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Aims and Scope

Journal of Neurocritical Care (JNC) aims to improve the quality of diagnoses and management of neurocritically ill patients by sharing practical knowledge and professional experience with our reader. Although JNC publishes papers on a variety of neurological disorders, it focuses on cerebrovascular diseases, epileptic seizures and status epilepticus, infectious and inflammatory diseases of the nervous system, neuromuscular diseases, and neurotrauma. We are also interested in research on neurological manifestations of general medical illnesses as well as general critical care of neurological diseases.

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Journal of Neurocritical Care

Targeted temperature management for postcardiac arrest syndrome

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REVIEW ARTICLE

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Neurocritical care management to improve neurologic outcome for postcardiac arrest syndrome (PCAS) has focused considerably on targeted temperature management (TTM). TTM attenuates the destructive processes following ischemia/reperfusion in PCAS. The principal indication of TTM is a patient with sustained coma after return of spontaneous circulation (ROSC). TTM can be strongly recommended with a target temperature between 32°C and 36°C for patients with shockable rhythm and out-of-hospital cardiac arrest (OHCA) and weakly recommended for patients with initial asystole or pulseless electrical activity with OHCA and those with in-hospital cardiac arrest. TTM is induced and maintained using a cooling device with body temperature feedback under appropriate analgosedation. It requires the intensive management of various systemic respiratory, circulatory, and metabolic parameters that control shivering to prevent secondary brain damage. Considering the cerebral perfusion pressure, it is suggested that the mean arterial pressure should be particularly maintained over 80 mm Hg. Seizure management, including continuous electroencephalography monitoring, is also needed. Finally, we must continue the above mentioned care during and after the rewarming phase, because high fever and shivering may appear again during this period. Furthermore, neurological prognostication should be performed at least 72 hours after ROSC through clinical investigations and multimodal testing without sedation.

Keywords: Hypothermia, induced; Critical care; Neurology; Shivering; Brain injuries

INTRODUCTION

Targeted temperature management (TTM) is a clinical treatment strategy to control core body temperature (target temperature) for a certain duration to reduce secondary brain injury. Fig. 1 shows the general definition of antihyperthermia, therapeutic normothermia, and therapeutic hypothermia. Generally, therapeutic hypothermia is defined as a core body temperature of 32°C to 34°C (TTM 32°C to 34°C) using various methods. It is important to know that therapeutic normothermia, which involves maintaining a core body temperature of 36°C to 37°C (TTM 36°C to 37°C) using various methods, is different from no cooling or normothermia. Therefore, it is more appropriate to use the terms TTM 32°C to 34°C or TTM 36°C instead of therapeutic

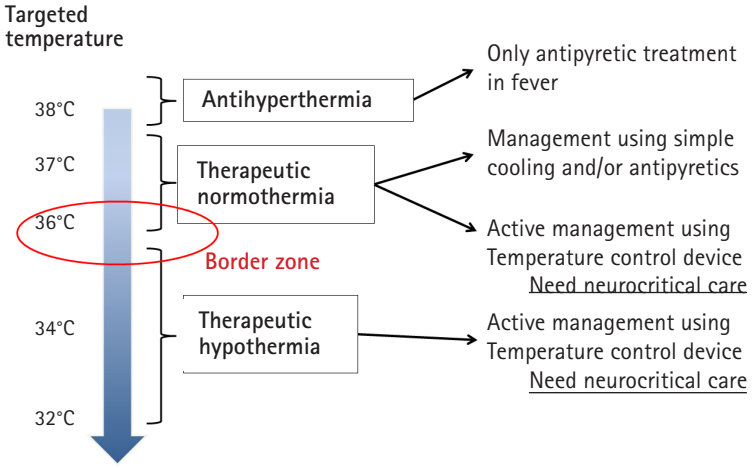

Fig. 1. Definition of targeted temperature management.

hypothermia or normothermia, respectively.

The destructive processes following ischemia/reperfusion in postcardiac arrest syndrome (PCAS) are divided into primary injury and secondary injury [1,2]. Primary injury begins immediately after cardiac arrest and is caused by cessation of cerebral blood flow (CBF). As cerebral oxygen delivery decreases, adenosine triphosphate (ATP) production stops, causing energy-dependent ion pump dysfunction. Intracellular Na+ accumulation results in cytotoxic edema, and depletion of ATP leads to anaerobic metabolism, cerebral lactate accumulation, and intracellular acidosis. Cellular ischemia causes influx of Ca^{2+} into cells, which activates lytic enzymes and mitochondrial injury, further depleting ATP. Excitatory neurotransmitter release activates lipases and proteases, causing apoptosis.

Secondary injury begins immediately after return of spontaneous circulation (ROSC) and takes place in the hours and days following cardiac arrest. After ROSC, reperfusion injury causes neuronal damage despite restoration of cerebral oxygen delivery. An initial period of cerebral hyperemia is followed by hypoperfusion, resulting in a "no-reflow" state that exacerbates secondary injury. The reason for "no-reflow" is microcirculatory dysfunction and/or impaired vasomotor regulation caused by microthrombi, decreased nitric oxide production, and increased intravascular viscosity due to extravasation of intravascular water (blood brain barrier disruption). Free radical release, glutamate production, and intracellular Ca^{2+} accumulation also leads to reperfusion injury and/or microcirculatory dysfunction.

These primary and secondary mechanisms are all stimulated by fever. Many observational studies have reported that fever after ROSC was related to poor neurological outcomes [3,4]. In the no control of TTM scenario, almost all patients will develop a fever early after ROSC [5,6]. Both mechanisms are also inhibited by hypothermia. Reduction in core temperature decreases the cerebral metabolic rate of oxygen ($CMRo_2$) and attenuates several intracellular pathways involved in secondary brain damage which occur in the minutes and days after collapse [1]. For TTM, active temperature control, shivering prevention, and intensive care unit (ICU) bundle care are needed, regardless of the selected targeted temperature. TTM to prevent fever is reasonable for neuroprotection.

EVIDENCE FOR TTM

For out-of-hospital cardiac arrest patients with shockable rhythm

TTM significantly improved neurologic outcomes in patients with PCAS of suspected cardiac origin who were treated under bundle care (Table 1) [5-7]. In 2002, a landmark study on TTM was published, which indicated that therapeutic hypothermia (TTM 32°C to 34°C, 24 hours cooling and 8 hours rewarming) resulted in better neurological outcomes at 6 months when compared to the outcomes without fever control in patients with out-of-hospital cardiac arrest (OHCA) due to an initial shockable rhythm [5]. In the same year, Bernard et al. [6] also showed that therapeutic hypothermia (TTM 33°C, 12 hours cooling and 6 hours rewarming) increased the proportion of patients with OHCA due to an initial shockable rhythm and of patients who could return home or participate in rehabilitation at discharge when compared to the outcomes without fever control. These two studies allowed managing physicians to make better decisions regarding prognostication and withdrawal of life-sustaining therapies. Another landmark study on TTM (the TTM trial) published in 2013 showed that TTM (36°C, 24 hours, followed by 8 hours of rewarming to 37°C and temperature maintenance below

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Table 1. Representative studies of TTM for shockable patients with out-of-hospital cardiac arrest

Research name	HACA		TTM		TTH		J-PULSE-HYPO
Study	Holzer et al. (2002) [5]		Nielsen et al. (2013) [8]		Kirkegaard et al. (2017) [7]		Yokoyama et al. (2011) [10]
Case no.	137	138	473	466	176	175	452
Initial rhythm VF/VT (%)	97	96	79	81	86	91	69
Archive to target temperature (hr)	8 (4–16)	-	4–8	4–8	4	4	3
Target temperature (°C)	32–34	37.5 (no control)	33	36	33	33	33.9
Target variation (°C) (2 SD)	0.5–1.0	0.5 (25 percentile)	1.5–3.2 [83]	1.5–2.2 [83]	1.0–1.5	1.0–1.5	-
TTM maintenance duration (hr)	24	24	24	24	24	48	24
Rewarming speed	Passive	-	0.5 c/hr	0.5 c/hr	-	-	-
Total TTM duration (hr)	32 (24+8)		72	72			
Intravascular device (%)	0		26 [83]		59	65	48
Infection (%)	50	36	56 [82]	51 [82]	43	49	13 [21]
Good neurologic outcome (%)	55	39	46	48	64	69	55
Outcome decision after collapse	6 months		6 months		6 months		30 days

HACA, hypothermia after cardiac arrest; TTM, targeted temperature management; TTH, time-differentiated therapeutic hypothermia; J-PULSE-HYPO, japanese population-based utstein-style study with defibrillation and basic/advanced life support education and implementation-hypothermia; VF, ventricular fibrillation; VT, ventricular tachycardia; SD, standard deviation.

37.5°C until 72 hours) was as effective (in terms of primary outcome and mortality) as therapeutic hypothermia (32°C to 34°C) and is an acceptable alternative to it [8]. Nevertheless, it is important to confirm the findings of the TTM trial, in which 80% of patients had ventricular fibrillation (VF)/ventricular tachycardia (VT) and 20% did not have VF/VT (pulseless electrical activity [PEA]/asystole), as the severity of brain injury might have been high (Table 1). In the TTM trial, providing a defined prognostication protocol resulted in a longer observation period. Lopez-de-Sa et al. [9] compared the temperatures of 32°C and 34°C for therapeutic hypothermia (24 hours) and reported that there was no significant difference in patient independence at 6 months. A multicenter registry in Japan enrolled 452 adult patients (shockable rhythm, 68.9%) undergoing therapeutic hypothermia (33.9°C ± 0.4°C) and showed that the proportion of patients with favorable neurologic outcome was 55.3% at 30 days after cardiac arrest [10]. These data support the use of temperature control. The International Liaison Committee on Resuscitation (ILCOR), American Heart Association (AHA), and American Academy of Neurology (AAN) recommend TTM at a target temperature between 32°C to 36°C for patients with OHCA due to shockable rhythm [11-13].

Although Deye et al. [14] reported that a target temperature between 32% to 34°C remained unchanged for 56% respondents in 2016 after TTM trial, the use of therapeutic hypothermia decreased in a United States registry of patients with OHCA reported in 2018 [15].

For OHCA patients with nonshockable rhythm

Regarding a nonshockable rhythm (PEA/asystole), the TTM trial presented data showing that there was no significant difference in death rates between patients who underwent therapeutic hypothermia (32°C to 34°C) or no therapeutic hypothermia (36°C) [8]. Other studies show an association between therapeutic hypothermia and favorable outcome [16-20] or survival [16,18]. In Japan, Soga et al. [21] reported that post-ROSC cooling is an effective treatment for patients with nonshockable cardiac arrest when the time interval from collapse to ROSC is short. TTM 32°C to 36°C for patients with initial asystole or PEA is also supported by the AHA, ILCOR, and AAN guideline [11-13]. Regarding TTM for nonshockable rhythm PCAS, the first large randomized control trial was published recently Therapeutic Hypothermia after Cardiac Arrest in Nonshockable Rhythm (HYPERION) [22]. In this French trial, 581 adult patients who were comatose after resuscitation from either an in-hospital cardiac arrest (IHCA) or OHCA with an initial nonshockable rhythm were randomized to either TTM 33°C or TTM 37°C, both for 24 hours. At 90 days, 29 of 284 patients (10.2%) in the 33°C group were alive with a cerebral performance category of 1 or 2, as compared with 17 of 297 (5.7%) in the normothermia group (risk difference, 4.5%; 95% confidence interval, 0.1 to 8.9; $P = 0.04$). This trial reinforces the recommendation of considering TTM 32°C to 36°C for PCAS patients with nonshockable rhythm. Patients with nonshockable rhythm tend to have numerous noncardiac issues and higher mortality than those in VF/VT [23]. Further studies are needed to determine the role of TTM in this patient population.

For IHCA patients

For patients with IHCA, the Guidelines-Resuscitation database suggested poor outcome (regarding survival to hospital discharge and neurologic outcome) with TTM [24]. A potential selection bias, however, should be pointed out while interpreting this data. According to the current guidelines, TTM should be considered for patients with IHCA [11-13]. We must also await further studies.

INCLUSION AND EXCLUSION CRITERIA FOR TTM

TTM is recommended for adult patients in a coma (Glasgow Coma Scale [GCS] ≤ 8 and E = 1 and V = 1 or 2 and M ≤ 5) after ROSC, irrespective of an initial cardiac rhythm, although patients with OHCA due to a shockable rhythm are expected to show better outcomes than those with nonshockable rhythm (Fig. 2). TTM is also considered to be performed in patients with OHCA due to nonshockable rhythm or in patients with IHCA. The most important consideration in a TTM operation is adequate neurocritical care with TTM.

If patient consciousness level has recovered rapidly recovered and they are able to follow verbal commands (GCS motor score = 6), TTM is not recommended. Although a patient with GCS motor score 5 is reported to not be a candidate for TTM in one study [25], further research is needed to determine whether GCS motor score 5 is a suitable threshold for patients to not be candidates for TTM. TTM is not indicated for patients who have a preexisting illness that precludes meaningful recovery or those considering a do-not-resuscitate order. Other contraindications are shown in Fig. 2. Finally, if the time interval between cardiac arrest and TTM initiation is long, the neuroprotective effect of TTM may be limited. Practically, this means that TTM is not applied for cardiac arrest patients 12 hours after collapse [26].

TEMPERATURE SELECTION: CONSIDERING 36°C

Therapeutic hypothermia (TTM 32°C to 34°C), which protects secondary brain injury more as compared to TTM 36°C, may produce coagulopathy and bleeding. If the patient has surgical bleeding, intracranial bleeding, hemorrhagic diathesis, or trauma, TTM 36°C should be considered, because it usually does not

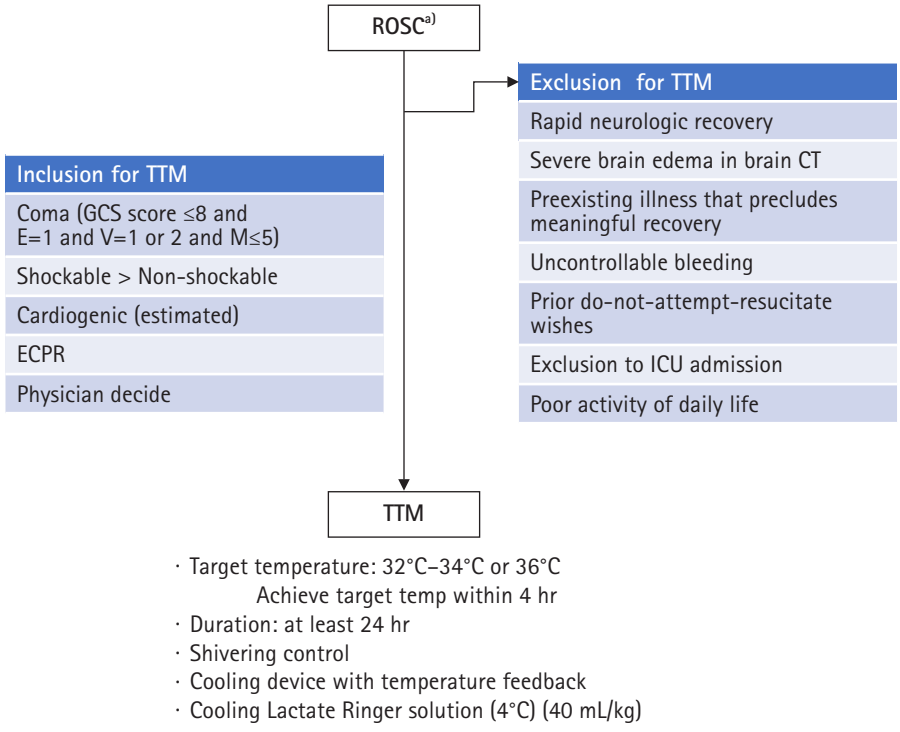

Fig. 2. Special considerations before and during targeted temperature management (TTM) induction. ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale; ECPR, extracorporeal cardiopulmonary resuscitation; CT, computed tomography; ICU, intensive care unit. [a)]Coronary angiography with percutaneous coronary intervention for ST-elevated myocardial infarction.

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cause coagulopathy. Finally, TTM 36°C using an intravascular cooling device can be performed in the rare cases of patients who have cold agglutinins (usually activated only below 31°C).

For circulatory management, compared to TTM 36°C, TTM 32°C to 34°C may result in more hemodynamic instability [27] that may require vasopressor support.

INDUCTION OF TTM

For patients eligible for TTM, tracheal intubation and monitoring of several aspects, including circulation, respiration, and metabolism, should be performed. Core body temperature is monitored using a bladder, endovascular, or esophageal probe.

If the patient is eligible for TTM, it must be induced and target temperature must be reached as soon as possible (Fig. 2). Table 1 shows longer time intervals to achieve targeted temperature, especially in Hypothermia after Cardiac Arrest Study Group study [5], possibly because cooling devices with temperature feedback were not used. Stanger et al. [28] reported that initiation of TTM (door-to-TTM) within 122 minutes of hospital admission was associated with improved survival. Care must be taken to control the time interval between collapse and ROSC, because this interval might determine the outcome.

In patients with cardiac failure, TTM should be induced under extracorporeal cardiopulmonary resuscitation (ECPR) which can manage core body temperature. If the patient does not have accompanying left ventricular dysfunction, TTM is induced using a temperature control device (endovascular, surface, intranasal, or esophageal cooling) with automated feedback temperature control through continuous input of the patient's core temperature [29]. Recent studies show rapid achievement of target temperatures using temperature control devices and shivering management.

Rapid infusion of cold (4°C) lactated Ringer infusion (40 mL/kg) decreases the core body temperature by 1°C for each liter [30,31] in the emergency room and/or ICU. However, prehospital use of cold fluids increases the risk of rearrest and pulmonary edema [32]. Shivering control and analgosedation is needed for rapid induction of TTM, regardless of targeted temperature with/without ECPR.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

Among patients without ROSC but with good neurological indicators (shockable rhythm, short time interval between collapse and ROSC), ECPR is an option for resuscitation. Ortega-Deballon et al. [33] reviewed several cohort studies and reported that the overall survival rate with ECPR was 20% among patients without ROSC; however, the survival rate is known to vary among studies. In Japan, the Study of Advanced Cardiac Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan (SAVE-J) study reported that among OHCA patients with a shockable rhythm on initial electrocardiography, the rate of good neurological outcomes (11.2%) at 6 months after insult was higher with treatment including ECPR, therapeutic hypothermia, and intraaortic balloon pump (IABP) than with treatment not involving ECPR (2.6%) [34]. Thus, ECPR is a good approach for resuscitation in selected patients.

One study revealed that IABP with percutaneous coronary intervention (PCI) contributed to improved neurologic outcome under cardiogenic shock after ROSC [35]. Another study revealed that ECPR in addition to PCI improved neurologic outcome in patients who failed to respond to conventional CPR if the collapse-to-bypass interval was less than 55.5 minutes [36]. IABP or ECPR may be considered in patients for whom the cause of cardiac arrest is suspected to be reversible.

Furthermore, cardiogenic shock should not be a reason to avoid TTM, and TTM before and/or during acute PCI is not a contraindication. Practically, if TTM has already been started before PCI, possible complications (low blood pressure and/or hypopotassemia due to massive urination, etc.) must be checked and treated even in catheter laboratory (see heading: circulatory care, electrolyte management).

TREATMENT FOR MYOCARDIAL DYSFUNCTION

Acute coronary syndrome is a common cause of cardiac arrest, and treatment for revascularization is necessary. In patients with ST-segment elevation or left bundle branch block on initial electrocardiography after ROSC, the prevalence of an acute coronary lesion is more than 80% [37]. If the cause of cardiac arrest is ST-elevation acute myocardial infarction (STEMI), immediate coronary angiography (CAG) with/without PCI is recommended. Even for non-STEMI that induces cardiac arrest, CAG with/without PCI is recommended, because prehospital electrocardiography does not identify an occluded coronary artery [38], and a previous study found that 25% of patients with non-STEMI had an occluded coronary artery [39]. Although Lemkes et al. [40] recently reported that a strategy involving immediate CAG was not found to be better than delayed CAG for PCAS patients who had no signs of STEMI, the relatively lower severity of the patients included was pointed out as a research limitation [41]. Further

study is needed regarding necessity of emergency CAG.

Reperfusion injury, in addition to ischemic insult, is a main cause of myocardial dysfunction. Many studies indicate that PCI improves survival or neurologic outcome [42,43]. Some studies have demonstrated that better survival and functional outcome is achieved after ROSC with a combination of TTM and PCI for STEMI [44,45]. In one randomized controlled trial and analysis that did not involve cardiac arrest patients, this combination reduced the size of the cardiac muscle ischemic lesion in case hypothermia was achieved before reperfusion of the coronary artery [46,47]. Clinical research reported that TTM (lower core temperature) before PCI can decrease the severity of myocardial infarction and might improve cardiac function after ROSC [48]. Studies of survival or neurologic outcome of emergency PCI for non-STEMI are inconsistent; some investigators did not find it helpful [49], but others reported favorable resolutions [42,43,45,50].

SHIVERING CONTROL

Shivering is a physiologic homeostatic mechanism to maintain body temperature and is usually initiated at approximately 36°C [51]. Shivering is severe at TTM 36°C due to the patient thermoregulatory defenses, which are partly suppressed at 32°C to 33°C [1,30]. One interesting report showed that shivering control and analgosedation use are difficult with TTM at 36°C [52]. Sustained shivering causes an increased metabolic rate and cardiac output, tachycardia, elevated blood pressure, increased lethal cardiac complications, increased carbon dioxide (CO_2) production, wound pain, increased $CMRo_2$ and intracranial pressure (ICP) [53], and increased stress response. Shivering commonly occurs during TTM and may lead to failure to achieve or maintain adequate hypothermia. Therefore, the management of shivering, including its evaluation and treatment using adequate analgosedation, is important and necessary during TTM to preserve the cerebral oxygen demand/supply balance and strict temperature management.

Warning signs of shivering are goose bumps, masseter palpation, electrocardiography artifacts, difficulty in cooling, and temperature increase in spite of TTM. Shivering should be assessed using a subjective, simple, and reliable clinical scale such as the Bedside Shivering Assessment Scale every 1 hour in the ICU [53]. To suppress shivering and prevent prolonged sedation and paralysis, a stepwise antishivering protocol during TTM is recommended [29,54]. However, it does not necessarily need to be stepwise and depends on the intensity of shivering. In general, patients with PCAS who are comatose during TTM need tracheal intubation and therefore require sedation and analgesia. At initiation of hypothermia, skin counter-warming using nonpharmacologic methods should be considered even when surface cooling methods are used for TTM (Fig. 3) [55-57]. This involves the warming of the noncooled areas of the skin (i.e., the face, hands, feet) using a warm-air blanket even when surface cooling methods are used. Drug therapy should include magnesium sulfate, dexmedetomidine, remifentanil, fentanyl, meperidine, and scheduled acetaminophen. If shivering is still not controlled, propofol, midazolam, and finally neuromuscular blockade (NMB) may be initiated [54]. To suppress shivering, a combination of methods should be used, and shivering should be aggressively controlled. It is presumed that the combined use of NMB in addition to complete analgosedation to achieve rapid induction of TTM and NMB titration after achieving targeting temperature are an alternative method.

On the other hand, one study reported that patients with the most severe brain injuries have less shivering [58]. Other studies have shown that shorter time to target temperature is associated with poor neurologic outcome [59,60]. It is hypothesized that patients with more severe or irreversible neurologic damage are less reactive to low temperatures, so there is less shivering [60] and a reduced requirement for NMB [61]. The relationship between shivering and outcome has yet to be fully elucidated.

