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Original Research

Association of Early Increase in Body Temperature with Symptomatic Intracranial Hemorrhage and Unfavorable Outcome Following Endovascular Therapy in Patients with Large Vessel Occlusion Stroke

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Abstract

Introduction: The aim of this study was to investigate for possible associations between an early increase in body temperature within 24 hours of endovascular therapy (EVT) for large vessel occlusion stroke and the presence of symptomatic intracranial hemorrhage (sICH) and other clinical outcomes. **Methods**: This was a retrospective study of consecutive patients with large vessel occlusion stroke who were treated with EVT from August 2018 to June 2021. Patients were divided into two groups based on the presence of fever, as defined by a Peak Body Temperature (PBT) of $\geq$37.3 °C. The presence of sICH and other clinical outcomes were compared between the two groups. **Results**: The median NIHSS admission score (IQR) was 16.0 (12.0, 21.0), with higher NIHSS scores in the PBT $\geq$37.3 °C group than in the PBT $<$37.3 °C group (18 *vs* 14, respectively; $p = 0.002$). There were no differences in clinical outcomes at 3 months between patients with PBT $<$37.3 °C and patients with PBT between 37.3 °C and 38 °C. However, patients with PBT $\geq$38 °C had an increased risk of sICH (adjusted odds ratio (OR) = 8.8, 95% confidence interval (95% CI): 1.7–46.0; $p = 0.01$), increased inpatient death or hospice discharge (OR = 10.5, 95% CI: 2.0–53.9; $p = 0.005$), poorer clinical outcome (OR = 25.6, 95% CI: 5.2–126.8; $p < 0.001$), and increased 3-month mortality (OR = 6.6, 95% CI: 1.8–24.6; $p = 0.01$). **Conclusions**: Elevated PBT ($\geq$38 °C) within 24 hours of EVT was significantly associated with an increased incidence of symptomatic intracranial hemorrhage, discharge to hospice or inpatient death, poorer clinical outcome and 3-month mortality, and with less functional independence. Further large-scale, prospective and multicenter trials are needed to confirm these findings.

Keywords: body temperature; symptomatic intracranial hemorrhage; endovascular therapy; ischemic stroke

1. Introduction

Stroke is the second leading cause of mortality worldwide and the third leading cause of patient disability, affecting approximately 1 in 4 people during their lifetime [1]. Endovascular therapy (EVT) has proven to be an effective treatment for patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO), with improved outcomes and reduced mortality compared to medical management alone [2,3]. Following the onset of stroke, about one-third of patients present with sub-febrile fever that can persist for up to 24 hours [4]. The findings in relation to the effects of body temperature on outcomes following AIS are contradictory. Prior studies showed that pyrexia was associated with poorer outcomes and increased short- and long-term mortality after AIS [5–9]. Increased body temperature within the first 24 hours of ischemic stroke is considered to be a risk factor for hemorrhagic transformation in patients with or without recombinant tissue plasminogen activator (rt-PA) thrombolysis [5,10,11]. However, other studies have shown a likely beneficial effect of higher body temperature on clot thrombolysis within the first three hours of hospital admission, and on neurological improvement within a few hours of hospital admission [12]. Moreover, a prospective study on 516 patients who presented with ischemia within 6 hours of stroke-onset found that low body temperature was independently associated with the development of severe ischemic stroke [13]. Only a few studies have examined the effects of post-EVT body temperature

on the outcomes from ischemic stroke [14,15], while the associations between body temperature, clinical outcome and symptomatic intracranial hemorrhage (sICH) following EVT are still unknown. The aim of this study was therefore to investigate for associations between elevated body temperature within 24 hours of EVT for large vessel occlusion stroke and sICH as well as clinical outcomes.

2. Methods

This was a retrospective study of consecutive patients who presented with acute large vessel occlusion stroke and were treated with EVT from August 2018 to June 2021 at a university hospital in China. The inclusion criteria were: patient age $\geq$18 years, presentation within 24 hours of the time last seen well (TLSW0), and occlusion of the terminal internal carotid, M1, or M2 segments of the middle cerebral artery or basilar artery. The exclusion criteria were: known or diagnosed infection on the day of stroke, pre-mRS $>$1, onset of TLSW $>$24 hours, patients who underwent intra-arterial thrombolysis only without mechanical thrombectomy, reperfusion of the suspected occlusion vessel before thrombectomy, a history of severe respiratory failure or malignant tumor, and lost to follow-up with no 3 month mRS data. Of 97 patients enrolled, 7 were excluded because they received only intra-arterial thrombolysis without thrombectomy, and one because of spontaneous reperfusion. Thus, a total of 89 patients were included in the study.

