[26] Moreover, Lee et al. reported that ONSD on brain CT after ROSC was not correlated with neurologic outcome at 6 months in patients who underwent TTM.[12] A meta-analysis study reported that ONSD measured within 6 h of ROSC had a low sensitivity for predicting neurologic outcome, and that ONSD on ultrasonography showed a higher sensitivity and similar specificity compared to ONSD on brain CT.[13] In this study, we measured ONSD using ultrasonography at 24, 48, and 72 h after ROSC, and found that the measurements were valuable tools for predicting the neurologic outcome. However, ONSD immediately obtained after ROSC showed limited performance in prognostication of post-CA patients. Concomitant increase in ONSD with an increase in ICP explains the higher sensitivity for predicting neurologic outcome at 24 h after ROSC since ICP increment was reported to begin at 24 h after ROSC in a poor neurologic outcome group treated with TTM.[7,8]

There were several limitations to our study. First, this was a single centre study. Second, other parameters such as cerebral blood flow, pressure reactivity, and arterial blood pressure were not measured. Third, ONSD was measured by only one investigator, which limits the generalisability of the results. Finally, we measured ICP and ONSD intermittently and not continuously. Future studies are needed to confirm the findings of our study.

Conclusions

ONSD obtained at 24, 48, and 72 h after ROSC in post-CA patients treated with TTM, were valuable tools to predict the neurologic outcome. In addition, we recommend that ONSD measured via ultrasonography at 24 h, rather than initially, after ROSC should be used to predict neurologic outcome in post-CA patients treated with TTM.

Conflict of interest

The authors have no conflict of interest to report.

Acknowledgements

None.

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