ANALGOSEDATION

Sedation may reduce secondary cerebral ischemia and decrease elevated ICP by reducing the $CMRo_2$, CBF, and cerebral blood volume (CBV) [62]. Sedation and analgesia also help control shivering and seizures, which is required for the induction and maintenance of TTM to reduce the risk of brain damage caused by seizures (Fig. 3).

On the other hand, sedation makes it difficult to perform an accurate neurologic examination and clinical assessment. After arrest, residual sedation or paralysis confounds the clinical examination [63]. One study showed that patients undergoing TTM ($\leq$ 33°C) recovered consciousness in a mean of 3.8 days, with approximately 20% awakening after 5 days postarrest [64]. Recently, Rey et al. [65] reported that increased utilization of midazolam during the TTM phase correlates with late awakening (median time to awakening 5 days; range, 3 to 23 days from sedation stop).

Early interruption of sedation during TTM causes shivering. In brain-injury patients, interruption of sedation causes increased ICP [66]. Therefore, a wake-up test should be avoided during the first 24 hours after ROSC [67]. It is suggested that the tapering of sedative infusions should not exceed 25% per day [51]. In patients at risk of brain edema or who have an elevated ICP, uncontrolled status epilepticus, or ongoing hypothermia, sedatives should not

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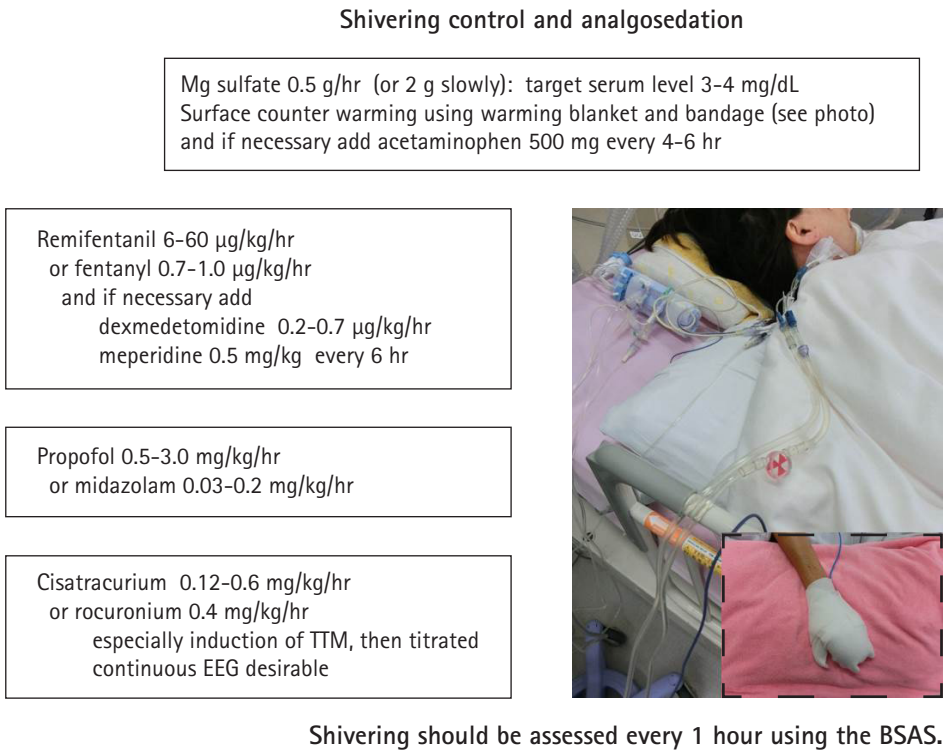

Fig. 3. Shivering control and analgosedation. TTM, targeted temperature management; EEG, electroencephalography; BSAS, bedside shivering assessment scale.

be abruptly discontinued. When weaning of sedation commences, attention should be paid to these risks with appropriate use of such tools as computed tomography, electroencephalography (EEG), and ICP monitoring.

Drugs for TTM

Propofol has a rapid onset and short duration of action which allows for meaningful neurologic examinations [68]. It is associated with a greater risk of hypotension with cerebral hypoperfusion than other drugs, as well as the risk of propofol infusion syndrome. Propofol significantly decreases CBV by causing vasoconstriction [69].

Midazolam results in less hemodynamic instability than propofol, but it prolongs the duration of mechanical ventilation and length of ICU stay [70]; furthermore, it may prolong the time to awakening and reduce the accuracy of the clinical examination, because the half-life of midazolam is prolonged by hypothermia [65,71]. During TTM, low continuous infusions of midazolam are preferred.

Dexmedetomidine is short-acting, provides mild to moderate sedation and analgesic effects, allows clinical assessment, and may be neuroprotective [72]. Dexmedetomidine directly lowers the shivering threshold by central alpha-2 agonism [73]. However, it frequently causes hypotension and bradycardia.

NMB is selectively administered during TTM, resulting in more rapid achievement and maintenance of target temperature and control of shivering [74]. A short-acting NMB can be helpful in patients with refractory shivering who are sedated with continuous propofol/midazolam use. Some older studies suggest that continuous NMB has a beneficial effect and improves outcome [75-77]. Currently, intermittent dosing is preferred to continuous infusions. Continuous NMB infusion was not associated with improved outcomes in one small randomized controlled trial [78]. A multicenter study found that intermittent as needed NMB was associated with improved outcomes when compared to continuous NMB [79]. NMB should be used only if the patients are completely sedated. Moreover, clinicians have to be careful of the risk of pressure injury, deep vein thrombosis, and critical illness polyneuropathy resulting from complete immobilization. NMB masks seizures that are typically detected during the neurological evaluation. EEG monitoring should be considered in comatose patients after cardiac arrest, particularly if NMB is used [12,80].

TTM MAINTENANCE AND DURATION

There are many guidelines and reviews for detailed discussion of

Neurology	cEEG: continuous pattern or not Pupil size, light reflex, and NPi Shivering control (Fig. 3) Seizure control
Circulation	Goal MAP > 80 mm Hg for cerebral perfusion pressure Differential diagnosis: hypovolemic shock: cold diuresis (most), bleeding due to CPR cardiogenic shock: stunning distributive shock: sepsis, anaphylaxis obstructive shock: tension pneumothorax, cardiac tamponade Bradycardia: usually no treatment, if not with hypotension
Respiration	Goal PaO_2 70-100 mm Hg Goal $PaCO_2$ 40±5 mm Hg
Renal, Electrolytes	Cold diuresis Decrease: K, Mg, phosphorus Intracellular shift during cooling: warning for re-increase with rewarming Goal K >4.0 mEq/L Goal Mg >2 mg/dL Goal phosphorus >3 mg/dL
Blood sugar	Goal blood sugar unknown (>90 mg/dL), avoid hypoglycemia/hyperglycemia Increased insulin resistance, insulin drip
Anemia	Disturbed coagulation ≤35°C Caution for mild bleeding, especially with ECPR
Drug	Decreased pharmacokinetics/drug metabolism

Fig. 4. Systemic considerations during the maintenance phase of targeted temperature management (TTM). cEEG, continuous electroencephalography; NPi, neurological pupil index; MAP, mean arterial pressure; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.

the entire course of TTM (Fig. 4) [29,81]. Patients are maintained at the target temperature for at least 24 hours (maintenance phase); different studies have reported a range of durations, from 12 to 48 hours, but 24 hours is generally recommended (Table 1) [29]. Regarding the optimal duration of TTM, Kirkegaard et al. [7] reported that there was no significant difference in 6-month survival between therapeutic hypothermia at 33°C for 24 and 48 hours among patients with combined cardiac rhythm (shockable, 90%). During the maintenance phase, the variation of temperature should be managed to be minimal, because trials have shown that huge variations of temperature (overcooling) might be linked to complications, like infection [8,82,83]. Several studies suggest the association between minimal variation in temperature and a high percentage of favorite neurologic outcomes; they are summarized in Table 1 [7].

SEIZURE MANAGEMENT AND CONTINUOUS EEG

Detection of seizures

Seizures are caused by abnormal excessive or synchronous neuronal activity in the brain [84]. Seizures are not only the result of brain injury caused by cardiac arrest but also a risk for secondary brain injury. They are classified as generalized convulsive seizures or nonconvulsive seizures; muscle contraction and relaxation are absent in the case of nonconvulsive seizures.

The incidence of nonconvulsive status epilepticus (NCSE) in comatose postarrest patients is 12% to 24% in adult PCAS [85-88]; an even higher incidence (47%) has been reported in pediatric cardiac arrest [86]. Other abnormal EEG patterns are found in maximally 40% of patients which are treatable [87]. Based on continuous EEG (cEEG) records, some studies indicate that seizures occur most often within the first 8 hours after ROSC [85,87,88]. Seizures are masked by NMB in 3% to 44% of cases [85,86,89,90]. For these reasons, cEEG monitoring and assessment of NCSE during the induction, maintenance, and rewarming periods are indicated for all TTM patients (Figs. 4, 5) [86,91,92]. Seizures following cardiac arrest are associated with increased mortality [85,87,88].

Prophylactic and therapeutic use of antiepileptic drugs

Some investigations have revealed that antiepileptic drugs (AEDs) do not decrease the incidence of convulsive seizures or improve neurologic outcome [93,94]; furthermore, the effects of AEDs are not standardized. As there is no standard method to diagnose seizures using cEEG and drugs may cause adverse effects (hypotension, etc.), the prophylactic use of AEDs is not recommended.

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Neurology	cEEG: continuous pattern or not Pupil size, light reflex, and NPi Shivering control (Fig. 3) After rewarming, stop neuromuscular blockade, then stop analgesics/sedatives Seizure control
Rewarming strategy	Target temperature: 36.0°C Speed: 0.1°C/hr Duration: generally need 36 hours (from 33.0°C)
Normothermia after rewarming	Until 72 hr after ROSC: >36.0°C After 72 hr after ROSC: >38.0°C
Circulation	Avoid hypotension
Electrolyte	Avoid hyperkalemia
Blood sugar	Avoid hypoglycemia

Fig. 5. Special considerations during the rewarming phase of targeted temperature management. cEEG, continuous electroencephalography; NPi, neurological pupil index; ROSC, return of spontaneous circulation.

There is no high-grade evidence showing a relationship between AED use and survival or neurologic outcome [95-97], but as seizures may lead to secondary brain injury, treatment of recurrent seizures could be considered as standard therapy in comatose patients with PCAS.

CIRCULATORY CARE

Optimal mean arterial blood pressure and cerebral perfusion pressure

Transient myocardial systolic or diastolic dysfunction [98-101] and a decline in systemic vascular resistance [100] has been observed in PCAS, but may be less clinically significant and can be managed conservatively [101]. One study showed the best survival in patients with a mean arterial blood pressure (MAP) of 76 to 86 mm Hg and mixed venous oxygen saturation of 67% to 72% [102]. Another study reported that a time-weighted average MAP ≥ 70 mm Hg was associated with a better neurologic outcome than lower levels [103]. MAP ≥ 100 mm Hg during the 2 hours after ROSC was associated with better neurologic recovery at hospital discharge (retrospectively examined) [104]. Young et al. [105], however, found no relationship between higher MAP during therapeutic hypothermia and neurologically intact survival. Bundled care with goals of MAP of 80 to 100 mm Hg, central venous pressure (CVP) ≥ 8 mm Hg, and central venous oxygen saturation ≥ 65% led to better neurologic outcomes and less mortality than in historic controls [106]. A bundle requiring MAP ≥ 65 to 70 mm Hg, CVP ≥ 8 to 12 mm Hg, and hemoglobin ≥ 9 to 10 g/dL showed a better survival rate to hospital discharge and neurologic outcome at 1 year [89].

Regarding cerebral perfusion pressure (CPP) in PCAS patients in a previous study [107], ICP increased to around median 10 mm Hg (interquartile range [IQR], 5 to 20) in patients with good outcomes and to 25 mm Hg (IQR, 10 to 30) in those with poor outcomes. A relatively low burden of intracranial hypertension (ICP > 20 mm Hg) was also reported [108,109]. After ROSC, prolonged cerebral hypoperfusion develops within hours and may last for hours to days [110]. During this hypoperfusion, cerebral vascular resistance is increased, and pressure autoregulation is right-shifted or absent, resulting in decreased blood flow oxygen delivery and increased CPP needed to maintain microvascular flow [111,112]. Observational studies show a consistent association between lower postarrest blood pressure and mortality [113,114]. Moreover, maintaining a MAP > 80 mm Hg is associated with improved outcomes, even if achieved using a vasopressor [89,106,113,115]. Recently, Sekhon et al. [116] reported that the optimal MAP to prevent brain hypoxia in case series with multimodal neuromonitoring is about 80 mm Hg.

Studies suggest that the MAP should be kept higher than a defined threshold during the postarrest period considering CPP in the damaged brain. Although there is some concern about higher MAP achieved using vasoactive agents and poor outcomes [27], recently, Jakkula et al. [117] reported, based on a multicenter study, that there is no significant difference in neuron-specific enolase concentration at 48 hours after cardiac arrest and neurologic outcome between low-normal (65 to 75 mmHg) and high-normal (80 to 100 mm Hg) MAP management [117]. There is no evidence that a higher MAP causes increased ICP and worsening of outcome. Taken together, it is important to maintain CPP normally, and considering CPP, it is suggested that MAP should be maintained over 80 mm Hg (Fig. 4).

Fluid resuscitation

The amount of fluid required to maintain MAP after arrest was reported to be 3.5 to 6 L [99,100]. However, the relationship between fluid or blood products and outcome after ROSC is unclear, in contrast to what is known about albumin in sepsis [118]. If fluid resuscitation alone is ineffective, it is reasonable to use vasoactive drugs [100,113]. In patients with acute coronary syndrome, emergency CAG with/without PCI should be considered [119].

Heart rate and arrhythmia management

In hypothermia, bradycardia occurs normally and is associated with reduced systolic dysfunction in animal models [120]. A heart rate of 30 to 40 beats/min is common at TTM 33°C and generally does not require therapy unless associated with hypotension [1]. Bradycardia may be more pronounced at lower target temperatures; symptomatic bradycardia may be treated using a beta agonist instead of atropine, which has been found to be ineffective [1].

A lowered heart rate during TTM is considered to be associated with favorable outcomes. A recent study has shown that bradycardia and a low heart rate are predictors of favorable neurological outcomes [121,122]. More recently, a relationship between the heart rate response during rewarming and favorable outcomes has been suggested [123]. In this study, an increased heart rate during rewarming predicted favorable neurological outcomes. The heart rate during TTM is a key indicator of brain variability.

Arrhythmias may develop if the core temperature accidentally falls below 28°C (30°C if electrolyte disorders are present); therefore, the core temperature must be maintained above 30°C. Arrhythmias should not be viewed as a reason to discontinue TTM. QT prolongation is common during TTM, and concomitant QT prolonging drugs should be used with caution [1].

RESPIRATORY CARE

Oxygenation

The cause of hypoxemia in patients with PCAS includes lung contusion induced by chest compressions, atelectasis, ventilator-associated lung injury, and others. It is no wonder that hypoxemia in PCAS may induce secondary brain damage beyond that during the arrest itself because of inadequate cerebral oxygen delivery. Some studies have indicated that hypoxemia after ROSC is associated with worse outcomes than normoxemia [124-126]; therefore, hypoxemia may need to be avoided after ROSC.

Positive end-expiratory pressure (PEEP) is another factor associated with oxygenation. Protective mechanical ventilation with a lower tidal volume and higher PEEP is more commonly used after cardiac arrest. This appears to reduce the incidence of pulmonary complications, although other organs are still at risk [127]. A consensus on PEEP settings for patients with PCAS is lacking, although increasing PEEP may elevate ICP [128]. It may be rational to maintain the PEEP as low as possible as long as higher concentrations of oxygen can be avoided.

Hyperoxemia after ROSC promotes the formation of reactive oxygen species (oxidative stress), which can induce secondary injury in brain tissue already damaged by cardiac arrest. Both observational studies [124,126,129,130] and metaanalyses [131-133] show that hyperoxemia is associated with poor survival and neurologic outcome in PCAS. Although the conclusions of other studies have differed [125,134], it may be necessary to avoid hyperoxemia after ROSC.

It may be concluded that both hypoxia and hyperoxia should be avoided, and a PaO_2 of 70 to 100 mm Hg is reasonable (Fig. 4).

Ventilation

Although cerebral pressure autoregulation may be impaired after resuscitation, CO_2 reactivity of the cerebral vasculature after ROSC is preserved during mild therapeutic hypothermia [135,136], and therefore, CO_2 should be controlled during TTM. Hypocapnia following hyperventilation causes cerebral vasoconstriction and inadequate blood flow, based on some observational studies, and it can certainly cause and/or worsen cerebral ischemia, worsen outcome, and cause injury to other organs in PCAS [137-140].

Increased $PaCO_2$ may cause further worsening of an elevated ICP by increasing the CBF. However, evidence of the effect of hypercapnia on outcome after ROSC is conflicting [134,138-140]. Although a phase II randomized controlled trial found that S100 calcium-binding protein beta concentrations decreased over time in patients with $PaCO_2$ maintained at 50 to 55 mm Hg but not in those with a $PaCO_2$ of 35 to 45 mm Hg and better functional recovery with a $PaCO_2$ of 50 to 55 mm Hg, hospital mortality did not differ significantly between the two groups [141].

Taken together, the risk of poor outcome appears to differ for hypocapnia and hypercapnia, even if $PaCO_2$ deviations from normal are comparable (Fig. 4). Although there is insufficient evidence to recommend routine use of mild hypercapnia after cardiac arrest, hyperventilation should be avoided.

ELECTROLYTE MANAGEMENT AND GLYCEMIC CONTROL

During hypothermia induction, particularly to lower target tem-

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peratures, an initial cold diuresis may result in hypokalemia, hypomagnesaemia, and hypophosphatemia. Moreover, hypothermia moves potassium from the extracellular to intracellular space. Frequent assessment of electrolytes and repletion is indicated. Repletion of potassium is carefully done, since serum potassium levels will predictably rise when rewarming is initiated. A target potassium level of 4.0 mmol/L is reasonable during TTM induction and maintenance [29]. Magnesium and phosphorus should be maintained in the high to normal range (Fig. 4).

Glycemic control is important in the management of critically ill patients. The current concepts of glycemic control recommend avoiding hypoglycemia and minimizing glycemic variability (GV). One database study in France showed that smaller magnitudes of GV were observed in patients with a good neurologic outcome compared with those with a poor outcome [142]. Other studies reported that increased GV was associated with increased mortality and unfavorable neurologic outcome [143,144]. This suggests that attention should be paid to GV. In patients with PCAS, the optimal target range remains unknown. However, insulin sensitivity increases and blood glucose levels decrease as body temperature rises during TTM. Further, patients with diabetes may be tolerant to higher glucose values. Blood glucose levels should be checked frequently to avoid hypoglycemia and hyperglycemia (Fig. 4).

REWARMING AFTER TTM

The rewarming phase follows maintenance and should be slow and controlled in order to avoid critical complications. Active normothermia is typically maintained for 24 to 48 hours after rewarming is completed (Fig. 5). Recently, Hifumi et al. [145] reported that a longer rewarming duration was significantly associated with and was as an independent predictor of favorable neurologic outcomes in OHCA patients who received therapeutic hypothermia.

PROGNOSTICATION

Even clinical findings like brain death are not definitive for at least 24 hours following ROSC [146]. In the first 72 hours after cardiac arrest, no sign, symptom, or combination of findings short of brain death precludes favorable recovery [12,147]. As in many neurocritical care conditions, however, accurate neurological prognostication after ROSC is challenging. Pupil diameter and/or pupil light reflex might be associated with brain injury. Recently quantitative pupillometry has allowed a more comprehensive assessment of pupillary function when using pupillary light reflex (PLR) and/or neurological pupil index (NPi). The PLR is expressed as the percentage pupillary constriction in response to a calibrated light stimulus, and PLR < 10% is considered as abnormal. The NPi is a scalar value (between 0 and 5, < 3 is considered as abnormal) which is calculated based on an algorithm that accounts for several measured pupillary variables, including size, percentage constriction, constriction velocity, dilation velocity, and latency. Oddo et al. [148] reported, based on a multicenter study, that NPi < 2.0 at day 1 to 3 after cardiac arrest has an association with poor neurologic outcome (specificity 1.0). Based on earlier estimation of neurologic outcome, Riker et al. [149] reported that 6 hours after ROSC, an NPi < 1.5 was associated with poor neurologic outcome (specificity 1.0). In both studies, sensitivity was low. In Japan, Tamura et al. [150] reported that 0 hour after ROSC, the cutoff value of PLR 11% was associated with favorable neurologic outcome (specificity 0.81). Regarding cEEG, Ruijter et al. [151] recently reported that continuous background patterns at 12 hours after cardiac arrest are associated with good recovery (specificity 0.91) and suppression (< 10 μV) pattern with poor outcome (specificity 1.0) [151]. Using EEG, poor outcome may be predicted within 24 hours after cardiac arrest under TTM.

Withdrawal of life-sustaining therapy based on perceived neurological prognosis has been linked to preventable deaths after cardiac arrest [152,153]. Early aggressive care must be performed initially.

CONCLUSION

TTM for PCAS is a fundamental strategy in neurocritical care. Further studies are needed to identify the types of cases in which patients would benefit from TTM and to determine the optimal target temperature and duration of TTM.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article.

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Central fever: a challenging clinical entity in neurocritical care

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Fever is probably the most frequent symptom observed in neurointensive care by healthcare providers. It is seen in almost 70% of neurocritically ill patients. Fever of central origin was first described in the journal *Brain* by Erickson in 1939. A significant number of patients develop this fever due to a noninfectious cause, but are often treated as having an infectious fever. Unjustified use of antibiotics adds to the increased cost of treatment and the emergence of resistant strains, contributing to additional morbidity. Since fever has a detrimental impact on the recovery of the acutely injured brain and contributes to an increased stay in the neurointensive care unit (NICU), timely and accurate diagnosis of the cause of fever in the NICU is imperative. Here, we try to understand the underlying mechanism, risk factors, clinical characteristics, diagnosis and management options of the central fever. We also make an attempt to differentiate two noninfectious causes of fever in the NICU: paroxysmal sympathetic hyperactivity and central fever.

Keywords: Humans; Fever; Brain; Intensive care units; Ant-bacterial agents

INTRODUCTION

Fever is probably the most frequent symptom observed in the neurointensive care unit (NICU) by healthcare providers. An oral temperature greater than 37.5℃ is considered a fever [1,2]. Hyperpyrexia is usually a diagnosis of exclusion, with temperatures exceeding 41℃ and nonresponsiveness to antipyretic treatment [3,4]. Fever is seen in almost 70% of neurocritically ill patients [5-10]. Fever of central origin was first described by in the journal *Brain* by Erickson [11] in 1939. A significant number of these patients have fever from noninfectious causes (47% in Kilpatrick et al. [6] and 25% in Commichau et al. [7]), but this is often treated as infectious fever. Unjustified use of antibiotics adds to the increased cost of treatment and the emergence of resistant strains, contributing to additional morbidity. Since fever has a detrimental impact on the recovery of the acutely injured brain [12-15] and contributes to an increase in length of stay in NICU [8]; timely and accurate diagnosis of the cause of fever in the NICU is imperative.

Here, we try to understand the underlying mechanism, risk factors, clinical characteristics, diagnosis and management options of central fever (CF). We also make an attempt to differentiate two noninfectious causes of fever in NICU, paroxysmal sympathetic hyperactivity and CF.