2.1 Measurement of Body Temperature

The patient's body temperature was measured using a forehead thermometer. Temperature readings were obtained upon admission and then routinely every 4 hours post-EVT. The peak body temperature (PBT) was recorded as the highest value within 24 hours of EVT. Fever was defined as a body temperature of $\geq$37.3 °C [16].

2.2 Data Collection

Patients with ischemic stroke post-EVT were divided into two groups according to the presence or absence of fever (PBT $\geq$37.3 °C) within 24 hours of EVT. The following variables were recorded for all patients upon admission: body temperature, age, sex, smoking status, history of atrial fibrillation (AF), diabetes mellitus (DM), chronic kidney disease (CKD), coronary heart disease (CAD), prior stroke, dyslipidemia, initial National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), and the pre-treatment modified Rankin Scale (mRS) score. In addition, the 3-month mRS score, stroke type as categorized by the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) classification, door-to-puncture time (DPT), door-to-recanalization time (DRT), and last-known normal-to-puncture time (LKNPT) times were also recorded. Furthermore, data on clinical evidence of pneumonia, urinary tract infection (UTI), sICH, subarachnoid hemorrhage, thrombolysis in cerebral infarction (TICI), and the mRS score upon discharge were collected. Discharge to palliative care or hospice, and patient deaths were also recorded.

2.3 Evaluation of Clinical Outcomes

Functional clinical outcomes were evaluated using the pre-stroke mRS score upon admission and at 3-months after EVT. Patients were assessed either remotely over the telephone, or in-person during outpatient follow-up. Favorable outcome (functional independence) was defined as an mRS score of 0–2, and poor outcome as an mRS score of $\geq$3 or mortality within 3 months of discharge. sICH was defined as any intraparenchymal or intraventricular hemorrhage visible on post-EVT CT that led to a 4-point NIHSS score increase, or that resulted in coma or death [17].

2.4 Statistical Analysis

Statistical analysis was performed using the SPSS Statistics Package (Version 26.0; IBM Corporation, Armonk, NY, USA). Continuous variables were presented as the mean $\pm$SD for normally distributed variables, or as the median with interquartile range (IQR) for non-normally distributed variables. Data were compared using independent samples, T-Test, and statistical analysis, χ^2 test, or Fisher's Exact Test for small, expected frequencies. Multivariable logistic regression models were constructed to calculate odds ratios (ORs) and corresponding 95% CIs. These were used to evaluate the associations between PBT and clinical outcomes in study participants. Statistical significance was defined as a p-value of less than 0.05.

3. Results

A total of 89 consecutive patients (mean age 66.35 $\pm$ 12.85 years, of which 74.16% were male) with large vessel occlusion ischemic stroke and who underwent EVT met the study inclusion criteria. Patients were divided into two groups according to their PBT reading within 24 hours of EVT. The clinical characteristics of these two groups are summarized in Table 1. The median NIHSS admission score (IQR) of the overall study group was 16.0 (12.0, 21.0), with a significant difference observed between the two groups (Table 1). No other differences in patient demographics or in baseline ASPECTS were bet between the two groups. Reperfusion (TICI $>$2b) occurred in 75 (84.3%) of the study patients.

The clinical outcomes of the study participants are shown in Table 2. Patients with elevated PBT had a higher mRS score upon discharge (4, IQR 1.5–5) compared to those with normal PBT (2, IQR 1–4; p = 0.002), with 17 (30.9%) requiring discharge to a hospice or palliative care compared to 3 (8.8%) for the normal PBT group (p = 0.015). Overall, 39 (43.8%) patients had a favorable outcome at 3 months post-discharge, with a lower incidence in the high PBT group (30.9%) than in the normal PBT group (64.7%; p = 0.002). The high PBT group showed increased mor-

Table 1. Baseline clinical characteristics of patients undergoing EVT.