EPIDEMIOLOGY

Overall in the intensive care unit (ICU), at least 50% of fever are reported to be due to noninfectious causes [16]. The incidence of noninfectious fever in the neurology ICU is 23% while in the neurosurgical ICU it is 47% [6]. Of these, the highest rates of febrile episodes occur in patients with subarachnoid hemorrhage (SAH; 50% to 65%), followed by traumatic brain injury (TBI; 4% to 40%) and intracerebral hemorrhage (ICH; 31%), with no cause of fever identified in 28% of patients, suggesting fever of central origin [7,10,17,18]. Hyperthermia is a frequent complication of acute ischemic stroke in 50% of these patients and carries a poor prognosis [19].

PATHOPHYSIOLOGY

An abnormal rise in temperature may be physiological, environmental, or even drug-related, rather than due to infection. The mechanism of CF in the NICU is not well defined but the literature suggests some probable mechanisms. Inflammatory markers causing fever may be triggered by extreme physiologic stress in acute neurologic injury [20,21]. Brain injury may also lead to the disruption of the mesencephalic-diencephalic mechanisms responsible for the inhibition of thermogenesis [22]. Monocytes and macrophages produce the cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α), which act on the organum vasculosum of laminae terminalis. This in turn leads to the release of prostaglandin E2 (PGE2) via activation of the cyclooxygenase-2 (COX-2) enzyme. PGE2 acts on the preoptic area of the hypothalamus leading to an increase in the set point of the hypothalamus, thereby increasing the body temperature [23-34]. Systemic pyrogens, such as IL-1, appear to enter the brain at regions where there is an incomplete blood-brain barrier (circumventricular organs) and act on the preoptic area of the hypothalamus to induce fever [24,35-38]. Various neurological events that take place in febrile patients affect this pathway. Direct hemotoxic damage to thermoregulatory centers in the preoptic region, interference with tonic inhibitory inputs from lower midbrain that ordinarily suppresses thermogenesis, and stimulation of prostaglandin production leading to temperature set point elevation, have all been implicated in the causation of CF [39]. CF is speculated to result from damage to the hypothalamus, midbrain, or pons, and be enhanced by increased sympathetic activity, opening of the ventricles, damage to the frontal lobes, physical distortion, diffuse axonal injury (DAI), or toxic blood metabolites [39]. CF may also be due to the selective loss of warm-sensitive neurons, the osmotic changes detected by the organum vasculosum laminae terminalis, or from hormonal changes (progesterone, prostaglandin) modifying the firing rate of temperature-sensitive neurons in the medial preoptic nucleus [40].

Posttraumatic hyperthermia, also known as neurogenic fever, is another common cause of fever. Stimulation studies have suggested that the mechanism involves an imbalance between the hypothalamus and the various temperature regulating centers in the brainstem and spinal cord [41]. Won and Lin [42], in their study conducted on rabbits, found that inhibition of five hydroxytryptamine receptors in the anterior hypothalamus increased heat production and decreased heat loss, leading to hyperthermia. Suggested mechanisms for this effect include increased metabolic rate, increased carbon dioxide production, decreased cerebral blood flow, acidosis, brain edema exacerbation, excitotoxic neurotransmitter release, and blood-brain barrier breakdown. Disease-specific mechanisms are also described in Table 1.

Subarachnoid hemorrhage

SAH may cause impairment of hypothalamic thermoregulation due to the presence of clots in the suprasellar cistern. It may also lead to an intense activation of the sympathetic nervous system, leading to peripheral vasoconstriction and thus diminishing the heat-dissipating mechanisms [43].

Intracerebral hemorrhage

Intraventricular hemorrhage (IVH) is thought to elevate the temperature set point in the hypothalamus by direct damage to the thermoregulatory centers in the preoptic region, stimulation of prostaglandin production, or decreased inhibitory feedback from the lower midbrain which suppresses thermogenesis [39].

Tumors

It is hypothesized that a tumor, or its necrotic products, may lead to inflammation of leptomeninges, thus triggering fever [44].

Traumatic brain injury

While TBI can affect all seven pituitary hormones [45], growth hormone (GH) deficiency is most frequently reported [46,47]. Patients with GH deficiency have a reduced sweating capacity which increases the risk of developing hyperthermia [48]. TBI-induced hypothalamic-pituitary damage may be due to direct injury to the hypothalamic-pituitary area, a secondary injury from hypoxia, or increased intracranial pressure [49]. CF in patients with TBI can also be caused by direct injury to the hypothalamus [15,50]. The development of CF is associated with inflammatory changes within the hypothalamus [51].

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Table 1. Various neurological diseases and their relation with central fever

Disease	Probable mechanisms	Risk factors	Effects on outcome
TBI	1. GH deficiency	1. Diffuse axonal Injury	1. A negative association between early peak fever greater than 39℃ and hospital mortality
	2. Direct injury to the hypothalamic-pituitary area or secondary injury from hypoxia or increased intracranial pressure.	2. Frontal lobe injuries	2. Possibility of antibiotic overuse, with the associated risk of the emergence of resistant microorganisms
		3. Young age, low GCS on presentation, skull fracture, presence of blood in the parenchyma/ventricles, and acute brain injury.	3. Prolonged coma or unawareness, diabetes insipidus and poor outcomes
		4. Location of the skull fracture in proximity to the hypothalamic region (for example, anterior fossa)	
ICH	1. Direct damage to thermoregulatory centres in the preoptic region, stimulation of prostaglandin production, and decreased inhibitory feedback from the lower midbrain which suppresses thermogenesis	1. ICH with intraventricular extension	1. High mortality and poor functional outcome at 3 months on modified Rankin Scale
		2. Larger hematoma volumes	2. Duration of fever was independently associated with poor outcome in those who survived past 72 hours.
		3. Basal ganglia and thalamic involvement	
		4. Third ventricular shift	
SAH	1. Impair hypothalamic thermoregulation due to presence of clots in suprasellar cistern.	Disease severity, amount of blood in the subarachnoid space and associated IVH	1. Even a single episode of fever after SAH is associated with poorer outcomes even in best-grade patients.
	2. Intense activation of the sympathetic nervous system		2. ↑ Vasospasm associated with CF
			3. More severe functional disability and cognitive impairment among survivors
Tumours	Tumour or its necrotic products may lead to inflammation of leptomeninges, thus triggering fever.	More prone with tumours located in the sella, diencephalon, and intraventricular region	Poor outcome
AIS	Hypothalamic dysfunction	It is probable, larger the ischemia more the chances of CF	1. May increase volume of the ischemic zone
			2. ↑ Mortality in stroke patients

TBI, traumatic brain injury; GH, growth hormone; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; CF, central fever; AIS, acute ischemic stroke.

Etiology

CF can occur following any acute brain injury (Table 2) [38,52-56].

RISK FACTORS

Various predisposing factors have been defined for the occurrence of CF in the NICU. Independent predictors of CF on multivariate analysis include blood transfusion, SAH, IVH, tumor, or onset of fever within 72 hours of hospital admission [57]. Intraventricular catheterization is a risk factor for unexplained fever, which suggests a role for ventricular hemorrhage in the pathogenesis of CF [7]. Risk factors among various acute neurological conditions are reported as follows (Table 1).

Subarachnoid hemorrhage

Disease severity, amount of blood in the subarachnoid space, and IVH are strong risk factors for the development of fever [7,58,59].

Intracerebral hemorrhage

ICH with intraventricular extension and larger hematoma volumes (86.7 ± 66.5 mL CF vs. 33.7 ± 54.4 mL in no fever) are associated with an increased probability of developing CF [18]. There were no significant differences related to the anatomical location of hematoma and presence of CF, but involvement of the basal ganglia and thalamus showed a trend towards an increased chance

Table 2. Causes of central fever

Subarachnoid haemorrhage
Intraventricular haemorrhage
Intracerbral haemorrhage
Tumours: sella, diencephalon, and intraventricular region [52]
Traumatic brain injury
Ischemic stroke
Pontine haemorrhage
Tuberculous meningitis [38]
Following hemispherectomies [53]
Following hemidecortication [54]
Traumatic spine injury [55]
Basilar artery occlusion [56]

of CF [18]. Third ventricular shift in ICH patients is associated with fever within 72 hours of admission and high discharge mortality [59].

Tumors

CF is more frequently associated with tumors located in the sella, diencephalon, and intraventricular regions [52,57].

Traumatic brain injury

Patients with DAI, as shown via imaging, and frontal lobe injuries were independently associated with the presence of CF [60,61]. Other risk factors were young age, low Glasgow Coma Scale on presentation, skull fracture, presence of blood in the parenchyma/ventricles, and acute brain injury [62]. CF is more common in severely ill TBI patients with diffuse white matter damage, brain edema, hyperglycemia, leukocytosis, and hypotension [61]. Frontal lobe injury may serve as an indication of hypothalamic injury, given the nature of mechanical forces within the skull during injury and the proximity of the hypothalamus to the ventricles. Location of the skull fracture in proximity to the hypothalamic region (for example, the anterior fossa) may increase this risk [60].

Ischemic stroke

Magnetic spectroscopy indicates that the temperature of the ischemic zone is higher than in normal areas of the brain. Therefore, larger ischemic infarcts are likely to increase the chance of CF [63].

Traumatic spine injury

CF is also reported after traumatic spine injury, with a mean incidence of 8% [55]. Cervical and thoracic level injuries are more commonly associated with fever, as compared to lumbar injuries. Complete spine injuries have a higher incidence than incomplete injuries [55]. The etiology of fever following spine injury is not thoroughly understood.

Age

CF generally occurs in the younger population, as compared to infectious fever [57].

Level of consciousness

Depressed level of consciousness has also been identified as an independent predisposing factor for noninfectious fever, mainly attributed to immobilization and the increased atelectasis found in these patients [7].

CLINICAL FEATURES OF CENTRAL FEVER

This is a diagnosis of exclusion. CF occurs early, typically within 72 hours of admission after acute brain injury. All the cultures are negative and the chest radiograph is normal. Fever is disproportionately high and persistent. The temperature peak is higher when the fever starts earlier, and will be higher when compared to infectious fever [18]. There is generally less fever-free period and the cumulative fever load is high, accounting for a longer stay in the NICU. Generally, CF is continuous in nature without diurnal variations, plateau-like, and without spikes. Patients with CF have relative bradycardia with a notable absence of perspiration. Sustained fever is another factor in favor of CF [57]. Fever is also resistant to antipyretic medications [62,64-67].

Continuous fever, lasting longer than 6 hours for 2 or more consecutive days, has been considered persistent [57]. The combination of negative cultures; absence of infiltrate on chest radiographs; diagnosis of SAH, IVH, or tumor; and onset of fever within 72 hours of admission, predict CF with a probability of 0.90 [57]. In a study conducted by Thompson et al. [15], fever persisted for weeks to months in 4% to 37% of patients with TBI. Vasospasm with SAH is also predictive of CF [22].

The criteria for systemic inflammatory response syndrome and leukocytosis are similar to central and infectious fever. This underscores the difficulty in differentiating central and infectious fever prospectively in the critically ill population. The extreme physiologic stress provoked by acute neurologic injury can cause a rise in inflammatory markers and increased sympathetic response [21,22]. The percentage of neutrophils is higher in patients with infectious fever, suggesting that while leukocytosis may not be a reliable clinical variable to decide whether to use empirical antibiotics or discontinue antibiotics early, the presence of a left shift remains useful [57].

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Extreme hyperpyrexia, defined as fever ≥41.1℃ (106°F), is usually noninfectious. Examples include CF, drug fever, malignant hyperthermia, transfusion reactions, adrenal insufficiency, thyroid storm, neuroleptic malignant syndrome, heat stroke, acalculous cholecystitis, mesenteric ischemia, acute pancreatitis, deep vein thrombosis, and pulmonary embolism [68,69]. A single fever spike of 102°F is classical for noninfectious disorders and is never due to infection. Fever associated with blood transfusions are usually transient, that is, they present as a single fever spike within < 1 week [68,70].

TEMPERATURE PULSE RELATIONSHIP

Relative bradycardia is a feature of CF. The following applies to adult patients with temperatures > 102°F and when pulse is taken simultaneously with temperature. Normally, the pulse rises in concert with the temperature, (e.g., for every degree Fahrenheit temperature is increased, the pulse should rise 10 beats/min). If the pulse rate is lower than predicted from a given temperature (> 102°F), then relative bradycardia is present, unless the patient is on a beta-blocker, verapamil or diltiazem, or has a pacemaker-induced rhythm or heart block. In absence of these exclusion criteria, relative bradycardia in neurosurgical ICU patients with fever strongly suggests a central or drug fever (Table 3) [71].

Diagnosis

A high index of suspicion is needed for the diagnosis of CF. Diagnosis of CF is a diagnosis of exclusion in predisposed patients with neurological injury. The practice guidelines from the task force of the Society for Critical Care Medicine suggest a "careful clinical assessment" and "cost-conscious approach" for obtaining a diagnosis through laboratory and radiological tests [72]. The clinical signs of pneumonia, bacteremia, sinusitis, urinary tract infection, catheter site infection, meningitis, or ventriculitis should be investigated. A chest radiograph, culture of blood, urine and trachea are the baseline tests done in all cases. Any long-standing venous line or catheter should also be removed.

Certain biomarkers have been developed to differentiate infectious from noninfectious causes, including serum procalcitonin (PCT) assays, endotoxin detection systems, triggering receptor expressed on myeloid cells-S (TREM-1), C-reactive protein, TNF-α, and IL-6. PCT of 0.5 ng/mL or greater was useful in differentiating infectious fever from CF in SAH and ICH patients [73]. This test is shown to have high specificity and a reasonably high negative predictive value. A decision tree has been suggested by Hocker et al. [57], but no specific diagnostic paradigm has been suggested for universal usage.

Table 3. Temperature pulse relationship

Temperature (°F)	Appropriate pulse response (/min)	Relative bradycardia
106	150	<140
105	140	<130
104	130	<120
103	120	<110
102	110	<100

DIFFERENTIAL DIAGNOSIS

Some common differential diagnoses are important to be distinguished before making a diagnosis of CF, since it a diagnosis of exclusion. Nonresponse to antibiotics in CF may lead to misdiagnosis of antibiotic failure or resistance in CF (Table 4).

Bacteremia

Bacteremia should be investigated by sending at least three blood cultures within 24 hours of suspected infection. Each culture should be sent from a separate venepuncture site or intravascular device. Intravascular catheters should be suspected as an infection risk in young nonimmune compromised patients with abrupt onset of septicemia. These patients may have inflammation at the site of insertion that can provide a clue to the diagnosis, though this is absent in 60% of patients. Difficulty in drawing a sample from the line may be another indicator of intravenous catheter-related infection.

Ventilator-associated pneumonia

Ventilator-associated pneumonia is the second most common cause of infectious fever in any ICU. It is distinguished by a culture of respiratory secretion which can be obtained by various techniques, including expectoration, nasopharyngeal washing, saline induction, deep tracheal suctioning, bronchoscopic specimen/brush samples, aspiration, and bronchoscopic or nonbronchoscopic lavage (mini-BAL). Chest radiography for abscess, atelectasis, effusion, and consolidation should also be done.

Urinary tract infection

Urinary tract infection is the next leading cause of fever. Diagnosis is excluded by sending urine for direct microscopic examination, staining, and culture.

Diarrhea

Diarrhea is another important cause of fever in the ICU. It should be suspected in any patient with diarrhea and who has been given

Table 4. Differential diagnosis of fever in neurointensive care unit

Infectious causes
Ventilator-associated pneumonia
Sinusitis
Meningitis
Encephalitis
Catheter-related sepsis
Sepsis
Clostridium difficile diarrhea
Abdominal sepsis
Complicated wound infections
Urinary tract infection
Acute respiratory distress syndrome, both late and fibro-proliferative stage
Systemic inflammatory response syndrome
Noninfectious causes
Alcohol/drug withdrawal
Postoperative fever (48 hours postoperative)
Post-transfusion fever
Drug fever
Connective tissue disease
Myocardial infarction
Pancreatitis
Acalculous cholecystitis
Ischemic bowel (without primary peritonitis)
Gastrointestinal bleed
Aspiration pneumonitis
Fat emboli
Gout/pseudo gout
Transplant rejection
Hematoma
Cirrhosis
Decubitus ulcer
Phlebitis/thrombophlebitis
Intravenous contrast reaction
Neoplastic fever
Deep venous thrombosis
Pulmonary emboli
Neurological diseases
Increased intracranial pressure
Nonconvulsive status epilepticus
Autonomic dysreflexia
Cushing response
Agitation
Dystonia
Malignant catatonia
Stiffman syndrome
Paroxysmal sympathetic hyperactivity
Mixed autonomic hyperactivity syndrome
Drugs/Toxins
Delirium
Serotonin syndrome
Acute drug withdrawal (intrathecal baclofen, dopamine agents)
Narcotic withdrawal
Neuroleptic syndrome
Malignant hyperthermia
Scorpion envenomation
Gamma hydroxybutyrate intoxication
Fenfluramine-phentirmine overdose
Drug overdoses (e.g., aspirin, anticholinergic drugs)
Endocrine diseases
Pheochromocytoma
Thyroid storm
Adrenal insufficiency
Other diseases
Carotid sinus injury
Baroreceptor failure
Renal artery stenosis
Irukandji syndrome

antibiotic treatment or chemotherapy in the past 60 days. The most common organism implicated is *Clostridium difficile* [74,75]. It can be excluded by enzyme immunosorbent assay (EIA) for detecting toxins A and B, or by culture (though it is more time consuming).

Sinusitis

Sinusitis is an uncommon cause of fever in the ICU, but may have a grave impact on patient outcomes. Risk factors include obstruction of the ostia draining the sinuses, nasal intubation of trachea, or the passage of a nasogastric tube. Though occult, it can spread to the brain, lungs, and blood, leading to serious consequences [76]. It can be ruled out by a radiograph, ultrasound, magnetic resonance imaging or computed tomography scan transnasal puncture.

Surgical site infection

Surgical site infection accounts for 3% of fever in the ICU, which can easily be diagnosed by local inspection and cultures from the wound site [77,78]. Abscess in the lung, abdomen or any other region may also be a cause of fever.

Drug fever

Drug fever is caused by some commonly used drugs in the NICU, such as phenytoin, salicylates, barbiturates, methyldopa, furosemide, penicillin, cephalosporin, sulfonamide, amphotericin B, rarely corticosteroids, clindamycin, tetracycline, macrolide. Onset of fever is usually within 1 to 2 weeks of drug initiation, and it can easily be diagnosed by stopping the drug. Suspicion of drug fever can also arise from relative bradycardia and the patient being inappropriately well for the degree of fever. Fever usually disappears within 3 days of stopping drugs or antibiotics in such cases

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Table 5. Paroxysmal sympathetic hyperactivity vs. central fever

Feature	PSH	CF
Onset	Usually after a week of ABI and may last up to 1 year. Generally seen after cessation of ICU sedation	Occurs within 72 hours of ABI
Associated signs and symptoms	Tachycardia, hypertension, tachypnoea, dystonia, diaphoresis	No such association
Fever	At least one episode per day for 3 consecutive days (2–3 cycles/day)	Unusually high fever remains for most of the time (plateau-like with no diurnal variation)
Trigger	Essential diagnostic criteria (mostly nonnoxious stimuli)	No such trigger defined
Mechanism	Excitatory-inhibitory model: most commonly accepted	Inflammatory cytokines increase the set point of hypothalamus
Leukocytosis	Generally absent	Present
Heart rate	Tachycardia	Relative bradycardia
Sweating	Generally present	Absent
Posturing/Dystonia	Generally present (one of the diagnostic criteria)	Absent
Pupil size	Usually increased	Normal
Paroxysmal nature	Yes	No
Most common pathology	TBI	SAH
Diagnostic criteria	Defined by multidisciplinary international committee (diagnostic likelihood tool)	No such diagnostic criteria
Core clinical features	Six core sympathetic and motor clinical features	No such clinical features

PSH, paroxysmal sympathetic hyperactivity; CF, central fever; ABI, acute brain injury; ICU, intensive care unit; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage.

[71,79].

Other differential diagnoses are listed in Table 4.

PAROXYSMAL SYMPATHETIC HYPERACTIVITY VS. CENTRAL FEVER

Both are diagnoses of exclusion in patients with neurological injuries during their stay in neurocritical care. They both occur in the NICU in acute brain-injury patients. Differentiating one from the other is very crucial in proper care and appropriate management, and thus ultimately affects patient outcomes. Differentiating features are listed in Table 5.

Impact on outcome

Fever predisposes the brain to harmful effects by disrupting the blood-brain barrier, an increasing excitatory amino acid release, and increasing the production of free radicals [80]. There is an exacerbation of neuronal injury in fever. The permeability of the blood-brain barrier is related to body temperature and higher temperatures increase the extravasation of proteins [81,82]. There is a lack of literature for a definitive association between the duration of fever and increased mortality. Studies conducted by Circiumaru et al. [83] and Peres Bota et al. [84] found that fever lasting longer than 5 days was associated with increased mortality. These results are in contrast to a study conducted by Schulman et al. [85], who found increased patient mortality when fever was aggressively controlled, although it should be noted that these were nonneurological trauma patients. Fever is also found to increase the length of ICU stay [8,9].

The brain injury patient is at risk of secondary injury from fever, as for every 1°C rise in body temperature there is a 13% increase in the metabolic rate [86]. Increased body temperature causes permanent neuronal damage and worsens prognosis in animal models of ischemic brain injury [40,87-91]. Fever is also known to increase delirium and agitation [92,93]. However, fever is not found to increase intracranial pressure [94]. Fever also increases cardiac output, oxygen consumption, and heart rate [95]. This increased demand on the heart is poorly compensated in patients with previously compromised cardiac function and in sepsis [96]. Fever has also been associated with increased multiorgan dysfunction and mortality [97]. Higher temperature is further associated with cell protein denaturation, susceptibility to acid-base and electrolyte disturbances, and impaired oxygen release [98].

Subarachnoid hemorrhage

Even a single episode of fever after SAH is associated with poorer outcomes, even in good-grade patients [99]. Vasospasm in SAH patients is associated with CF, independent of hemorrhage severity or the presence of infection [7,12,22,57,100-102]. Treatment-refractory fever during the first 10 days after SAH is associ-

ated with increased mortality, more severe functional disability, and cognitive impairment among survivors [58]. Cumulative fever burden, defined as the sum of time with temperatures >38.3℃ in the first 13 days, is associated with worse outcomes, including incomplete recovery in good-grade SAH patients and potentially late recovery in poor-grade patients [102].

Intracerebral hemorrhage

The presence of CF leads to poor outcomes and is an independent risk factor for mortality in ICH patients [18]. This results in high mortality and poor functional outcomes at 3 months on the modified Rankin Scale. In one study, the presence of CF led to unfavorable outcomes in 100% cases at 90 days postictus, while the absence of fever was associated with unfavorable outcomes in only 46.9% of patients [18]. In a retrospective study of 251 patients with spontaneous ICH, the duration of fever was independently associated with poor outcomes in those who survived past 72 hours [14].

Acute ischemic stroke

Pyrexia in experimental animals may increase the volume of the ischemic zone [40,84-87]. Also, fever greater than 39℃ increases mortality in stroke patients [103].

Traumatic brain injury

In a cohort of more than 100,000 patients, a negative association was observed between early peak fever greater than 39℃ and hospital mortality in patients with TBI [103]. Further, this correlation was not seen in patients with central nervous system infection. Because CF starts earlier and lasts longer than infectious fever, there is a high risk of antibiotic overuse and the associated risk of the emergence of resistant microorganisms [57]. CF may be associated with prolonged coma or unawareness, diabetes insipidus, and overall poor outcomes [50,64,65,67,104].

TREATMENT

Although many treatment regimens have been suggested, none have been identified as superior to others in the treatment of fever [65,105]. However, controlling fever is an important part of management in CF, owing to its detrimental effects on the brain. Pharmacologic methods include acetaminophen, acetylsalicylic acid, and other nonsteroidal antiinflammatory medications and corticosteroids [106,107].

Other methods to decrease temperature include rotary fans, sponging, and surface cooling devices. However, these have had limited efficacy and are uncomfortable for the patient. Surface cooling devices have also been reported to increase the incidence of shivering, increase oxygen consumption and even cause thermal burns [107,108]. Hypothermia blankets can lead to large temperature fluctuations [109,110]. Air blankets have been increasingly used and are found to have better efficacy and produce better patient comfort [110]. Some authors have suggested the use of sand body-conformed wraps, intravascular cooling devices, head-only cooling caps, or inhaled perfluorocarbon cooling systems [111].

Several studies have tried intravenous infusion of cold saline, showing promising results and no increase in complications [112]. A few studies have tried local (brain) cooling. This may prevent the side effects of global hypothermia, such as impaired coagulation, arrhythmias and deep vein thrombosis [113-116]. However, no large multicentre trial is available, leading to no definitive conclusions on the use of selective brain cooling.

IL-1 antagonists have been shown to produce significant improvements in rat models of TBI [117], although no human trials have been conducted. However, it has been shown that even a small temperature decrease in febrile patients can improve neurologic outcomes [118].

Morphine

Remission of CF is reported with morphine post-TBI [119].

Chlorpromazine

Sometimes, when traditional management fails, chlorpromazine has been tried with variable success. Chlorpromazine produces antipyretic actions because of its ability to render the patient thermolabile and its effect on thermoregulation [120,121]. Hyperpyrexia following hemispherectomy has been reported to respond to chlorpromazine [121].

Baclofen

Baclofen successfully abolished prolonged central hyperthermia in a patient with basilar artery occlusion leading to brain stem infarction [56].

Bromocriptine

There are anecdotal case reports of the successful use of bromocriptine for treatment of CF [122,123].

Growth hormone therapy

Successful treatment of CF by GH therapy has been reported, with the mechanism related to the improvement of sweat production [124].

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FUTURE DIRECTIONS

There are no guidelines or directions to help differentiate CF from other noninfectious causes of fever in the NICU. The literature is sparse and unclear. The diagnostic criteria are not well defined and not standardized. Treatment modalities for this clinical entity have been symptomatic only and mostly rely on over the counter drugs. No standard therapy has been defined in the literature. Multicentre large studies are required to better define CF, understand its pathophysiology, and guide standard management protocols in neurocritical care settings.

CONCLUSION

CF is an important diagnosis in neurocritical care. It not only prevents unnecessary antibiotic use, but its early recognition would also help improve patient management and prevent delayed discharge from the hospital. The current key to diagnosis in a predisposed patient is a high index of suspicion, along with thorough clinical examination, radiological, microbiological, and biochemical tests. Immediate attainment of normothermia is the current recommendation, as fever worsens the brain insult. Treatment includes various pharmacological agents and surface cooling methods to decrease body temperature. Studies are lacking on the best methods for diagnosis, treatment, and prevention of CF. Thus, more human trials are needed in this field to make any definitive recommendations.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

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Robotically assisted transcranial Doppler with artificial intelligence for assessment of cerebral vasospasm after subarachnoid hemorrhage

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ORIGINAL ARTICLE

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Background: Transcranial Doppler (TCD) ultrasound is an essential tool for the detection of cerebral vasospasm after subarachnoid hemorrhage (SAH) but is limited by the availability of skilled operators. We examined the clinical feasibility and concordance of a robotically assisted TCD system with artificial intelligence with routine handheld TCD after SAH.
Methods: We evaluated TCD velocities in the anterior cerebral artery (ACA) and middle cerebral artery (MCA) of two patients with high-grade SAH and angiographic evidence of vasospasm. A single channel TCD device with a handheld diagnostic probe as well as a robotically assisted TCD device was used, the relationship of the two tests was evaluated using the bootstrap method of resampling for the concordance correlation coefficient (CCC) paired with a Pearson's correlation analysis, followed by a Bland-Altman plot.
Results: Patient 1 developed angiographic and TCD evidence of vasospasm in the proximal right MCA, but except for periods of disorientation remained neurologically intact. Angiographic, TCD and clinical evidence of ACA spasm occurred 6 days after ictus in patient 2. Robotically measured mean flow velocities were comparable to manual TCDs in the MCAs (CCC=0.83; 95% confidence interval [CI], 0.42 to 0.96; P=0.001) but not in the ACAs (CCC=0.26; 95% CI, −0.01 to 0.71; P=0.26).
Conclusion: Robotically assisted TCD system with artificial intelligence provides an alternative to manual TCD for assessment of MCA velocities in patients with SAH, expanding the availability of TCD to settings in which specialized clinicians are not available. Further studies for validation of this technology are warranted.

Keywords: Vasospasm, intracranial; Subarachnoid hemorrhage; Middle cerebral artery; Ultrasonography, Doppler, transcranial; Anterior cerebral artery; Artificial intelligence

INTRODUCTION

Delayed cerebral ischemia (DCI), defined as cerebral infarction or neurological deterioration caused by cerebral vasospasm, is a significant cause of mortality and poor neurological outcome after nontraumatic subarachnoid hemorrhage (SAH) [1,2]. Although a growing body of evidence suggests that early brain injury, spreading depolarization, microcirculatory dysfunction and impaired autoregulation may be necessary for the pathophysiology of neurological injury after SAH [3], the association with large-vessel cerebral vasospasm remains undisputed. Indeed, symptomatic vasospasm with neurological deterioration has been reported to occur with an incidence of up to 40% after SAH. Consequently, timely application of therapies aimed at mitigating vasospasm remains an essential cornerstone of SAH management [4,5]. Oral administration of the calcium channel blocker nimodipine is considered standard of care in the prevention of cerebral vasospasm [6]. Intravenous milrinone according to the Montreal Neurological Hospital protocol [7] may also have beneficial effects, although well-controlled trials to verify its long-term effects on the neurological outcome are needed.

Early diagnosis of vasospasm is critically dependent on frequent and high-quality neurological examinations, but the noninvasive assessment of the blood flow velocity in the basal cerebral arteries or angiographic studies are also important [8]. Changes in diameter are inversely proportional to the mean velocity of the blood within the vessel, which can be measured using transcranial Doppler (TCD) sonography. High TCD velocities are generally associated with DCI, although some patients may remain asymptomatic despite TCD or radiographic evidence of vasospasm [9]. For angiographic vasospasm, the predictive value of TCD flow velocities in the middle cerebral artery (MCA) is exceptionally high. Indeed, a mean flow velocity > 200 cm/sec in the MCA has a positive predictive value of 87% for angiographic spasm, whereas velocities of < 120 cm/sec have a negative predictive value of as high as 94% [10]. A velocity increase of more than 50 cm/sec within 24 hours is also a strong predictor for the development of symptomatic vasospasm [11].

A significant limitation of the routine use of TCD is that it is time-consuming and highly operator dependent [8]. Examination of patients using the handheld technique requires that the examiner has detailed three-dimensional knowledge of cerebrovascular anatomy and its variations, as well as the ultrasound technology and various TCD indicators of vasospasm. Recently, a robotically assisted ultrasound system that integrates ultrasound, robotics, and machine learning (Lucid™ M1 Transcranial Doppler Ultrasound System® and NeuralBot™ System, Neural Analytics, Los Angeles, CA) was approved by the Food and Drug Administration, providing a tool that can potentially eliminate the interoperator variability of TCD findings. This system combines TCD with a boxy headset containing robotic wands that employ artificial intelligence (AI) in the form of a machine learning software platform with algorithms to automatically adjusts the ultrasound probes in order to detect and insonate intracranial vasculature, particularly the MCA M1 segments. It can also readjust the probe position after patient movement to continue to insonate a previously obtained location. The use of robotic TCD has been explored in the literature among stroke and traumatic brain injury patients. For instance, in 2018, researchers reported using this system for noninvasive neuromonitoring by obtaining continuous, bilateral TCD recordings in critically ill brain injury patients. Nevertheless, the use of robotic TCD has not been explored among SAH patients [12,13].

In this study, we aimed to examine the feasibility and accuracy of robotically assisted TCD for measuring cerebral blood flow velocities in the anterior cerebral artery (ACA) and MCA in patients with high grade SAH and angiographic vasospasm.

METHODS

Patients

After approval from Institutional Review Board at Beth Israel Deaconess Medical Center (Protocol number: 2019P001001), we reviewed the clinical data, the TCD results, and imaging reports from two patients, with high-grade SAH and intraventricular blood, requiring placement of external ventricular drain (EVD) for hydrocephalus management. Written informed consent by the patients was waived by the board. Both patients received standard monitoring and therapies, including nimodipine prophylaxis, optimization of their hemodynamics and volume status, as well as fever control and correction of metabolic and electrolyte disturbances.

Patient 1

A 47-year-old male developed a thunderclap headache without any known triggering factors. He awoke the next morning with a severe headache and mental status changes and was brought to the hospital by his family. A computed tomography (CT) scan of his head showed a modified Fischer 3 SAH (Fig. 1A), CT angiogram revealed a 4 mm anterior communicating artery aneurysm. The patient was then transferred to our hospital and was found to follow commands inconsistently (Hunt and Hess Grade III). His level of arousal deteriorated, and he was intubated for airway protection. An EVD was placed in the setting of acute hydrocephalus.

He was admitted to the intensive care unit, and an angiogram was performed the next day, with coiling of the aneurysm.

Patient 2

A 60-year-old previously healthy male presented after acute onset of severe headache followed by vomiting and unresponsiveness (Hunt and Hess Grade V). A head CT showed extensive and thick SAH with intraventricular hemorrhage, a modified Fischer 4 SAH (Fig. 1B) with effacement of the basal cisterns and foramen magnum concerning for uncal and tonsillar herniation. The patient was started on nicardipine infusion for blood pressure control, and a right frontal EVD was placed. CT angiogram showed an anterior communicating artery aneurysm (Fig. 2). Cerebral angiography confirmed the aneurysm, which was then embolized without complication. Eight days after ictus, TCD showed moderately increased mean flow velocities in the left MCA (mean 106 cm/sec), and although it did not reach the threshold for vasospasm, the interval change compared to the day prior raised concern for evolving vasospasm. Cerebral angiogram showed bilateral severe ACA (A2) vasospasm, which improved after selective arterial injection of nitroglycerin and verapamil.

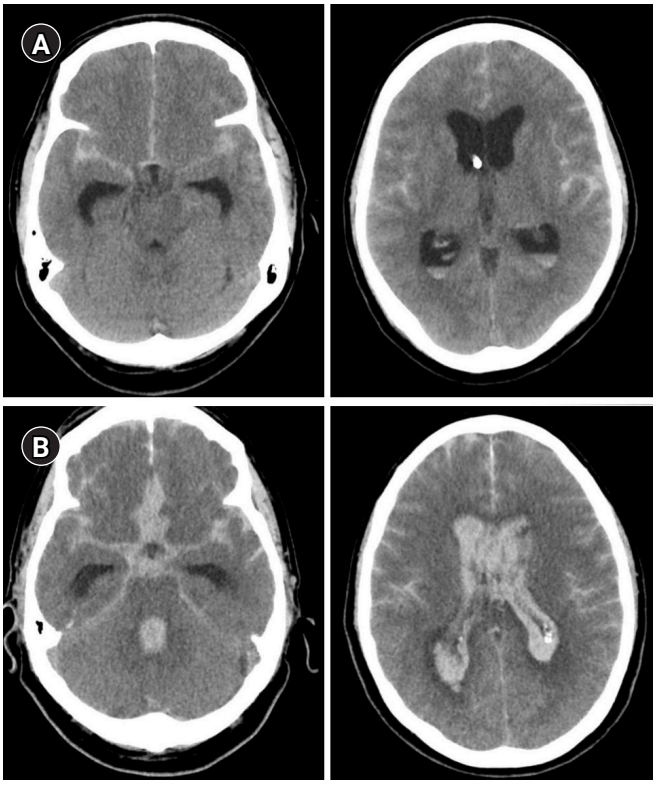

Fig. 1. Computer tomography imaging of (A) patient 1 and (B) 2 showing diffuse thick subarachnoid hemorrhage with intraventricular blood.

TCD imaging

Manual TCD imaging was completed by vascular neurologists using a single channel TCD device with a handheld diagnostic probe (ST3 Transcranial Doppler, Spencer Technologies, Redmond, WA, USA). Once applied to the head, the Lucid® Robotic System (Neural Analytics) with AI and machine learning algorithm automatically searched for and detected the bilateral MCAs independent of an operator. The device also allowed for identification and measurement of TCD velocities in other cerebral vessels, but required control and adjustment of the TCD probes through a computer screen by a vascular technologist. The ACA measurements were, hence, not fully automated. We compared results of attempted insonation of the terminal internal carotid artery (ICA), MCA, ACA via the transtemporal window. We did not compare attempted insonation of the posterior cerebral artery, also visible via the transtemporal window. We recorded all suitable quality waveforms along the terminal ICA and MCA. The robotic system consistently automatical-

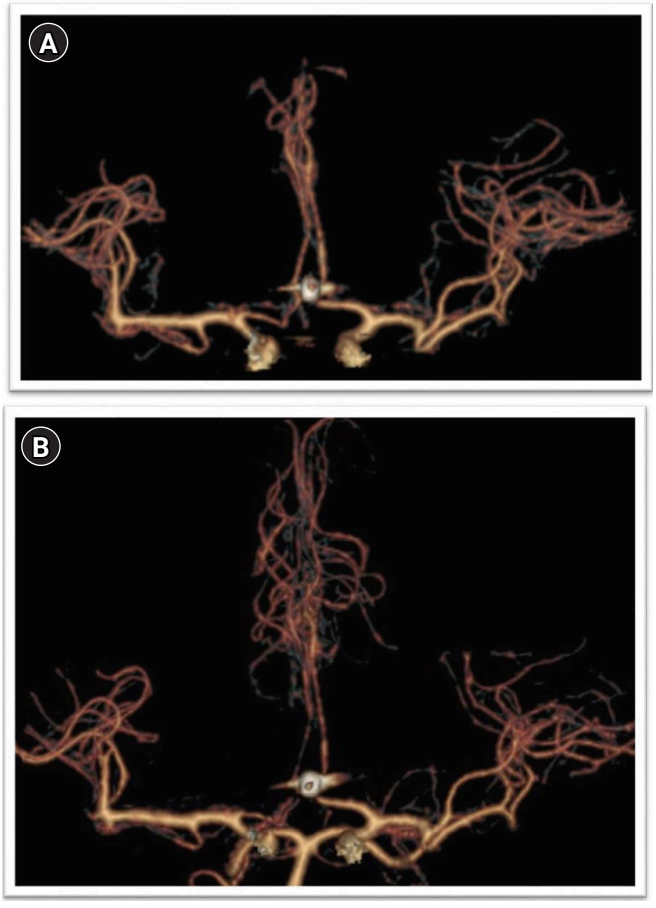

Fig. 2. Angiographic findings in patient 2, (A) initially demonstrating normal calibers in all cerebral vessels and (B) significant vasospasm in bilateral anterior cerebral arteries 6 days after ictus.

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ly located at least one (and often several) depths of the MCA. Manual manipulation of the robotic TCD probe was then performed to optimize signals, check additional depths, and to locate ACA signals.

Statistical analysis

The dependent concordance correlation coefficient (CCC) was calculated to measure the agreement between robotic and manual TCD methods. A resampling method was used for interference on dependent CCCs. The bootstrap method was used as the choice of resampling approach [14]. A set of 1,000 bootstrap samples was used as a proxy for independent samples and the bias-corrected and accelerated bootstrap confidence intervals (CIs) were reported. For quantitative comparison of the measured velocities, and to interpret the strength of agreement the CCC was paired with a Pearson's correlation analysis using the bootstrap approach [15]. Further, to visually assess the agreement between these methods, we pooled data from the MCA and ACA measurements separately, and plotted the differences between measurements at each time point against their means based on Bland and Altman [16] method of assessing agreement between methods of measurement with multiple observations per individuals. Data were analyzed using BlandAltmanLeh [17] and epiR [18] packages in R [19], and a *P* value of less than 0.05 was considered significant.

RESULTS

TCD findings

For patient 1, manual and robotic TCD ultrasonographic studies were performed on the same day on three occasions, on postictus days 10, 11, and 12 (Fig. 3). The mean range of ICA/MCA depths insonated via the transtemporal window was 33 mm manually and 21 mm robotically per side. The highest mean flow velocities of each day's manual and robotic TCD were mostly concordant with few exceptions (Table 1).

For patient 2, manual and robotic TCD ultrasonographic studies were performed on the same day on two occasions, on postictus days 15 and 17 (Table 1). The mean range of ICA/MCA

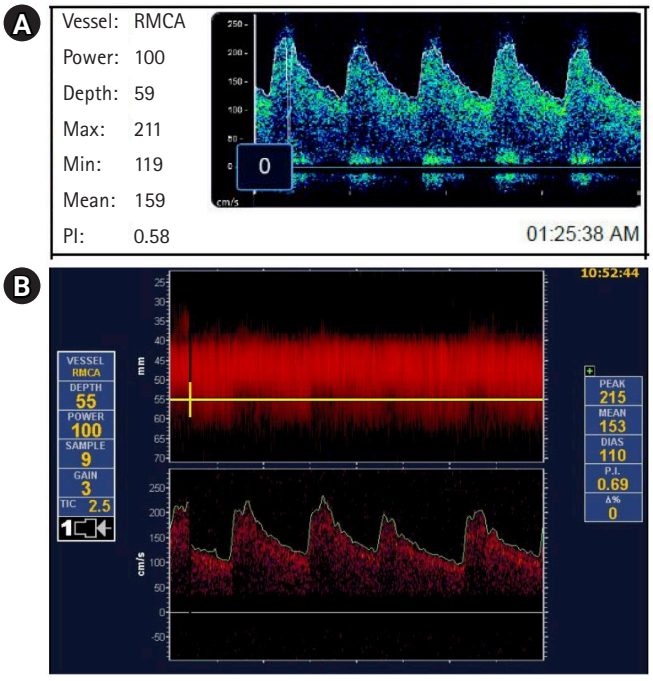

Fig. 3. (A) Robotic and (B) manual transcranial Doppler waveform of the right middle cerebral artery (MCA) of patient 1 on postictus day 10 demonstrating elevated right MCA mean flow velocity, consistent with vasospasm in both techniques.

Table 1. Mean flow velocities in anterior circulation reported by manual and robotic TCD imaging

	Patient 1 (days after SAH)						Patient 2 (days after SAH)			
	Manual TCD			Robotic TCD			Manual TCD		Robotic TCD	
	10	11	12	10	11	12	15	17	15	17
RMCA velocity (cm/sec)	153 at 55 mm	149 at 48 mm	140 at 49 mm	159 at 59 mm	130 at 59 mm	154 at 50 mm	80 at 51 mm	73 at 62 mm	78 at 51 mm	71 at 59 mm
LMCA velocity (cm/sec)	142 at 45 mm	139 at 51 mm	147 at 41 mm	203 at 54 mm	119 at 54 mm	140 at 51 mm	75 at 54 mm	81 at 56 mm	89 at 55 mm	69 at 56 mm
RACA velocity (cm/sec)	−49 at 63 mm	−40 at 61 mm	−39 at 63 mm	−87 at 79 mm	NR	−65 at 71 mm	−27 at 70 mm	−23 at 62 mm	NR	NR
LACA velocity (cm/sec)	−45 at 64 mm	−104 at 66 mm	−101 at 64 mm	−121 at 66 mm	−100 at 70 mm	−99 at 68 mm	−38 at 66 mm	−31 at 66 mm	−83 at 79 mm	−58 at 75 mm
Duration of the imaging (min)	52	43	57	40	33	36	24	17	32	17

TCD, transcranial Doppler; SAH, subarachnoid hemorrhage; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; RACA, right anterior cerebral artery; NR, not reported; LACA, left anterior cerebral artery.

depths insonated via the transtemporal window was 28 mm manually and 21 mm robotically per side. The average time required to conduct a complete TCD examination of the bilateral MCA and ACA vessels was 38.6 ± 17 minutes with manual technique, and 30.8 ± 8 minutes for robotic technique (95% CI, –13.6 to 29.2; $P = 0.4$) (Table 1).

Representative plot of the robotic and manual TCD are presented in Fig. 4. Overall, robotically measured mean flow velocities were comparable to manual TCDs with AI assisted technology in the MCAs (CCC = 0.83; 95% CI, 0.42 to 0.96; $P = 0.001$) but not in the ACAs (CCC = 0.26; 95% CI, –0.01 to 0.71; $P = 0.26$). The statistics for 1,000 bootstrapped correlations applied to the data is reported in Table 2 (Fig. 4). Bland-Altman plot showed overall agreement between measurements from both techniques, with most of the variables within 95% CI indicating agreement between the two methods for both ACA and MCA velocities (Fig. 5).

Patient outcome

Patient 1 was extubated soon after the coiling of his aneurysm with his neurological examination returning rapidly to his baseline, apart from intermittent confusion and delirium. He remained neurologically intact and was discharged to his home in stable condition 17 days after his bleeding (modified Rankin Scale score = 0). Patient 2 improved gradually after intraarterial vasospasm therapy and initiation of milrinone. He was successfully extubated 11 days after admission. Milrinone was weaned as his vasospasm improved, and his EVD was removed 1 week later (on hospital day 18). The patient was discharged to a rehabilitation facility in stable condition with moderate cognitive deficits and moderate left hemiparesis (modified Rankin Scale score = 4).

DISCUSSION

We report that robotically assisted TCD with AI is a feasible alternative to the standard handheld technique for obtaining flow ve-

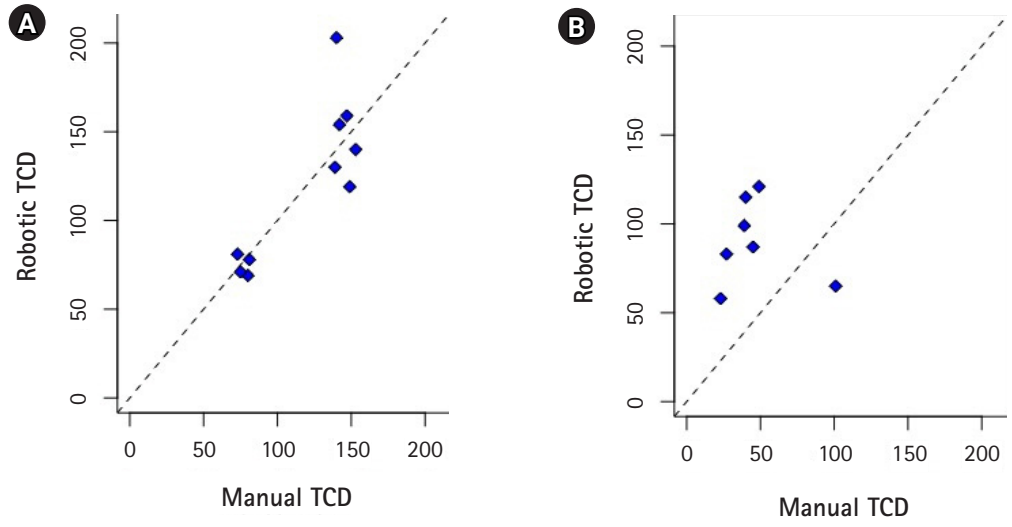

Fig. 4. (A) Moderate agreement between transcranial Doppler (TCD) findings using robotic technique and TCD findings using manual technique for the middle cerebral artery (concordance correlation coefficient=0.83; 95% confidence interval [CI], 0.42 to 0.96). (B) Poor agreement between TCD findings using robotic technique and TCD findings using manual technique for the anterior cerebral artery (concordance correlation coefficient=0.26; 95% CI, –0.01 to 0.71).