	Total	PBT <37.3 °C	PBT ≥37.3 °C	χ^2/t/z	*p*
Patients	89	34	55		
AT, Mean ± SD	36.62 ± 0.61	36.55 ± 0.21	36.66 ± 0.76	–0.977	0.332
Age, Mean ± SD	66.35 ± 12.85	65.82 ± 11.36	66.673 ± 13.78	–0.301	0.764
Male, n, %	66 (74.16)	21 (61.76)	45 (81.82)	4.409	0.036
Female, n, %	23 (25.84)	13 (38.24)	10 (18.18)	4.409	0.036
Hypertension, n, %	55 (61.80)	22 (64.71)	33 (60.00)	0.197	0.657
AF, n, %	35 (39.33)	9 (26.47)	26 (47.27)	3.811	0.051
DM, n, %	17 (19.10)	9 (26.47)	8 (14.55)	1.934	0.164
CAD, n, %	22 (24.72)	7 (20.59)	15 (27.27)	0.505	0.478
Previous Stroke, n, %	21 (23.60)	9 (26.47)	11 (20.00)	0.505	0.477
Dyslipidemia, n, %	13 (14.61)	5 (15.15)	8 (14.82)	0.002	0.966
CKD, n, %	10 (11.24)	3 (8.82)	7 (12.73)	0.321	0.571
Current smoker, n, %	27 (30.34)	13 (38.24)	14 (25.46)	1.624	0.203
NIHSS admission (IQR)	16.0 (12.0, 21.0)	14.0 (10.0, 17.0)	18.0 (13.0, 22.0)	–3.032	0.002
ASPECTS pre-treatment (IQR)	8.00 (8.00, 9.00)	8.0 (7.75, 9.00)	8.00 (8.00, 9.00)	–0.773	0.44
mRS pre-treatment (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	–1.009	0.312
PC-stroke, n, %	10 (11.24)	1 (2.9)	9 (16.4)	2.569	0.109
AC-stroke, n, %	79 (88.76)	33 (97.1)	46 (83.6)	2.569	0.109
TOAST					
LAA, n, %	39 (43.82)	19 (55.88)	20 (36.36)		
CE, n, %	40 (44.94)	12 (35.29)	28 (50.91)		
SVO, n, %	1 (1.12)	0 (0.00)	1 (1.89)	4.522	0.340
SOE, n, %	5 (5.62)	1 (2.94)	4 (7.27)		
SUE, n, %	4 (4.49)	2(5.88)	2 (3.64)		
Bridging rt-PA, n, %	42 (47.19)	12(35.29)	30 (54.55)	3.125	0.077
DPT (IQR), min	150.00 (107.00, 204.00)	121.50 (99.50, 162.25)	177.00 (115.00, 233.00)	–2.534	0.011
LKNPT (IQR), min	296.00 (207.00, 490.00)	330.00 (201.50, 556.50)	290.50 (209.25, 437.50)	–0.717	0.473
TICI post ≥2b, n, %	75 (84.27)	31 (91.18)	44 (80.00)	1.98	0.159

Abbreviations: AT, Admission Temperature; AC, Anterior Circulation; AF, Atrial Fibrillation; CE, Cardioembolic; CKD, Chronic Kidney Disease; CAD, Coronary Artery Disease; DM, Diabetes Mellitus; DPT, Door-to-Puncture Time; LAA, Large Artery Atherosclerosis; LKNPT, Last-Known Normal-to-Puncture Time; PBT, Peak Body Temperature; PC, Posterior Circulation; SVO, Small Vessel Occlusion; SOE, Stroke of Other Etiology; SUE, Stroke of Undetermined Etiology; TICI, Thrombolysis in Cerebral Infarction.

Table 2. Clinical outcomes of patients with normal or elevated PBT during the first 24 hours after EVT.

	Total = 89	PBT <37.3 °C (n = 34)	PBT ≥37.3 °C (n = 55)	χ^2/t/z	*p*
Pneumonia, n, %	35 (39.32)	9 (26.47)	26 (47.27)	3.81	0.051
Urinary tract infection, n, %	5 (56.18)	3 (8.82)	2 (3.64)	0.31	0.579
sICH, n, %	15 (16.85)	3 (8.82)	12 (21.82)	2.53	0.112
mRS discharge (IQR)	4 (1.5, 5)	2 (1.00, 4.00)	4 (2.00, 5.00)	–3.11	0.002
Inpatient Mortality/hospice discharge, n, %	20 (22.47)	3 (8.82)	17 (30.91)	5.88	0.015
Favorable outcome, n, %	39 (43.82)	22 (64.71)	17 (30.91)	9.75	0.002
Mortality at 3 months, n, %	32 (35.96)	7 (20.59)	25 (45.45)	5.64	0.018
Poor outcome, n, %	50 (56.18)	12 (35.29)	38 (69.09)	9.70	0.002