Table 2. Comparison between the mean flow velocities in anterior circulation reported by manual and robotic transcranial Doppler imaging

	Average bootstrap estimate of concordance coefficient	Bootstrap standard error	Bootstrap 95% BCa confidence interval	Bootstrap estimates of bias
MCA	0.83	0.12	0.42 to 0.96	–0.01
ACA	0.26	0.20	–0.01 to 0.71	–0.001

Bootstrapping was applied with n=1,000 to obtain concordance coefficient results.
BCa, bias-corrected and accelerated; MCA, middle cerebral artery; ACA, anterior cerebral artery.

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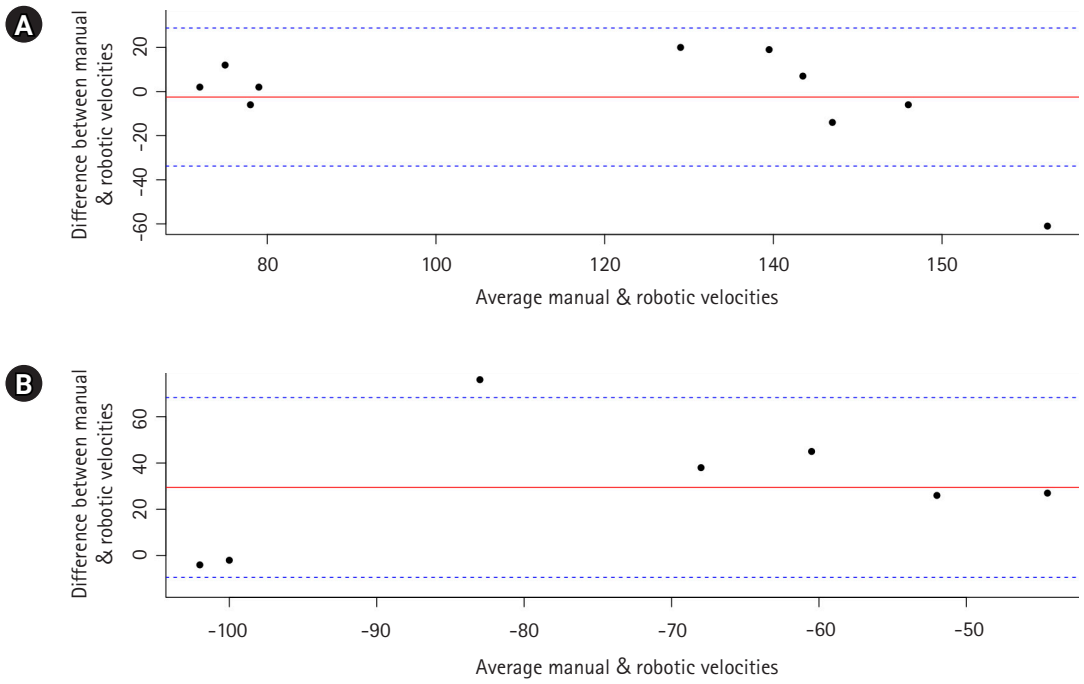

Fig. 5. Bland-Altman plot shows no proportional bias, indicating agreement between the two methods for the (A) middle cerebral artery and (B) anterior cerebral artery.

locities in patients with cerebral vasospasm after high grade SAH. Despite significant vasospasm in both patients, MCA and ACA velocities could be identified without significant delay, and the AI guided MCA velocities were comparable to those obtained with the manual technique by expert clinicians.

The importance of early TCD monitoring in patients with high-grade SAH is demonstrated by the previous findings that elevated velocities may precede clinical symptoms by 24 to 48 hours [20,21], which can signal the clinicians to intensify preventive strategies and implement therapeutic measures as soon as signs of clinical deterioration are noted. Clinicians should be alerted when a rapid increase in the TCD velocities is recorded, or when a high absolute mean flow velocity is obtained. The latter is indeed highly specific for angiographic vasospasm. As an example, in a study of 34 consecutive patients with SAH, Sloan and associates reported a specificity of 100% and sensitivity of 59% for the detection of angiographic spasm with a threshold of the mean flow velocity of > 120 cm/sec [22].

The Lucid Robotic System combines TCD with a headset containing robotic wands and uses machine learning to find the best cranial window and insonation angle based on patterns in the data it gathers (Fig. 6). In contrast to traditional ultrasound systems, the robotic system does not require the presence of a trained professional to locate MCA waveforms. Use of robotic TCD may increase the availability of this technique, and therefore the ability to implement early interventions to mitigate the potential neurological consequences of vasospasm and cerebral ischemia. In its current version, the AI allows automatic detection of flow velocities only in the bilateral MCAs. This is, nevertheless, clinically important because of the high positive and negative predictive values for angiographic spasm for mean MCA flow velocities [10], whereas the predictive value of TCD velocities in other vascular territories is not as strong [23]. The robotic system does, nevertheless, allow a full examination of other intracranial vessels when directed and

Fig. 6. The robotically assisted transcranial Doppler system used in this study (Neural Analytics Lucid Robotic System. Credit: Neural Analytics).

controlled by an examiner, although the current version of its self-learning software is limited to only the bilateral MCAs. It is important to note; however, that our data failed to show a significant correlation or concordance between the robotic and manual TCD findings in the ACAs, and this lack of correlation may also exist for other intracerebral vessels not examined in the current report. Nonetheless, given the absence of proportional bias in the Bland-Altman plot, an agreement between the methods appears to exist even for the ACA velocities. Further studies with larger sample size are therefore warranted to decipher these findings.

It is important to note that although the two methods were performed on the same day, the discrepancies in the mean flow velocities in ACAs were higher than MCAs. In addition to underlying physiologic changes, the discrepancy in ACA flow velocities can indicate an inherent difference in training and technical skills between the two operators: a vascular neurologist versus a vascular technologist. It can also imply technical limitations with the manually controlled ACA measurements with the robotic TCD: the AI machine learning technology was only available and used for the MCAs, whereas the ACA measurements remained operator dependent.

Limitations of the TCD imaging in SAH patients include an inability to insonate intracranial vessels in 10% to 20% of patients. Indeed, Seidel et al. [24] reported insufficient acoustic temporal bone window in about 20% of the studied population. A significant limitation that is inherent to the TCD technique is related to the measurement of a cerebral blood flow velocity as a surrogate for cerebral blood flow. Cerebral blood flow velocity is, however, proportional to the cerebral blood flow only if the cross-sectional vessel area remains constant [25]. Moreover, the spatial resolution of TCD is limited for the posterior circulation [26], which, combined with its relatively low sensitivity, makes clinical examination the most crucial factor in decision making for patients with posterior circulation vasospasm.

The robotically assisted TCD system used in this study has additional limitations such as inability to insonate posterior circulation with its current headset, as well as its large size and weight (Fig. 3), which may not be well tolerated by some patients, particularly after craniotomy or cervical spine injury. Moreover, healthcare providers need to be trained to initiate the robot and apply the head device to the patient. Importantly, this technology is currently only capable to find and assess the MCA velocities, as it is supported with our findings. To assess other cerebral vessels the technology needs upgrading. Despite these limitations, the robotically assisted TCD system can be useful in institutions without or with limited access to professionals trained to obtain manual TCD waveforms. Furthermore, this technology allows for extended monitoring of a single vessel, which could allow for visualization of immediate effects of any treatment that is employed to enhance cerebral blood flow and manage vasospasm after SAH. Needless to say, even with robotic TCD a skilled clinician is always required for evaluation and interpretation of the data.

Although our results are compelling, it is important to discuss the limitations of our study. First, we have a very small sample size in this study which may affect our results and findings. Second, in this study the robotic and manual TCD measurements were often conducted many hours apart, albeit on the same day. Although unlikely, any physiological changes over the course of the day may have affected the velocities and lead to the discrepancy between data. These and other limitations described above will need to be addressed in future studies.

In our two patients, robotically assisted TCD with AI was feasible for evaluation of MCA waveforms in SAH-associated vasospasm and provided results that were overall comparable to manual TCD performed the same day. Further studies to assess the validity of this technology in SAH patients are warranted.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

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Safety and feasibility of ultrasound-guided insertion of peripherally inserted central catheter performed by an intensive care trainee

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ORIGINAL ARTICLE

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Background: We investigated the safety and feasibility of ultrasound-guided peripherally inserted central venous catheter (PICC) placements performed by intensive care medical trainees in comparison to PICC placements performed by intensivists.
Methods: This was a retrospective and observational study of adult patients who underwent PICC placement and were admitted to the intensive care unit (ICU) between July 2013 and March 2018. Ultrasound-guided PICC was performed at the bedside by an intensivist or intensive care medical trainee if intrahospital transport was inappropriate. The primary endpoint was PICC-induced complications. The secondary endpoint was initial success of PICC.
Results: A total of 209 patients underwent PICC placement during the study period. There were no significant differences in age, sex, body mass index, comorbidities, causes of ICU admission, or severity scores between the trainee-led PICC and intensivist-led PICC groups. Difficult venous access (42.6%) and requirement for central line infusion (39.2%) were the most common reasons for PICC placement. The basilic vein (62.2%) was the most common target vein among patients who underwent PICC. There were no significant differences in complications between the two groups (P=0.473). In addition, the initial success rate and procedural time were similar between the two groups (P=0.108 and P=0.076, respectively). There were no insertional injuries and moderate or severe bleeding in patients with PICC.
Conclusion: Ultrasound-guided PICC placement by an intensive care medical trainee may be safe and feasible compared to PICC placement by an intensivist.

Keywords: Peripherally inserted central venous catheter; Ultrasound; Specialist; Trainee

INTRODUCTION

Peripherally inserted central venous catheters (PICCs) are commonly used as an alternative to central venous catheters in critically ill patients [1,2]. There are many theoretical advantages to using PICC such as easy placement and a lower rate of complications [1-5]. In the past, interventional radiologists inserted PICCs in the interventional radiology suite under fluoroscopic guidance

[2,6,7]. However, serious adverse events may occur during intrahospital transport of critically ill patients due to respiratory failure or hemodynamic instability [8-10]. Therefore, PICC may be implemented at the bedside by intensivists for critically ill patients who have transport risks [8]. In addition, ultrasound-guided PICC placements performed by intensivists have been gradually increasing due to its safety and ease-of-use [11].

A subspecialty training program was recently established in the field of intensive care medicine in Korea [12]. Therefore, intensive care medical trainees have been recently trained in and implemented PICC placements. However, there is limited data on the safety and feasibility of ultrasound-guided PICC placement performed by trainees of intensive care medicine. Therefore, the objective of this study was to investigate the safety and feasibility of ultrasound-guided PICC placements performed by intensive care medical trainees compared to PICC placements performed by intensivists.

METHODS

This was a retrospective and observational study of adult patients admitted to the intensive care units (ICUs) at Samsung Medical Center between July 2013 and March 2018. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2018-09-011). The requirement for informed consent was waived due to its retrospective nature.

Study population

Adult patients who underwent ultrasound-guided PICC performed by an intensive care medical trainee or an intensivist during their ICU stay were included in the study. Of these patients, patients younger than 18 years of age, those with insufficient medical records, and those discharged before 14 days after PICC placement were excluded. A total of 209 patients with PICC placement were analyzed in this study (Fig. 1). To assess the safety and feasibility of PICC performed by subspecialty trainees in critical care medicine, postprocedural outcomes were compared between trainee-led and intensivist-led procedures.

Definitions and outcomes

We retrospectively reviewed all placements of PICCs in the ICU during the study period. The illness severity on ICU admission was estimated by the Simplified Acute Physiology Score 3 (SAPS 3) and Sequential Organ Failure Assessment (SOFA) systems. Central line-associated bloodstream infections (CLABSIs) were defined as an infection resulting from the same bacteria as confirmed by line and blood cultures [4,11,13,14]. CLABSIs were also identified in collaboration with the Infection Prevention and Control Team of Samsung Medical Center who monitors for CLABSIs [11]. Compression ultrasonography and duplex Doppler were performed only when the patient had clinical signs and symptoms suggesting venous occlusion such as a swelled arm, unexplained local pain, or malfunctioned PICC [1,11].

In this study, the primary outcome was PICC-induced complications. The secondary outcome was initial success of central line placement.

Procedure

An intensivist determined the PICC placement in critically ill patients. The ultrasound-guided PICC was preferred at the bedside for patients with hemodynamic instability, on mechanical ventilation, or those who were critically ill. In this study, all PICCs were inserted as an elective procedure. Indications for placement of PICC included the need for a central line for parenteral nutrition, infusion of drugs requiring a central line, need for frequent blood sampling, or difficult venous access [1,11]. Contraindications to PICC placement were small deep veins of the arm (diameter of target vein < 3 mm), local contraindications due to specific arm conditions such as skin infection, burns, or an arteriovenous fistula for renal failure [11]. Obesity or severe edema were not considered contraindications for PICC placement. We used 5 Fr single-lumen silastic catheters or 5 Fr dual-lumen Turbo-Ject Power-Injectable PICCs (Cook, Bloomington, MN, USA), 5 Fr triple-lumen PowerPICC Catheters (Bard Access Systems, Salt Lake City, UT, USA), or 6 Fr dual-lumen Vaxel PICCs with PASV

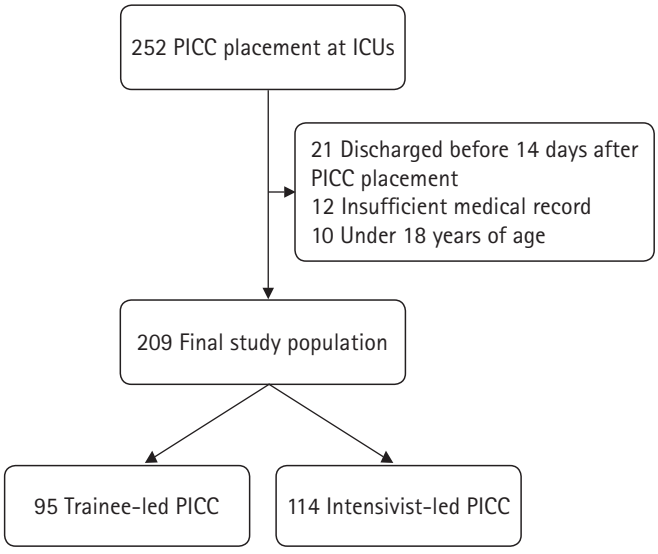

Fig. 1. Study flow chart. PICC, peripherally inserted central catheter; ICU, intensive care unit.

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Valves (Navilyst, Marlborough, MA, USA) [11]. PICC placement was performed by an intensivists or intensive care medical trainee. After trainees had seen the procedure three times, intensivists supervised their procedures two or three times before they performed the PICC placement independently. In the supine position, the patient's arm was abducted and externally rotated. Usually, the target vein is either the basilic, brachial, or cephalic vein, and a tourniquet is sometimes applied to help find the target veins. The PICC placement was performed by an ultrasound-guided puncture of the deep veins in the upper midarm using the microintroducer technique. A standard 5 to 10 MHz linear ultrasound probe was used. The optimal length was determined for placement of the catheter tip in the cavoatrial junction, which is commonly done by measuring the distance from the site of insertion through the humeral head to the sternal notch, and down to the 3rd intercostal space. Maximal barrier precautions were consistently used during the procedure [11]. Ultrasound was used to anesthetize the skin and reidentify veins. After the ultrasound-guided puncture of the deep vein, the syringe was removed and the guide wire was advanced through the needle. The needle was removed and the wire placement in the vein was confirmed using ultrasound. Using a scalpel, a small nick at the insertion site was created to accommodate the dilator. The dilator and introducer were inserted over the guide wire. After removal of the guide wire and dilator, only the introducer was left in place. Finally, the catheter was inserted through the introducer and advanced to the predetermined length before the introducer was removed. The target veins and procedure are shown in Fig. 2. The correct position of the tip of the catheter was verified by chest radiographs. Malposition was defined as a catheter tip that was not located at the cavoatrial junction

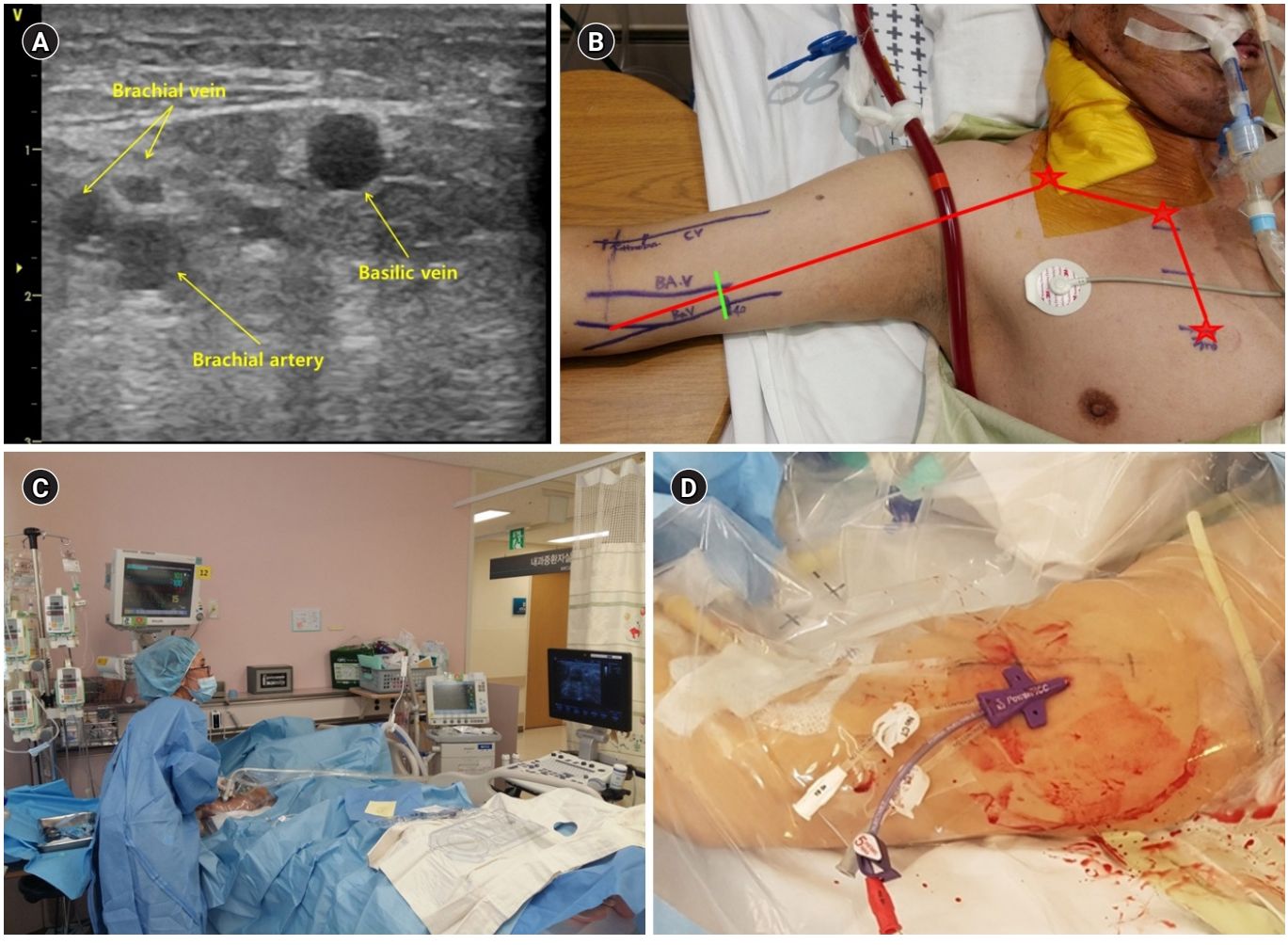

Fig. 2. (A) Target veins and procedure of the ultrasound-guided insertion of the peripherally inserted central catheter (PICC). Target veins were accessed by ultrasound. The cephalic vein is not shown in this ultrasound image. (B) The optimal length of the inserted PICC is measured from the site of insertion through the humeral head to the sternal notch, and down to the 3rd intercostal space. (C) The PICC is being inserted with the ultrasound-guided method in the intensive care unit (Eunmi Gil). (D) Finally, the PICC insertion is completed.

in chest radiographs. Dressing changes occurred every 7 days, or if soiled in all placements [11].

Statistical analyses

All data are presented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables. We compared data using Student's *t* test for continuous variables and chi-square test or Fisher's exact test for categorical variables. All tests were two-sided and *P* values < 0.05 were considered statistically significant. Data were analyzed using IBM SPSS statistics ver. 20 (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 209 patients underwent PICC placements during their ICU stay. The mean age of the patients with PICC was 59.3 ± 15.9 years. Of 209 patients, 116 (55.5%) were males. Hypertension (54.5%) and malignancies (53.6%) were the most common comorbidities among patients who underwent PICC placement. Respiratory failure (27.3%) and sepsis (23.4%) were the most common causes of ICU admission. There were no significant differences in age, gender, body mass index, comorbidities, causes of ICU admission, or severity scores of illness on ICU admission between the two groups (Table 1).

Procedural characteristics

Difficult venous access (42.6%) and requirement for central line infusion (39.2%) were the most common reasons for PICC placement. Almost all patients (92.8%) used a mechanical ventilator and 70 patients (33.5%) had hemodynamic instability. Renal replacement therapy was more frequently used in the trainee group compared to the intensivist group. The basilic vein (62.2%) and the brachial vein (20.6%) were the most common target veins among patients who underwent PICC placement. Activated partial thromboplastin time was prolonged in the trainee-led PICC group compared to the intensivist-led PICC group. There were no significant differences in reasons for PICC placement, use of anticoagulant and antiplatelet agent, insertional veins, platelet count, and international normalized ratio between the two groups (Table 2). The procedure times of the intensive medical trainees and intensivists according to procedure number are shown Fig. 3. Although the procedure times of intensive medical trainees decreased after three or four procedures (Fig. 3A), those of intensivists according to procedure number were similar (Fig. 3B).

Clinical outcomes

There were no significant differences in complication between

Table 1. Baseline characteristics

Characteristic	Insertion by intensivist (n=95)	Insertion by trainee (n=114)	*P* value
Age (yr)	58.4±15.6	60.1±16.2	0.444
Male sex	52 (54.7)	64 (56.1)	0.949
BMI (kg/m^2)	23.3±4.5	22.5±4.5	0.222
Obese (BMI >30 kg/m^2)	6 (6.4)	4 (3.8)	0.522
Comorbidities			
Hypertension	55 (57.9)	59 (51.8)	0.454
Malignancy	53 (55.8)	59 (51.8)	0.658
Diabetes mellitus	36 (37.9)	45 (39.5)	0.928
Chronic kidney disease	22 (23.2)	26 (22.8)	0.999
Chronic liver disease	7 (7.4)	16 (14.0)	0.190
Ischemic heart disease	7 (7.4)	13 (11.4)	0.452
Cause of ICU admission			0.242
Respiratory failure	24 (25.3)	33 (28.9)	
Sepsis	21 (22.1)	28 (24.6)	
Cardiovascular problems	20 (21.1)	28 (24.6)	
Neurological abnormalities	27 (28.4)	18 (15.8)	
Other	3 (3.2)	7 (6.1)	
SOFA score	7.7±4.5	8.5±4.1	0.267
SAPS 3	36.1±14.6	10.6±15.0	0.059

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score.