Favorable outcome: mRS (0–2) at 3 months. Poor outcome: mRS ≥3. sICH, Symptomatic Intracranial Hemorrhage.

tality at 3 months post-discharge (45.5% *vs* 20.6%, respectively; $p = 0.018$) and a poorer outcome as defined by an mRS of ≥3 (69.1% *vs* 35.3%, respectively; $p = 0.002$). The PBT ≥37.3 °C group also had a higher sICH than the PBT <37.3 °C group, but this was not statistically significant ($p = 0.11$).

In the group of patients with a PBT between 37.3 °C and 38 °C, no significant associations were found with poor clinical outcome. However, PBT ≥38 °C was associated with an increased risk of poor clinical outcomes, with an adjusted OR of 25.6 (95% CI: 5.2–126.8; $p < 0.001$), as shown in Table 3.

Table 3. Association of PBT with poor outcome at 3-months post-discharge.

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
<37.3 °C	/	/	/	/
37.3 °C ≤ PBT <38 °C	1.22 (0.42, 3.54)	0.71	0.90 (0.27, 2.99)	0.871
PBT ≥38 °C	25.66 (5.19, 126.83)	<0.001	12.86 (2.40, 68.78)	<0.001
Female			0.73 (0.22, 2.40)	0.606
NIHSS admission			1.14 (1.01, 1.28)	0.024
DPT			1.01 (1.00, 1.01)	0.109

Table 4. Association of PBT with mortality at 3-months post-discharge.

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
<37.3 °C	/	/	/	/
37.3 °C ≤ PBT <38 °C	1.22 (0.35, 4.20)	0.755	1.52 (0.41, 5.69)	0.533
PBT ≥38°C	6.66 (2.19, 20.31)	0.001	6.56 (1.75, 24.59)	0.005
Female			1.97 (0.64, 6.11)	0.239
NIHSS admission			1.03 (0.94, 1.13)	0.485
DPT			1.00 (0.99, 1.01)	0.612

Table 5. Association of PBT with sICH.

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
PBT <37.3°C	/	/	/	/
37.3 °C ≤ PBT <38 °C	0.90 (0.13, 5.82)	0.911	1.16 (0.17, 8.01)	0.883
PBT ≥38 °C	5.17 (1.26, 21.10)	0.022	8.84 (1.70, 46.01)	0.010
Female			0.77 (0.17, 3.42)	0.727
NIHSS admission			0.93 (0.83, 1.04)	0.208
DPT			1.00 (0.99, 1.01)	0.650

Table 6. Association of PBT with inpatient death or hospice discharge.

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
PBT <37.3 °C	/	/	/	/
37.3 °C ≤PBT <38 °C	1.41 (0.26, 7.64)	0.691	1.16 (0.30, 10.22)	0.530
PBT ≥38 °C	9.04 (2.26, 36.12)	0.002	10.48 (2.04, 53.92)	0.005
Female			1.61 (0.42, 6.15)	0.488
NIHSS admission			1.04 (0.93, 1.15)	0.518
DPT			1.00 (0.99, 1.01)	0.356

In patients with PBT between 37.3 °C and 38 °C, no association was seen with mortality at 3 months. However, the high PBT group had an increased risk of 3-month mortality, (OR = 6.56, 95% CI: 1.75–24.6; $p = 0.01$) (Table 4). After adjustment for sex, NIHSS admission scores and DPT, a PBT ≥38 °C within 24 hours of EVT was associated with an increased risk of sICH (OR = 8.84, 95% CI: 1.70–46.01; $p = 0.01$) (Table 5). PBT ≥38 °C within 24 hours of EVT was also associated with an increased risk of in-patient death or hospice discharge (OR = 10.48, 95% CI: 2.04–53.92; $p = 0.005$) (Table 6).

4. Discussion

This study found that elevated PBT (≥38 °C) within 24 hours of EVT in patients with large vessel occlusion stroke was associated with a higher incidence of discharge to hospice or death, poorer clinical outcome (mRS ≥3 at 3 months post-discharge), increased 3-month mortality, and less functional independence. In contrast to previous studies that reported no relationship between PBT and the risk of hemorrhagic transformation [14,15], we found that PBT ≥38 °C within 24 hours of EVT was associated with an increased risk of sICH. In patients who present with high initial NIHSS, posterior circulation stroke or AF, this may be an indicator of increased severity of disease and thus explain the association with PBT.

The body temperature of patients with ischemic stroke increases in the first 72 hours, with the harmful effects of hyperthermia occurring in the first 48 hours. In contrast, the neuroprotection afforded by hypothermia occurs during the first 24 hours following stroke onset [18]. With cerebral ischemia, increased body temperature leads to subsequent neurotransmitter release, increased metabolic demand, free-radical production, and disruption of the blood-

brain barrier [19]. These events increase the risk of brain cell death and lead to a potentially larger cerebral infarct volume and unfavorable clinical outcomes [19,20]. Higher body temperature was independently associated with major neurological improvement in patients with severe ischemic stroke treated with thrombolysis via rtPA [21].

Inflammatory factors may also play an important role in the elevated temperatures observed following EVT. Following an acute ischemic stroke, inflammatory factors are regarded as an inevitable pathological consequence of post-cerebral ischemia, which can begin within a few minutes and last for days to weeks or even longer [22]. Elevated levels of acute inflammatory response markers, including interleukin-6 (IL-6) and C-reactive protein (CRP), are associated with poor outcomes after stroke [23]. The IL-6 level is independently associated with futile reperfusion in the setting of EVT and with poor outcome [24]. CRP is also independently associated with early complications and with patient outcome following recanalization by EVT [25]. A high neutrophil-lymphocyte ratio (NLR) at admission may predict poorer functional outcomes following EVT in patients with AIS [22]. A low lymphocyte-monocyte ratio (LMR) or high NLR within 24 hours of EVT was also independently associated with poorer functional outcome, whereas the LMR and NLR at admission were not significant predictors of outcome at 3 months [26].

A multicenter randomized controlled trial (The Cooling for Ischemic Stroke Trial, COOLIST) on the effects of hypothermia following ischemic stroke failed to demonstrate any benefit from surface cooling [27]. Mild hypothermia is a precipitating factor for the development of pneumonia, thus reducing its potential therapeutic efficacy [27].

Inadvertent hypothermia following EVT for anterior circulation stroke is not associated with improvement in functional outcome or a reduction in mortality, but with increased risk of bradyarrhythmia and pneumonia [28]. Although therapeutic hypothermia has a positive effect on the molecular pathways of ischemic injury, the benefits from systemic hypothermia remain limited due to the time taken to reach targeted temperatures and to the related complications. Endovascular delivery of hypothermia is a novel approach to cool the affected brain tissue using selective and rapid local control of the local temperature [29]. Maintaining normothermia might be preferable to therapeutic hypothermia in the early phase of post-ischemic stroke. Paracetamol may also have a favorable effect on functional outcomes in patients with higher temperature, but further research is warranted [29–31]. The maintenance of normal body temperature may therefore be more suitable and safer than hypothermia therapy.

5. Limitations

This was a single-center retrospective study that included anterior and posterior circulation strokes. Data on inflammatory markers such as C-reactive protein was not collected. Prospective, multicenter, large-scale trials are warranted in the future.

6. Conclusions

This study found that elevated PBT ($\geq$38 °C) within 24 hours of EVT was significantly associated with a higher incidence of discharge to hospice or inpatient death, poorer clinical outcome, higher 3-month mortality, lower incidence of functional independence, and increased risk of symptomatic intracranial hemorrhage. Prospective, multicenter, large-scale trials are warranted to confirm these findings.

Author Contributions

YC, BC, and SY conceived and designed the study. YC, SY, BC, TNN, MM, MA, and JWellington drafted the manuscript. ZY, WL, and GC performed the surgery. ZY, GC, WL, JWu, DL, and JL collected the data and followed up with patients. SY, YC, and BC analyzed and interpreted the data. All authors discussed, edited, and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by Foshan Sanshui District People's Hospital review board (shengwei202105) and individual consent for this retrospective analysis was waived. Written informed consent was not required due to the retrospective nature of the study and the blinded data acquisition.

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Conflict of Interest

The authors declare no conflict of interest.

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