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the two groups ($P=0.473$). There were five cases of CLABSI (2.4%) and three cases of symptomatic PICC-related venous thrombosis (1.4%) in all patients who underwent PICC placement. However, there were no insertional injuries and moderate or severe bleeding in patients with PICC (Table 3). In addition, there were no significant differences in the rate of initial success and procedure time between the two groups ($P=0.108$ and $P=0.076$, respectively).

DISCUSSION

In this study, we investigated the safety and feasibility of ultrasound-guided PICC placement performed by intensive care medical trainees compared to PICC placements performed by inten-

Table 2. Procedural characteristics of peripherally inserted central venous catheter line placement

Characteristic	Insertion by intensivist (n=95)	Insertion by trainee (n=114)	*P* value
Reason for PICC insertion			0.799
Difficult venous access	39 (41.1)	50 (43.9)	
For infusion of drugs requiring a central line	38 (40.0)	44 (38.6)	
Parenteral nutrition	13 (13.7)	11 (9.6)	
Frequent blood sampling	4 (4.2)	6 (5.3)	
Other	1 (1.1)	3 (2.6)	
Anticoagulation	33 (34.7)	40 (35.1)	0.999
Use of antiplatelet agent	4 (4.2)	8 (7.0)	0.569
Use of mechanical ventilator	91 (95.8)	103 (90.4)	0.212
Use of renal replacement therapy	32 (33.7)	57 (50.0)	0.025
Use of vasopressor or hypotension	27 (28.4)	43 (37.7)	0.156
Insertional site			0.654
Basilic vein	60 (63.2)	70 (61.4)	
Brachial vein	21 (22.1)	22 (19.3)	
Cephalic vein	14 (14.7)	22 (19.3)	
Laboratory results of coagulation on the day of PICC			
Platelet count ($\times 10^3/\mu L$)	191.0±128.3	158.5±126.2	0.068
INR	1.4±0.9	1.7±1.1	0.154
aPTT (sec)	47.4±15.4	52.1±16.1	0.049

Values are presented as number (%) or mean±standard deviation.
PICC, peripherally inserted central catheter; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

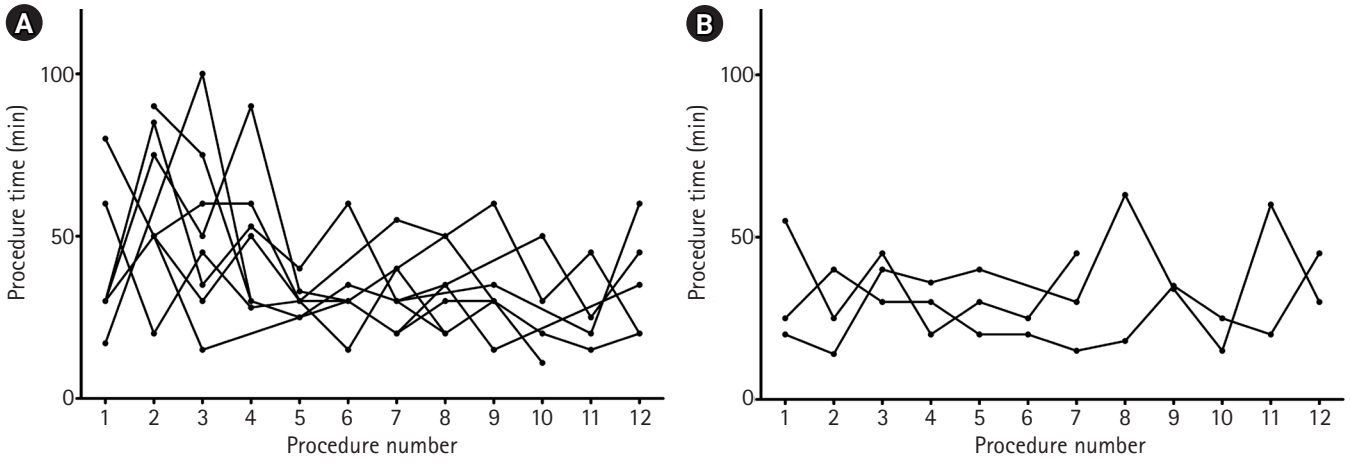

Fig. 3. The procedure times of (A) intensive medical trainees and (B) intensivists according to procedure number. (A) Although the procedure times of intensive medical trainees were decreased after three or four procedures, (B) those of intensivist according to procedure number were similar.

Table 3. Clinical outcomes

Characteristic	Insertion by intensivist (n=95)	Insertion by trainee (n=114)	*P* value
Procedural data			
Initial success of PICC	87 (91.6)	96 (84.2)	0.108
Malposition & reinsertion	8 (8.4)	6 (5.3)	0.363
Procedure time (min)	32.3±19.9	37.6±20.8	0.076
Duration of using PICC (day)	80±20.1	102±32.4	0.112
Complication	5 (5.3)	3 (2.6)	0.473
CLABSI	3 (3.2)	2 (1.8)	0.661
Symptomatic PICC-related venous thrombosis	2 (2.1)	1 (0.9)	0.179
Insertional injury	0	0	NS
Moderate or severe bleeding and hematoma	0	0	NS
Cause of removal			0.723
Unnecessary	58 (61.1)	77 (67.5)	
Malfunction	22 (23.2)	21 (18.4)	
Fever	9 (9.5)	8 (7.0)	
Self-removal	6 (6.3)	8 (7.0)	

Values are presented as number (%) or mean±standard deviation.
PICC, peripherally inserted central catheter; CLABSI, central line-associated bloodstream infection; NS, not significant with $P>0.05$.

sivists. We report multiple major findings in this study. First, there were no significant differences in complications associated with PICC insertion between the two groups. In addition, there were no insertional injuries and severe bleeding in both groups. The incidence rates of CLABSI and symptomatic PICC-related venous thrombosis were low in patients with PICC. Second, the rate of initial success and procedural time were similar between the two groups. In addition, the procedure times of trainees decreased after three or four procedures. Third, PICC placement was performed in patients with intrahospital transport risks due to mechanical ventilator or hemodynamic instability. Fourthly, difficult venous access and requirement for central line infusion were the most common reasons for PICC placement. Overall, we show that ultrasound-guided PICC placement is a well-established procedure and easy to learn by an intensive care medical trainee.

Critically ill patients often need central venous access using either a central venous catheter or PICC due to various reasons such as parenteral nutrition, long-term antibiotic therapy, frequent blood sampling, and difficult venous access [15,16]. PICC insertion cannot lead to hemothorax, pneumothorax, clinically significant bleeding, or hematoma, even in patients with coagulative disorders or difficult neck anatomy. In addition, PICC placement has a low risk for CRBSI compared to standard central venous catheters [1-5]. Therefore, PICC placement may be safe and useful in critically ill patients [1,3].

In the past, PICC was only inserted by an interventional radiologist in the interventional radiology suite under fluoroscopic guidance PICC placements have been also performed by interventional radiologists [2,6,7]. As this procedure is performed in the interventional radiology suite, critically ill patients should be transferred from the ICU to the interventional radiology suite. However, various complications may occur during intrahospital transport of critically ill patients from the ICU to other locations because of their respiratory failure or hemodynamic instability [8-10]. In addition, it may be difficult for radiologists to perform the PICC placement in the interventional radiology suite in a timely manner due to other procedures that may be ongoing in the suite. Therefore, ultrasound-guided PICC placement should be performed at the bedside in critically ill patients.

Ultrasound for vein localization and the modified Seldinger technique have been used for safe placement of PICCs at bedside [16,17]; these techniques could allow trainees to place the PICC easily and safely. In this study, ultrasound-guided PICC placement performed by an intensive care medical trainee was feasible compared to PICC placement performed by an intensivist. There were no significant differences in the rate of initial success and procedure times between the two groups. In addition, the intensive care medical trainees were able to safely perform the PICC placements. Additionally, the rates of PICC-related complications were similar between the two groups. A recent study also revealed that interventional radiologic placement of PICC is a well-established procedure, easy to learn by residents, and has a small learning curve [18].

This study had several limitations. This study was a retrospective review of medical records. An intensivist determined the placement of the PICC rather than following a protocol-based

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plan [11]. Therefore, a selection bias may have affected the results in this study. Additionally, there were no routine screening procedures for central line-related venous thrombosis or pulmonary thromboembolism. Finally, the statistical power of our study was limited due to the small sample size. Although it still provides valuable insight, prospective large-scale studies are needed to evaluate the safety and feasibility of ultrasound-guided PICC placement by an intensive care medical trainee.

In conclusion, ultrasound-guided PICC placement by an intensive care medical trainee may be safe and more feasible compared to PICC placement by an intensivist. Therefore, ultrasound-guided PICC placement can be performed at the bedside by an intensive care medical trainee for critically ill patients if intrahospital transport is contraindicated.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

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Predicting parenchymal hematoma associated with endovascular thrombectomy for acute occlusion of anterior circulation large vessel: the GuEss-MALiGn scale

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Background: Endovascular thrombectomy (EVT) is an emergency treatment for stroke caused by anterior circulation large vessel occlusion (ACLVO). This study aimed to identify the predictors for post-EVT parenchymal hematoma (PH) and to develop a predictive tool using the identified factors.

Methods: Using the clinical and imaging data of consecutive patients with acute ACLVO who underwent EVT, we performed a multivariate binary logistic regression analysis to identify predictors for PH. With the predictors proved by the regression, we developed a scale for predicting PH using receiver operating characteristic (ROC) curve analyses.

Results: In 233 enrolled patients, the mean age was 72.3 years old, and the male proportion was 46.4%. The rate of PH after EVT was 18.0%: the rate of type 1 PH was 12.9%, and the rate of type 2 PH was 5.2%. The significant predictors for PH were basal ganglia involvement, embolism, male sex, antihyperlipidemic use, lobar infarction, and serum glucose level. We developed the GuEss-MALiGn scale with the six significant predictors. Each of these six items was placed on a Likert scale and scored as a 0 or 1. The ROC curve analysis revealed that the area under the curve was 0.771. The cutoff score for the risk of PH was >3. The sensitivity was 59.5%, and the specificity was 78.0%.

Conclusion: We propose the GuEss-MALiGn scale as a tool for predicting PH associated with EVT. Future external validation is needed to determine the reliability of this scale.

Keywords: Cerebral infarction; Middle cerebral artery; Thrombectomy; Endovascular procedures; Postoperative complications; Cerebral hemorrhage

INTRODUCTION

Endovascular thrombectomy (EVT) is an intraarterial treatment for acute cerebral infarction due to anterior circulation large vessel occlusions (ACLVOs). The reperfusion accomplished by EVT may prevent the progression of cerebral infarction caused by the occluded vessels. Prior randomized controlled studies have shown that EVT could be the standard care for patients with ACLVO [1-5].

Parenchymal hematoma (PH) may occur in association with

EVT for ACLVO. The posttreatment PH may negatively impact the outcome of patients who have undergone EVT. A multicenter study of 13 stroke centers retrospectively gathered patients who underwent EVT to treat ACLVO. The incidence of posttreatment PH increased with an odds ratio of 3.53 in patients with EVT for ACLVO. The occurrence rate of posttreatment PH was 8.5%. In the multicenter study, atrial fibrillation was a risk factor for PH, but intraarterial tissue plasminogen activator (IA tPA) reduced the occurrence of PH [6]. Another single-center study also presented a 9.0% prevalence of posttreatment PH after EVT for an ACLVO. In that study, hyperlipidemia and successful reperfusion reduced the occurrence of PH, while hypertension and longer procedure duration increased the occurrence of PH [7].

The European Cooperative Acute Stroke Study (ECASS) categorized hemorrhagic transformation (HTR) into hemorrhagic infarction (HI) and PH [8]. For the patients treated by EVT, the impact of PH is more crucial than that of HI [6]; therefore, we focused on PH for this study.

A few studies have examined the factors that predict the PH after treatment with EVT in patients with ACLVO. The primary purpose of this study is to find the predictors of post-treatment PH associated with EVT. The secondary purpose of this study is to develop a tool that can be used to predict the risk of developing PH after performing EVT for ACLVO.

METHODS

Patient selection

Consecutive patients with acute ACLVO treated by EVT at the Cerebrovascular Center at Gyeongsang National University Hospital were enrolled retrospectively. The recruitment period was from February 2016 to November 2018. We included patients only when the occlusion site was the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA). Unilateral occlusions of an anterior cerebral artery (ACA) were not enrolled in this study because we do not perform EVT in those cases. Patients treated with EVT in this study were those who were within 24 hours after ACLVO and had sufficient ischemic penumbra as evaluated by brain imaging.

We excluded patients with any of the following: no initial magnetic resonance imaging (MRI), no follow-up MRI within 1 week, and in-hospital stroke. The reason for the exclusion of the patients with an in-hospital stroke was the lack of data on the initial laboratory findings and initial blood pressure. Finally, 233 patients were enrolled in this study.

Extraction of data

The demographic and clinical information obtained from the electronic medical records are summarized in Table 1. The variables associated with the EVT procedures were also from the medical records and are summarized in Table 2. The demographic and clinical information were as follows: demographics (age, sex), infarction state (basal ganglia involvement, occlusion location, embolism, initial pattern of infarction, and National Institute Health Stroke Scale [NIHSS] score at admission time), medical history (hypertension, diabetes, prior stroke or transient ischemic attack, smoking, coronary heart disease, atrial fibrillation, and/or hyperlipidemia), and current medication (oral anticoagulants, antiplatelet drugs, antihypertensive drugs, antidiabetic drugs, and/or statins). In this study, the subtypes of ischemic stroke were classified into two categories, embolic stroke, and large artery disease. Embolic strokes included cardiogenic embolism and embolic stroke of undetermined source [9].

The extracted variables associated with the EVT procedure were as follows: initial laboratory and clinical findings (serum glu-

Table 1. Demographic and baseline clinical characteristics of the enrolled patients (n=233)

Characteristic	Non-PH group (n=191)	PH group (n=42)	*P* value
Age (yr)	72.4±11.6	71.8±9.6	0.774
Male sex	84 (44.0)	24 (57.1)	0.128
Location of thrombus			0.855
Internal carotid artery	57 (29.8)	13 (31.0)	
Middle cerebral artery	134 (70.2)	29 (69.0)	
Embolism	136 (71.2)	36 (85.7)	0.263
Basal ganglia involvement	126 (66.0)	36 (85.7)	0.015
Lobar infarction	79 (41.4)	28 (66.7)	0.004
NIHSS score, initial	13.6±5.2	15.1±4.2	0.078
Preexisting medication use			
Antithrombotics	70 (36.6)	17 (40.5)	0.725
Antihypertensives	106 (55.5)	25 (59.5)	0.732
Antidiabetics	33 (17.3)	13 (31.0)	0.054
Antihyperlipidemics	47 (24.6)	16 (38.1)	0.086
Smoking history	41 (21.5)	11 (26.2)	0.541
Prior medical history			
Hypertension	123 (64.4)	26 (61.9)	0.859
Diabetes	48 (25.1)	15 (35.7)	0.181
Hyperlipidemia	67 (35.1)	15 (35.7)	1.000
Atrial fibrillation	90 (47.1)	23 (54.8)	0.398
Coronary artery disease	22 (11.5)	4 (9.5)	1.000
Stroke	35 (18.3)	9 (21.4)	0.665

Values are presented as mean±SD or number (%).
PH, parenchymal hematoma; NIHSS, National Institute Health Stroke Scale.

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cose levels, prothrombin time international normalized ratio [PT INR], hemoglobin A1c, and systolic blood pressure), and interventions (intravenous recombinant tissue plasminogen activator, use of balloon guiding catheter, thrombectomy technique, use of tirofiban during EVT, intervals from symptom onset to puncture time, number of retrievals, and procedure time).

In this study, we classified the PH according to the ECASS criteria [8]. The ECASS classification grades PH as PH type 1 (PH1) and PH type 2 (PH2). PH1 is the hematoma that occupies less than 30% of the infarcted area. PH2 is the hematoma occupying more than 30% of the infarcted area and has a significant space-occupying effect. To determine the grade of the PH, each of the two authors (CHK and JK) evaluated the cases independently. If the decision was not initially concordant between them, a consensus was achieved through discussion.

The state of reperfusion after EVT was defined based on the Treatment in Cerebral Ischemia Scale (TICI) [10]. In the TICI scale, the degree of perfusion after vascular therapy for acute ischemic stroke has five grades: grade 0, grade 1, grade 2a, grade 2b, and grade 3. Grade 0 means no perfusion, and grade 3 indicates complete reperfusion of the prior occlusion of the target artery and its distal branches. We defined complete reperfusion as the vascular state of TICI grade 3 for this study.

Table 2. Variables associated with endovascular therapy procedures in the enrolled patients (n=233)

Characteristic	Non-PH group (n=191)	PH group (n=42)	*P* value
IV thrombolysis	64 (33.5)	16 (38.1)	0.593
Onset to puncture time (min)	408.9±372.9	385.7±239.5	0.045
Systolic BP, initial (mm Hg)	144.42±25.125	145.24±22.978	0.847
PT INR, baseline	1.06±0.14	1.09±0.17	0.225
Serum glucose level ≥145, initial (mg/dL)	49 (25.7)	21 (50.0)	0.003
Balloon guiding catheter	81 (42.4)	20 (47.6)	0.619
Thrombectomy technique			0.304
Stent retriever	102 (53.4)	21 (52.4)	
ADAPT	50 (26.2)	7 (16.7)	
Multimodal	26 (13.6)	12 (28.6)	
Other techniques	5 (2.6)	1 (2.4)	
Use of tirofiban	18 (9.5)	0	0.050
Complete reperfusion (yes)	88 (46.1)	17 (40.5)	0.509
Procedure time (min)	84.1±35.7	83.6±44.9	0.937

Values are presented as number (%) or mean±SD.
PH, parenchymal hematoma; IV, intravenous; BP, blood pressure; PT INR, prothrombin time-international normalized ratio; ADAPT, a direct aspiration first pass technique.

EVT procedure

Three interventionists (DSC, CHK, and JK) performed the procedures in all recruited patients according to their shift schedule. They obtained digital subtraction angiography images by placing a guiding catheter at the cervical segment of the ICA or the common carotid artery. Those images were used to evaluate the occlusion site of the cerebral infarction.

For EVT, they used a stent retriever or a direct aspiration catheter with a femoral artery approach under conscious sedation. In the case of using the stent retriever, they inserted the microcatheter under the guide of a microwire. After locating the microcatheter at the distal part of the clot, they captured the clot with the stent retriever deployed across the clot. They then retrieved the stent device through the guide catheter while aspirating with a 50 mL syringe. In cases of using a direct aspiration catheter, they located the catheter at the proximal end of the clot. In that state, they performed the aspiration using a 50 mL syringe through the aspiration catheter.

When successful recanalization was not achieved with one of the two devices, they also used the other device. If they found chronic severe stenosis of the target artery, they additionally administered intraarterial tirofiban up to 2 mg to prevent reocclusion. Just after finishing the entire procedure, another angiography was performed to evaluate the degree of recanalization.

Statistical analysis

We grouped the patients into two groups to compare the extracted factors between the two groups: patients with PH and patients without PH. For simple comparisons of variables, we used chi-square tests for categorical variables and Student *t* tests for continuous variables. We converted the glucose level at EVT to a binary variable: <145 and ≥145 mg/dL. In addition, we calculated the interrater kappa regarding the decision as to the presence or absence of PH between the two authors (CHK and JK) to provide the degree of accuracy of the decision.

For the regression analysis, we performed a univariate regression of the extracted variables first to find factors that had significant effects on the occurrence of PH. For this univariate regression, we set the level of significance as $P < 0.2$. Next, we performed a binary multivariate logistic regression for the factors against the occurrence of PH. For this multivariate regression, we set the level of significance as $P < 0.05$. For these statistical analyses, we used IBM SPSS Statistics software ver. 25 (IBM Corp., Armonk, NY USA).

Through gathering the significant factors from the binary multivariate regression, we developed a clinical inventory tool to predict PH associated with EVT. For the validation of the inventory

tool, we performed receiver operating characteristic (ROC) curve analyses using MedCalc software ver. 8.0 (MedCalc Software BVBA, Ostend, Belgium). The ROC curve analyses determined the most appropriate cutoff score when the Youden's J index was the highest, the area under the curve (AUC) value, and other statistical results from the case. Additional statistical analyses were performed to observe how the AUC value changes as the cutoff score changes. Whenever the cutoff score was changed, we added ROC curve analyses repeatedly after artificially converting the GuEss-MALiGn scale score to a binary classification based on the individual case.

Ethical statement

This study was approved by the Institutional Review Board of the Gyeongsang National University (2019-10-044-001), and the need for written informed consent was waived because of the retrospective nature of the currrent study.

RESULTS

Characteristics of the patients

The mean age of the enrolled 233 patients was 72.3 years old, with a standard deviation (SD) of 11.3. One hundred eight of the patients were male (46.4%). PH after EVT occurred in 18.0% (n=42) of the enrolled patients. According to the subtype of PH, the occurrence rate was 12.9% (n=30) for PH1 and 5.2% (n=12) for PH2. The interrater agreement rate for the decision of PH was 99.6% between the two investigators (CHK and JK), and the kappa value of the agreement was 0.875±0.41 ($P<0.01$).

Comparisons of demographic and clinical characteristics between the non-PH and PH groups

The number of enrolled patients who underwent EVT for ACLVO was 233. We summarized the demographic and baseline clinical characteristics with the comparison between the non-PH and PH groups in Table 1, Fig. 1. Basal ganglia involvement and lobar infarction were significantly different between the two groups ($P<0.05$). The percent of basal ganglia involvement was 66.0% and 85.7% for the non-PH and PH groups, respectively. The rate of lobar infarction was 41.4% and 66.7% for the non-PH and PH groups, respectively.

Differences between the two groups for age, sex, location of thrombus, embolic infarction, the NIHSS score at the admission time, previous medication use, smoking history, and previous medical history in the univariate analysis did not reach the level of significance. The mean age of the non-PH and PH groups was 72.4±11.6 and 71.8±9.6 years, respectively. For the non-PH and PH groups, the male proportion was 44.0% and 57.1%, respectively; the frequency of embolic infarction was 71.2%, and 85.7%, respectively; and the rate of antihyperlipidemic use was 24.6% and 38.1%, respectively. The proportion of patients using antithrombotics as a preexisting treatment was 36.6% for the non-PH group and 40.5% for the PH group.

For patients included in our study, the occlusion was located in either the ICA or the MCA, for 29.8% and 70.2%, respectively, in the non-PH group, and 31.0% and 69.0%, respectively, in the PH group. There was no case where the ACA was the occlusion site. For cases of solitary and unilateral ACA occlusion, we do not perform EVT treatment. For this reason, this study excluded cases with solitary ACA occlusion.

Comparison of factors associated with the EVT procedure between the non-PH and PH groups

We summarized the factors associated with the EVT procedure with a comparison between the two study groups in Table 2, Fig. 1. The initial glucose level was significantly different between the two groups. The incidence of the initial glucose level equal to or higher than 145 mg/dL was 25.7% and 50.0% in the non-PH and PH groups, respectively. IV thrombolysis, onset to puncture time, initial systolic blood pressure, baseline INR, balloon guid-

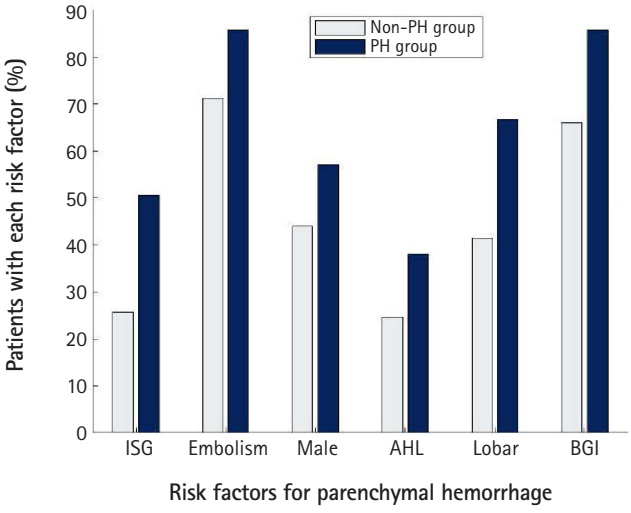

Fig. 1. The occurrence rate of parenchymal hematoma (PH) associated with endovascular therapy (EVT) according to each item of the GuEss-MALiGn scale: comparisons between the non-PH group and the PH group. In patients with acute stroke by the occlusion at the internal carotid artery or the M1 segment of the middle cerebral artery, the six factors were associated with the occurrence of PH associated with EVT. Those factors were: the initial serum glucose (ISG) level, embolism, male sex, antihyperlipidemic (AHL) use, lobar infarction (Lobar), and basal ganglia involvement (BGI).

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ing catheter, thrombectomy technique, use of tirofiban, complete reperfusion, and procedure time were not significantly different between the two groups in the univariate analysis. The onset to puncture time in the non-PH group was 408.9 ± 372.9 minutes, and 385.7 ± 239.5 minutes in the PH group.

Binary logistic regression analysis

Univariate regression

Nine factors were significantly associated with the occurrence of PH ($P < 0.2$): male sex, embolism, basal ganglia involvement, lobar infarction, antidiabetic use, antihyperlipidemic use, diabetes mellitus history, NIHSS score, and initial serum glucose level (Table 3).

Binomial multivariate logistic regression

Six factors were significant in the multivariate regression combining with the nine factors mentioned above ($P < 0.05$): initial serum glucose level, embolism, male sex, antihyperlipidemic use, lobar infarction, and basal ganglia involvement.

A clinical inventory tool for predicting PH associated with EVT

GuEss-MALiGn scale

We developed a clinical inventory tool to predict PH associated with EVT, with the six significant factors obtained through multiple regression analysis. We named this as "GuEss-MALiGn scale" using the six upper case characters to indicate the six predictors: serum glucose level at EVT (G), embolic infarction (E), male sex (M), antihyperlipidemic use (A), lobar infarction (L), and basal ganglia involvement (G). All six predictors were binary conversions making it convenient to compose a six-item Likert scale inventory. For each item, the score is 0 or 1, according to the state of each patient being assessed. Therefore, the range of the total score of the GuEss-MALiGn scale is 0–6.

The optimal cutoff point for the high risk of PH

For the patients in this study, the mean score of the GuEss-MALiGn scale was 2.9 ± 1.1. Table 4 shows the results of the ROC curve analysis of the score of the GuEss-MALiGn scale for predicting a high risk of PH associated with EVT, and Fig. 2A shows the ROC curve drawn by the analysis. The GuEss-MALiGn scale score was suited for discerning a high risk of PH associated with

Table 3. Binary logistic regression analysis for independent predictors of parenchymal hematoma associated with endovascular thrombectomy

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Male sex	1.70	0.87–3.33	0.12	3.16	1.39–7.15	0.01
Embolism	2.44	0.98–6.13	0.06	3.47	1.15–10.48	0.03
Basal ganglia involvement	3.10	1.24–7.73	0.02	2.98	1.09–8.13	0.03
Lobar infarction	2.84	1.40–5.73	0.00	2.94	1.30–6.63	0.01
Antidiabetic medications	2.15	1.01–4.56	0.05	2.80	0.48–16.49	0.26
Antihyperlipidemics	1.89	0.93–3.81	0.08	2.56	1.13–5.85	0.03
Diabetes history	1.66	0.81–3.37	0.17	0.64	0.11–3.65	0.62
NIHSS score, initial	1.07	0.99–1.15	0.08	1.00	0.91–1.09	0.95
Serum glucose, initial	2.90	1.46–5.76	0.00	2.56	1.09–6.02	0.03

OR, odds ratio; CI, confidence interval; NIHSS, National Institute Health Stroke Scale.

Table 4. The receiver operating characteristics curve analysis of the GuEss-MALiGn scale for predicting the risk of parenchymal hematoma

Cutoff point	Sensitivity (%)		Specificity (%)		PPV (%)	NPV (%)	AUC		
	Value	95% CI	Value	95% CI			Value	95% CI	*P* value
>1	100.0	91.6–100.0	11.0	6.9–16.3	19.8	100.0			
>2	95.2	83.8–99.4	40.8	33.8–48.2	26.1	97.5			
>3[a]	59.5	43.3–74.4	78.0	71.5–83.7	37.3	89.8	0.771	0.712–0.824	<0.001
>4	26.19	13.9–42.0	95.81	91.9–98.2	57.9	85.5			
>5	2.38	0.06–12.6	100.0	98.1–100.0	100.0	82.4			

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.
[a]Optimal cutoff point

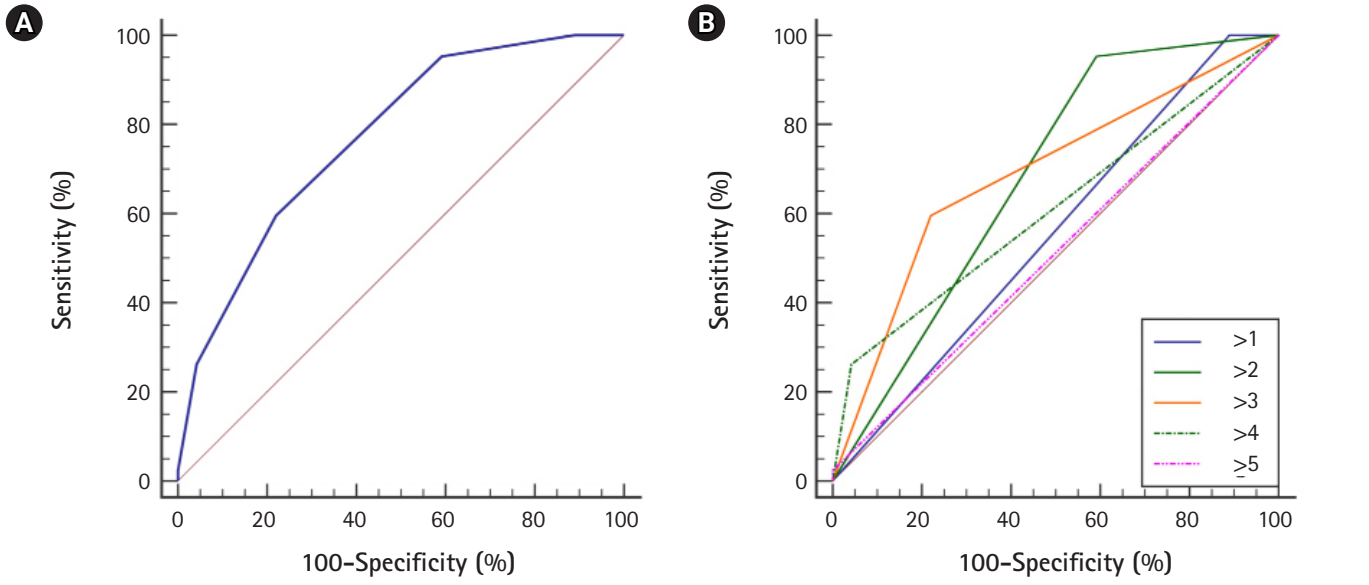

Fig. 2. The receiver operating characteristic (ROC) curves of the score of the GuEss-MALiGn scale for detecting the risk of parenchymal hematoma after EVT of the acute occlusion of anterior circulation large vessel. (A) For detecting the risk, ROC analysis of the score of the GuEss-MALiGn scale determined an area under the curve (AUC) of 0.771. At a cutoff score of >3, the sensitivity and specificity for detecting the risk were 59.5% and 78.0%, respectively. (B) When comparing the AUC values between the different scores in the cases that they were hypothetically the GuEss-MALiGn cutoff points, the AUC value was also the highest at 0.688 when the cutoff point was >3.

Table 5. Comparison of AUC values between the various scores when they were hypothetically the GuEss-MALiGn cutoff point

Hypothetical cutoff point	AUC	SE	95% CI
>1	0.555	0.0113	0.489–0.620
>2	0.680	0.0244	0.616–0.740
>3	0.688	0.0412	0.624–0.747
>4	0.610	0.0351	0.544–0.673
>5	0.512	0.0119	0.446–0.578

AUC, area under the curve; SE, standard error; CI, confidence interval.

EVT (AUC, 0.771; $P < 0.0001$; 95% confidence interval, 0.712 to 0.824) (Table 4, Fig. 2A). The optimal cutoff point was > 3. At the cutoff point of > 3, the sensitivity and specificity were 59.5% and 78.0%, respectively, with a positive predictive value of 37.3% and a negative predictive value of 85.5%. To observe how the AUC changes as the cutoff score shifts, we conducted additional statistical analyses. Even in this comparison between the different scores, when the cutoff point was > 3, the AUC value was at its highest, at 0.688 (Table 5, Fig. 2B).

DISCUSSION

Posttreatment PH associated with EVT results in adverse impacts on the outcome of patients with ACLVO. PH increased poor functional outcomes by 6.24 times and mortality by 3.53 times in a multicenter study [6]. Through ROC curve analyses, we proved that the GuEss-MALiGn scale was clinically useful to predict the posttreatment PH. The optimal cutoff point of the GuEss-MALiGn scale for predicting the PH was more than 3 points. The GuEss-MALiGn scale may help us identify patients with a high risk of PH associated with EVT. We could provide particular attention and effort toward reducing PH for the patients determined to be at high risk by the GuEss-MALiGn scale.

Studies regarding the occurrence rate of PH associated with EVT in patients with ACLVO are scant. Nogueira et al. [6] gathered patients with ACLVO who underwent EVT within 8 hours after EVT from 13 stroke centers. The rate of PH associated with EVT was 8.5% among the enrolled patients [6]. Lee et al. [7] also recruited patients with EVT for ACLVO in a single-center study, and the rate for PH was 9.0% in their collection. In our study, PH occurred in 18.0% of enrolled patients. There was a marked difference in the rate between our study and the previous two studies.

There are a number of potential reasons for the difference in the occurrence rate of PH associated with EVT between the previous studies and our study. One plausible explanation is that the imaging modalities for determining the occurrence of PH were different among the studies. Small PHs, which are not easy to detect with computed tomography (CT), will be detected more frequently by MRI. Nogueira et al. [6] evaluated the PH associated with EVT with CT as well as MRI, and Lee et al. [7] used only CT. Meanwhile, we defined the occurrence of PH using MRI in

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all enrolled cases. Considering the difference in imaging modalities, we calculated the occurrence rate of PH2. PH2, whose size was defined as more than 30% of the infarcted area, occurred in 5.2% of enrolled patients in our study. The occurrence rate of PH2 was less than that of PH in the two previous studies [6,7]. The two previous studies did not report the occurrence rates of PH2. Visual inspection may similarly detect massive bleeding between the CT-based and MRI-based decision paradigms, so our incidence of PH2 might have been similar to the previous studies.

In the study by Nogueira et al. [6], the use of IA tPA was a beneficial factor in reducing the posttreatment PH. In contrast, the effect of IA tPA could not be evaluated in our research because we did not use IA tPA in our enrolled patients. The lack of IA tPA use might explain the higher rate of PH in our study than in their previous study. The occurrence rate of the PH2 subset in our study was less than that of total PH in the previous two studies. The use of IA tPA might have reduced the occurrence of small hemorrhages in the previous study because the occurrence rate was markedly less than that in our research.

Six items in the GuEss-MALiGn scale are known to be associated with the HTR of cerebral infarction. A previous study also showed that the basal ganglia infarction occurred before the EVT treatment and was associated with the risk of HTR in patients with ACLVO [11]. HTR is associated with reperfusion after occlusion on the perforators, which are more vulnerable to blood brain barrier failure than larger arteries are [12]. Hyperperfusion after reperfusion and restoration of blood pressure associated with embolic infarction can damage brain parenchyma and cerebral vessel walls [13]. Therefore, embolism is a risk factor for posttreatment PH, and its effect was independent of anticoagulant or antithrombotic use [14,15]. Intracerebral hemorrhage in the general population was more prevalent in males than females in an epidemiological study performed in Japan [16]. As shown in the results of our study, the PH associated EVT treatment may also occur more frequently in males.

Hyperlipidemia is a beneficial factor for the prevention of posttreatment PH [7,17]. A low level of serum cholesterol can enhance the necrosis of smooth muscle cells in the medial layer of the artery. The vascular endothelium, damaged by the low level of serum cholesterol, may be an ideal site for the development of microaneurysms [18]. Brain edema caused by massive cerebral infarction compresses and damages the vasculatures peripheral to the volume of the infarction. Delayed perfusion that occurs after resolution of the edema increases the likelihood of HTR in damaged blood vessels [19-22]. Hyperglycemia causes diffuse damage in the microvasculature, increasing the volume of the cerebral infarction. The increment of infarct volume increases the risk of HTR [23-26].

There were several limitations to this study. Firstly, the most significant limitation of our proposed GuEss-MALiGn scale is that there has not yet been external validation. In the future, additional validation performed with patients extracted from other populations will improve the efficacy of the GuEss-MALiGn scale. Secondly, the sensitivity of the GuEss-MALiGn scale was relatively low at 59.5% for detecting PH after EVT. Contrastingly, the specificity was a reasonable 78.0%, and this may make the GuEss-MALiGn scale clinically significant when the score indicates a high risk of PH occurrence. Thirdly, we did not obtain the Alberta Stroke Program Early CT Score (ASPECTS), which is a surrogate for infarction volume. Nevertheless, in this study, we analyzed the involvement of the basal ganglia and lobar infarction as substitutes for the ASPECTS score. Both were significant EVT-related risk factors for PH. Fourthly, there may have been bias in the patient selection as this study was a retrospective study from a single center. Therefore, there is a possibility that cultural aspects deriving from the local area might have affected the outcome results. Lastly, a difference in the skills among the interventionists might have affected the outcome of EVT.

ARTICLE INFORMATION

Conflict of interest

Dr. OY Kwon is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. There are no other potential conflicts of interest relevant to this article to declare.

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Cervical myelitis in a patient with pulmonary sarcoidosis

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CASE REPORT

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Background: Sarcoidosis is a multisystemic disease characterized by noncaseating granulomas, predominantly affecting organs such as the lungs and lymph nodes. Spinal cord involvement of sarcoidosis is uncommon.
Case Report: A 32-year-old male presented with pain and numbness in bilateral upper extremities for 1 year. He had pulmonary sarcoidosis 4 years ago. Spinal magnetic resonance imaging showed a cord lesion with enhancement at the C5 to C6 level. Chest computed tomography revealed the increased size of the lymph nodes compared to previously. His serum angiotensin-converting enzyme level was elevated. He was diagnosed with myelitis caused by sarcoidosis. After steroid treatment, the numbness improved, but the pain still persisted.
Conclusion: To enable the early detection and treatment of neurosarcoidosis among patients with systemic sarcoidosis, a high degree of suspicion is required. Neurological complications can be minimized if it is detected and treated early.

Keywords: Neurosarcoidosis; Myelitis; Spinal cord

INTRODUCTION

Sarcoidosis is a multisystemic disease characterized by noncaseating granulomas, that predominantly affect organs such as the lungs and lymph nodes. The neurological manifestation of sarcoidosis has been described in 5% to 10% of patients [1,2]. Neurosarcoidosis can involve the cranial nerves, meninges, brain parenchyma, spinal cord, dura, muscle, and peripheral nerves. Spinal cord involvement, including intramedullary and extramedullary lesions, is uncommon [3]. Here, we report a patient with cervical myelitis and a previous diagnosis of pulmonary sarcoidosis. His clinical course, magnetic resonance imaging (MRI) findings, and clinical management are described.

CASE REPORT

A 32-year-old male presented with a 1-year history of pain in his neck, arms, and hands. He also complained bilateral numbness of his upper extremities 2 months prior to admission.

Four years ago, he had no pulmonary symptoms, but bilateral hilar and lower paratracheal lymphadenopathy was incidentally discovered during a routine medical chest radiography and com-

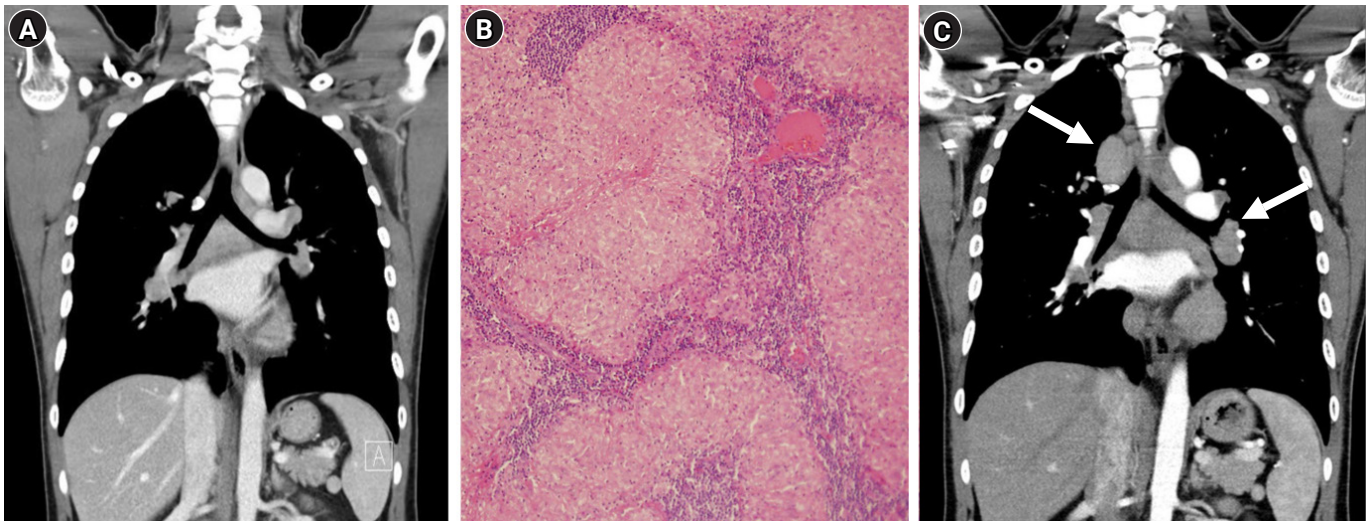

Fig. 1. (A) Four years ago, contrast-enhanced chest computed tomography (CT) showing enlargement of multiple lymph nodes. (B) Histopathology showing noncaseating granulomatous inflammation (hematoxylin and eosin stain, ×100). (C) At the time of diagnosing cervical myelitis. Chest CT shows the slightly increased size of the paratracheal and hilar lymph nodes (arrows).

puted tomography (CT) (Fig. 1A). A biopsy via video-assisted thoracoscopic surgery showed noncaseating epithelioid granulomatous lesions compatible with pulmonary sarcoidosis (Fig. 1B). Tissue cultures for mycobacteria and fungus were negative. He was treated with low-dose oral steroids for 2 years but discontinued the medication arbitrarily.

On physical examination, the muscle strength in his limbs was normal. Sensory examination revealed that his light touch was decreased on the medial aspect of the bilateral upper arm, forearm, and hand. Deep tendon reflexes were normal. His visual analog scale (VAS) score was 7.

The findings of his nerve conduction studies, electromyography, median, and tibial nerve evoked potential studies we were normal. Brain MRI scan was normal. A spinal cord MRI showed T2 hyperintensity from C5 to C6, with focal patchy gadolinium enhancement between C5 and C6 (Fig. 2). Cerebrospinal fluid (CSF) was acellular with an elevated protein level (52.2 mg/dL). There were no oligoclonal bands in the CSF or serum. The immunoglobulin G (IgG) index was normal (0.52). CSF cytology was negative for malignancy. There were no oligoclonal bands in the CSF or serum. Test results for antinuclear antibody, antineutrophil cytoplasmic antibodies, aquaporin (AQP4) IgG, and myelin oligodendrocyte glycoprotein (MOG) IgG were negative. Thyroid function and the serum IgG4 levels were within the normal range. His serum angiotensin-converting enzyme (ACE) level was elevated (79 U/L [normal range, 12 to 68]). A chest CT revealed increased enlargement of the hilar lymph nodes compared to the previous study (Fig. 1C).

He was diagnosed with a spinal cord manifestation of sarcoidosis and treated with intravenous methylprednisolone (1,000 mg/day, 3 days) followed by oral prednisolone. Azathioprine was administered in addition to prednisolone. At the 2-month follow-up, diminishing enhancement could be seen on the MRI (Fig. 3). The numbness had improved, but mild pain (VAS score, 3) persisted even though he was on continuous oral prednisolone (20 mg) and azathioprine (75 mg) treatment.

This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH 2020-03-026). Since this was a retrospective case study, the requirement for informed consent was waived.

DISCUSSION

Neurological manifestation occurs in 5% to 10% of patients with sarcoidosis [1,2]. Spinal cord sarcoidosis rarely occurs, and intraspinal sarcoidosis is rarely reported (0.1% to 50% of neurosarcoidosis) [3]. However, neurologic involvement can manifest 2 to 3 years after the development of systemic sarcoidosis [4,5]. Additionally, autopsy studies show that up to half of pathologic neurosarcoidosis cases are not diagnosed during an individual's lifetime [6]. Therefore, the emergence of neurological symptoms in patients with systemic sarcoidosis should raise suspicion of neural involvement associated with sarcoidosis.

Diagnosis of spinal cord sarcoidosis can be challenging, given that a biopsy of the spinal cord is necessary to establish a "definitive" diagnosis of neurosarcoidosis (Table 1) [7]. Spinal cord bi-

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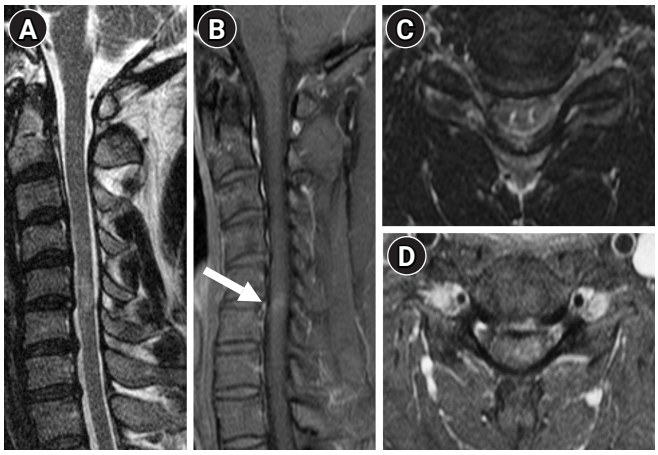

Fig. 2. (A) Sagittal T2-weighted magnetic resonance imaging (MRI) of the cervical spine showing a short segment of high signal intensity at the C5–C6 level. (B) T1-weighted gadolinium-enhanced image showing subtle enhancement between C5 and C6 segments (arrow). (C) Axial T2-weighted MRI showing bilaterally asymmetric linear foci of high T2-weighted signals. (D) Subtle enhancement can be seen on the left side of the spinal cord.

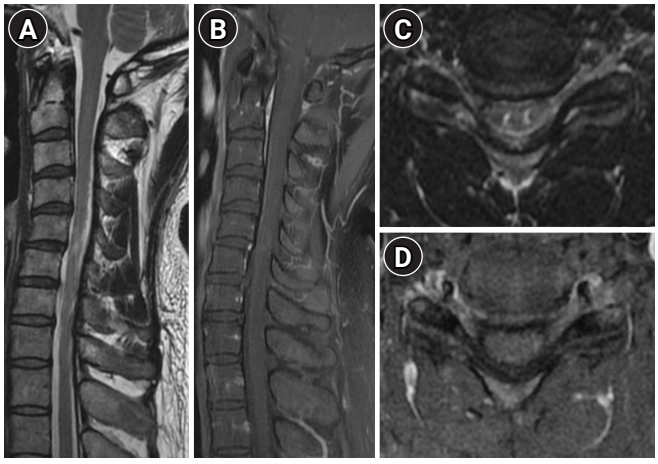

Fig. 3. Follow-up cervical spinal magnetic resonance imaging 2 months after intravenous methylprednisolone treatment. (A, C) T2-weighted images with a persistent high signal intensity. (B, D) T1-weighted gadolinium images showing diminished enhancement.

opsies can lead to increased morbidity and mortality [8]. Furthermore, biopsy samples do not always show abnormalities [8-10]. Our case had myelopathy with an elevated CSF protein level, elevated serum ACE level, positive histology of the hilar lymph node, and exclusion of alternative diagnoses, which led to the diagnosis of "probable" neurosarcoidosis [7]. Concerning differential diagnoses, the absence of brain lesions, oligoclonal bands, AQP4, and MOG antibodies and the enlargement of the hilar lymph node on the follow-up chest CT reduced the possibility of a demyelinating

Table 1. Proposed criteria for diagnosing neurosarcoidosis [7]

Definite	Clinical presentation suggestive of neurosarcoidosis with the exclusion of other possible diagnoses and the presence of positive nervous system histology
Probable	Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, presence of oligoclonal bands, and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (through positive histology, including Kveim test, and/or at least two indirect indicators from a Gallium scan, chest imaging, and serum ACE levels)
Possible	Clinical presentation suggestive of neurosarcoidosis with the exclusion of alternative diagnoses where the above criteria are not met

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CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ACE, angiotensin-converting enzyme.

disorder of the central nervous system, such as multiple sclerosis and neuromyelitis optica.

In spinal cord sarcoidosis, clinical symptoms and MRI findings depend on the anatomic distribution and stage of the illness. There have been several MRI studies of spinal cord sarcoidosis involving lesions in the thoracic and cervical cord [3,11]. Most MRI findings can be relatively nonspecific, mimicking demyelinating disorders, as well as infectious and neoplastic diseases. An MRI analysis of 16 patients with intramedullary spinal sarcoidosis showed leptomeningeal enhancement, fusiform spinal cord enlargement, focal or diffuse intramedullary disease, and spinal cord atrophy depending on the clinical course [11]. Additionally, gadolinium enhancement occurred in the spinal cord even during the chronic phase of the disease course [11], similar to the heterogeneous intramedullary gadolinium enhancement seen in this case 1 year after symptom onset. This intramedullary T2 high signal intensity and faint enhancement without cord swelling may be related to a result of ischemia and disruption of the neural pathways by sarcoidosis in the chronic phase [11].

Our case showed elevated CSF protein without pleocytosis. Lymphocytic pleocytosis (40% to 70%), elevated protein (40% to 73%), positive oligoclonal bands (22% to 55%), and a low CSF glucose (10% to 20%) were reported in the CSF of neurosarcoidosis patients [7,12,13]. Wengert et al. [12] reported that CSF abnormalities in neurosarcoidosis are related with diffuse leptomeningeal enhancement on MRI and disease activity. Therefore, the CSF study may play a crucial role in assessing disease activity as well as a differential diagnosis.

In sarcoidosis, treatment is aimed at remission and symptom relief. Symptoms caused by inflammation are treated with corticosteroids, preferably in combination with immunosuppressants to

prevent relapsing chronic sarcoidosis [14]. In this case, 2 years ago, the patient was lost to follow-up while on steroids. At the time of diagnosis of cervical myelitis, numbness recovered after the steroid pulse, but the patient continued to experience pain. At this point, systemic and periodic monitoring is essential to detect any subsequent inflammation to ensure timely treatment.

In conclusion, a high degree of suspicion of neurosarcoidosis is needed to enable early detection and treatment among patients with systemic sarcoidosis. Early detection and treatment will minimize neurological complications.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

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Journal of Neurocritical Care

Nonconvulsive status epilepticus associated with leptomeningeal carcinomatosis and positive SOX1 antibodies

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CASE REPORT

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Background: Nonconvulsive status epilepticus (NCSE) is a disorder with varying prognoses depending on the underlying etiology. It is increasingly recognized as a cause of altered mental status but is difficult to diagnose without continuous electroencephalogram (EEG) monitoring.
Case Report: A 75-year-old woman visited our emergency department with acute altered mental status. A cerebrospinal fluid study showed meningeal carcinomatosis. The EEG showed NCSE. Brain magnetic resonance imaging showed diffuse meningeal enhancement around the brain stem. There were no other masses except suspected primary lung cancer on chest computed tomography. However, no malignant cells were detected in a bronchial washing. Levels of carbohydrate antigen 19-9 (CA19-9), CA125, and CA 15-3 were elevated. Autoimmune antibodies were all negative except for SOX1. The patient was unresponsive to first intrathecal chemotherapy and expired two days later.
Conclusion: This is a case report of NCSE caused by paraneoplastic autoimmune encephalitis associated with SOX1 antibodies.

Keywords: Nonconvulsive status epilepticus; Meningeal carcinomatosis; SOX1 antibodies

INTRODUCTION

Nonconvulsive status epilepticus (NCSE) is a disorder with varying prognoses depending on the underlying etiology. NCSE is increasingly recognized as a cause of altered mental status or coma and accounts for 25% of all cases of status epilepticus. NCSE is difficult to diagnose without continuous electroencephalogram (EEG) monitoring. NCSE due to paraneoplastic autoimmune encephalitis associated with SOX1 antibodies has been rarely reported.

CASE REPORT

A 75-year-old woman visited our emergency department with acute altered mental status preceded by a headache, nausea, and vomiting for 3 days. Except for a drowsy mental status, there were no focal neurological signs. Her initial vital signs were wblood pressure 220/120 mm Hg, body temperature 36.1°C, heart rate 51 per minute, respiratory rate 20 per minute, and O2 saturation 95%. No abnormalities were noted on brain computed tomography. A cerebrospinal fluid (CSF) analysis revealed elevated open-

ing pressure (210 mm Hg) and mononuclear pleocytosis (60 cells/mm^3) with elevated proteins (183 mg/dL) and decreased glucose (30 mg/dL) with a low CSF-to-serum glucose ratio (Table 1). The EEG showed an evolving pattern of rhythmic delta activity (> 2.5 Hz) with response to intravenous benzodiazepine, a finding compatible with NCSE (Fig. 1). Antiepileptic treatment for NCSE was started with valproic acid 2,000 mg as a loading dose and 1,000 mg twice daily for maintenance. Burst suppression was achieved on EEG using midazolam (0.2 mg/kg/hr) continuous infusion treatment. Brain magnetic resonance imaging showed diffuse meningeal enhancement (Fig. 2). Through further evaluation, a lesion of suspected primary lung cancer was noted on chest computed tomography (Fig. 3), but no masses were noted in the abdomen or pelvis. Bronchoscopy-guided biopsy failed because it was difficult to approach to the lesion's site. Instead, bronchial wash-

Table 1. Cerebrospinal fluid analysis findings

Variable	Value
Intracranial pressure (mmH_2O)	210
Color	Colorless
pH	7.5
SG	1.01
Cell count (WBC) (mm^3)	60
Differential count (polymorphonuclear leukocyte) (%)	-
Differential count (lymphocyte) (%)	43
Differential count (monocyte) (%)	57
Glucose (CSF/serum)	30/158
Protein (mg/dL)	183

SG, specific gravity; WBC, white blood cell; CSF, cerebrospinal fluid.

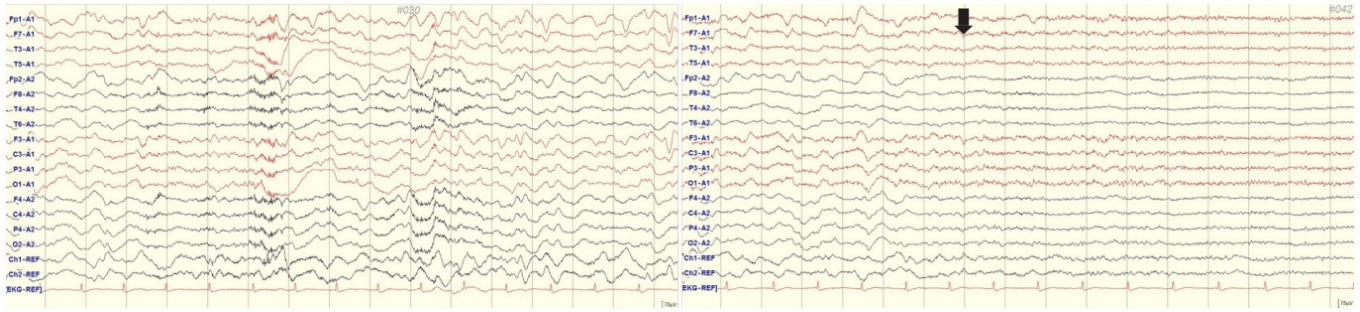

Fig. 1. Initial waking electroencephalography showed semirhythmic delta activity which showed responsiveness (arrow) after 2 mg intravenous lorazepam injection.

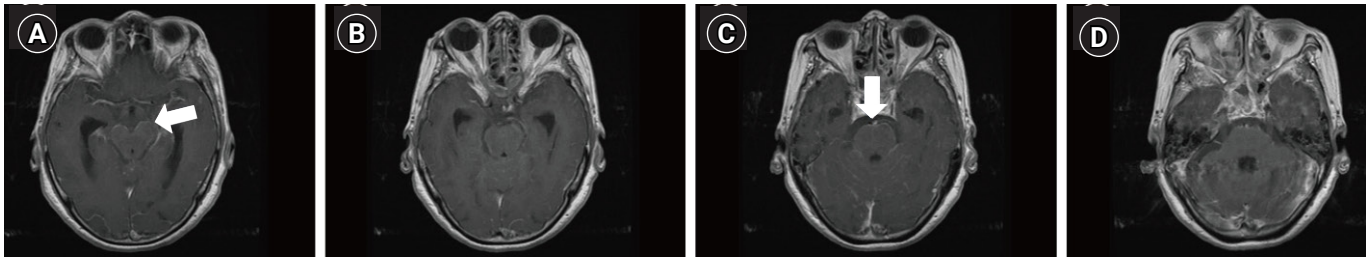

Fig. 2. (A-D) Brain magnetic resonance imaging shows meningeal enhancement around brainstem with focal nodular enhancement (arrows).

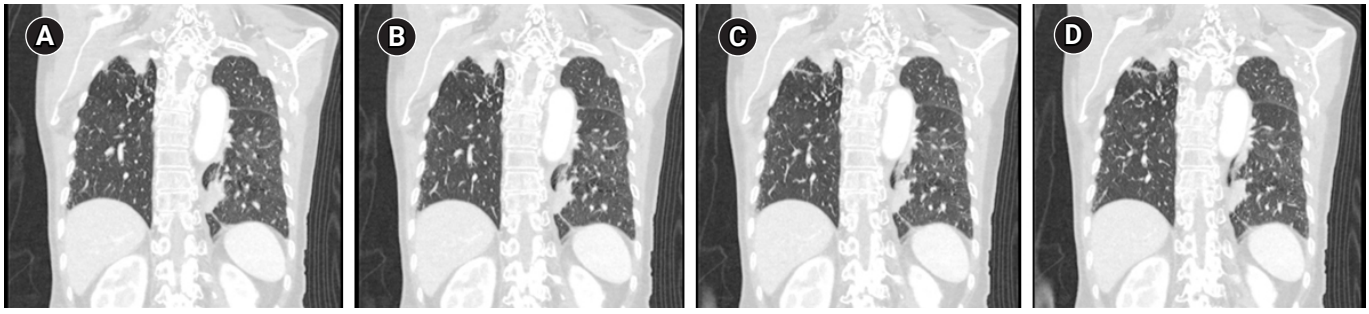

Fig. 3. (A-D) Chest computed tomography showing focal mass like conolidation in left lower lobe posterior basal segment medial aspect.

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ing cytology was done, but no malignant cells were detected. In a tumor marker screening test, elevated levels of carbohydrate antigen 19-9 (CA19-9), CA125, and CA 15-3 were detected (Table 2). CSF cytopathology revealed metastatic adenocarcinoma, which was confirmed as being of lung origin (Fig. 4). Autoimmune synaptic encephalitis antibodies (N-methyl-D-aspartate receptor [NMDAR], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPA1/2], leucine-rich glioma inactivated 1 [LGI1], contactin-associated protein-like 2 [CASPR2], gamma-aminobutyric acid [GABA]-B) and paraneoplastic syndrome antibodies (anti-ANNA-1, antineuronal nuclear antibody-type 1 [anti-Hu], anti-PCA-1, Purkinje cell cytoplasmic anti-body type 1 [anti-Yo], ANNA-2, antineuronal nuclear antibody-type2 [anti-Ri], anti-paraneoplastic antigen MA2 [anti-PNMA2; Ma2/Ta], collapsing response-mediator protein-5 [CV2/CRMP5], antiamphiphysin, antirecoverin, antititin [MGT-30]) were negative; only SOX1 antibodies were detected (Table 2). Despite the use of midazolam continuous infusion treatment and burst suppression being achieved on EEG, the patient was unresponsive to the first intrathecal chemotherapy (methotrexate 15 mg/day, cytarabine 30 mg/day, cortisol 50 mg/day) and expired suddenly 2 days later due to uncontrolled increased intracranial pressure.

Table 2. Paraneoplastic syndrome antibodies, autoimmune synaptic encephalitis antibodies, and serum tumor markers

Variable	Result
Paraneoplastic syndrome antibodies	
Hu	(–)
Yo	(–)
Ri	(–)
Ma2	(–)
CV2/CRMP5	(–)
Amphiphysin	(–)
Recoverin	(–)
SOX1	(+)
Titin	(–)
Autoimmune synaptic encephalitis antibodies	
NMDAR	(–)
AMPA1	(–)
AMPA2	(–)
LGI1	(–)
CASPR2	(–)
GABA-B	(–)
Tumor marker	
AFP (ng/mL)	1.02
CEA (ng/mL)	14.2
CA19-9 (U/mL)	<2.00
CA125 (U/mL)	37.6
CA15-3 (U/mL)	59.8

Hu, ANNA-1, antineuronal nuclear antibody-type 1; Yo, PCA-1, purkinje cell cytoplasmic antibody type 1; Ri, ANNA-2, ,antineuronal nuclear antibody-type 2; Ma2, PNMA2, paraneoplastic antigen MA2; CV2/CRMP5, collapsing response-mediator protein-5; SOX1, AGNA, anti-glial nuclear antibody; NMDAR, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LGI1, leucine-rich glioma inactivated 1; CASPR2, contactin-associated protein-like 2; GABA-B, gamma-aminobutyric acid; AFP, alphafetoprotein; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

This study was approved by the Institutional Review Board of Dong-A University Hospital (IRB No: DAIHIRB-20-089). Informed consent was waived by the board.

DISCUSSION

Leptomeningeal metastasis (LM) from cancer was first described in 1870. The identification of malignant cells on CSF cytology has been the diagnostic gold standard, although its sensitivity is limited. An estimated 10% to 30% of patients with solid tumors develop neuraxis metastases, of which 4% to 15% represent LM

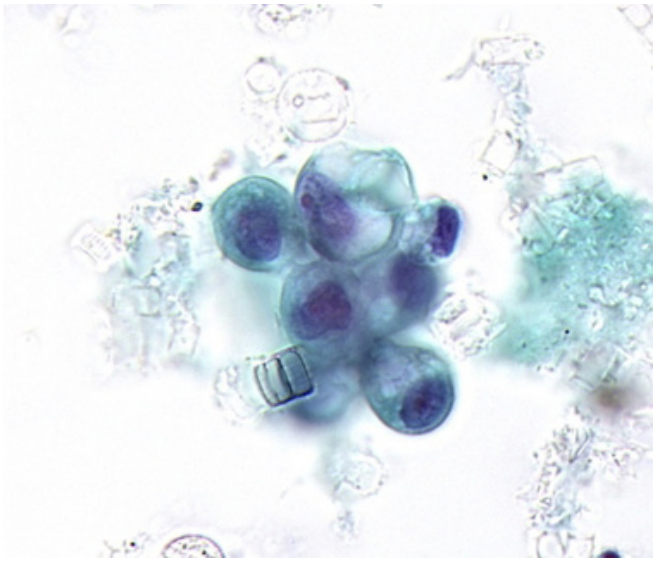

Fig. 4. Cytologic examination of the cerebrospinal fluid shows a few clusters of cells with enlarged eccentric nucleoli, prominent nucleoi and bubbly cytoplasm, suggesting metastatic adenocarcinoma (Papanicolaou stain, ×100).

[1]. Breast tumors, lung tumors, and malignant melanomas are the principal tumors responsible for LM. Adenocarcinoma is the most frequently encountered histological type [2].

The median overall survival of LM patients is 2.4 months (95% confidence interval, 1.9 to 3.1) [3]. The diagnosis and treatment of NCSE usually depend on etiology, EEG findings, and the patient's clinical status. It is not always possible to identify to what extent the electrographic activity contributes to clinical impairment or ongoing neuronal injury.

The underlying causes of NCSE vary and differ according to the patient population being studied. Approximately one-half to two-thirds of affected patients will have a prior history of seizures or epilepsy. NCSE can be the presenting symptom of infectious or autoimmune encephalitis [4-6]. The NCSE in our case could have been caused by paraneoplastic autoimmune encephalitis associated with SOX1 antibodies rather than LM, which may have been difficult to induce NCSE considering its extent and severity.

SOX1 antibodies are rarely detected but have been reported to occur in paraneoplastic neuropathy, Lambert-Eaton syndrome, and unclear forms of neuropathy and ataxia. SOX1 antibodies are often associated with antibodies against voltage-gated calcium channel, Hu, CV2/CRMP5, or amphiphysin. The most common cancer form associated with SOX1 is small cell lung cancer, but other lung cancer forms have also been reported [7,8]. In our case, no autoantibodies other than SOX1 were detected.

In conclusion, this case showed NCSE due to paraneoplastic autoimmune encephalitis associated with SOX1 antibodies rather than LM, although primary lung cancer was not confirmed pathologically. Although the NCSE was controlled by a continuous midazolam infusion, the patient did not respond to the first intrathecal chemotherapy and expired 2 days later.

Conflict of interest

No potential conflict of interest relevant to this article.

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Favorable clinical course after early-intensive immunotherapy for new-onset refractory status epilepticus

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CASE REPORT

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Background: New-onset refractory status epilepticus (NORSE) refers to the newly established concept of a disease characterized by refractory status epilepticus without an identifiable etiology. Recent reports have indicated the importance of immunotherapy for NORSE.
Case Report: A 37-year-old man with no past history of epilepsy was admitted for a presenting complaint of confusion. He was treated with acyclovir and anti-epileptic drug (AED) for presumed herpes encephalitis. However, he developed generalized tonic-clonic seizures on day 6 of admission that worsened despite treatment with multiple AEDs. NORSE was considered to be a probable diagnosis and immunotherapy with methylprednisolone and immunoglobulin was scheduled. However, persistent seizure activity was observed on the electroencephalogram after the completion of initial immunotherapy. Subsequently, rituximab was administered for 4 weeks. He eventually regained consciousness and was able to resume social activity.
Conclusion: Our patient exhibited a favorable outcome with early-intensive immunotherapy and subsequent rituximab treatment for NORSE.

Keywords: New-onset refractory status epilepticus; Immunotherapy; Rituximab

INTRODUCTION

Although there is lack of consensus regarding the definition of refractory status epilepticus (RSE), it can be defined as continuous or repetitive seizures that do not respond to first and second-line antiepileptic drug (AED) therapy [1]. RSE is considered to be a life-threatening emergency with a high mortality rate of at least 15% or even 40%, if it is left untreated [2].

Currently, immunotherapy is thought to be an important newly established concept for treating new-onset refractory status epilepticus (NORSE), which is characterized by RSE, without an identifiable etiology in otherwise healthy individuals [3].

We describe a favorable outcome in a patient with NORSE, who was treated with early-intensive immunotherapy in the form of sequential administration of intravenous methylprednisolone and immunoglobulin, followed by subsequent rituximab adminis-

tration within 2 weeks of initiating immunotherapy.

CASE REPORT

A 37-year-old man with no past history of epilepsy was transferred to our center. He presented with confusion preceded by fever, chills, and headache. Baseline laboratory tests and computed tomography imaging revealed no definite evidence of systemic inflammation/infection. Cerebrospinal fluid (CSF) examination was unremarkable, except for a mild elevation in CSF proteins (60.7 mg/dL), with an opening pressure of 16 cm, no cells (0/μL), and a glucose level of 95 mg/dL (for comparison, the serum glucose level was 150 mg/dL). Red blood cells were not detected on CSF. Staining, culture, antibodies, and polymerase chain reaction tests for the detection of bacteria, fungi, viruses, and mycobacterium tuberculosis in the CSF were negative. CSF cytology for the detection of abnormal malignant cells was also negative. Serum influenza virus A/B antigen, herpes simplex virus, and varicella-zoster virus antibodies, blood culture, and autoimmune antibodies (e.g., antinuclear, antidouble-stranded DNA, antithyroid peroxidase, antithyroglobulin, and antineutrophilic cytoplasmic antibodies) were absent. Brain magnetic resonance imaging (MRI) revealed a diffusion restricted lesion in the right medial temporal lobe with increased gadolinium enhancement (Fig. 1A, red line). Baseline electroencephalogram (EEG) (obtained at admission) revealed slow background activity.

The patient was administered acyclovir 10 mg/kg, every 8 hours, and levetiracetam 500 mg, every 12 hours, following a probable diagnosis of herpes encephalitis. However, episodes of focal seizures with lip smacking and eyeball deviation to the left side increased in frequency, which were accompanied by a newly developed epileptiform discharge on the EEG that required multiple AEDs: valproic acid 600 mg, every 8 hours; phenytoin 200 mg, every 8 hours; levetiracetam 1,000 mg, every 12 hours; and phenobarbital 100 mg, every 8 hours.

On day 6, he developed a generalized tonic-clonic seizure, which lasted for more than 5 minutes, which worsened, and led to a drastic increase in the need for multiple anesthetics and AEDs. A probable diagnosis of NORSE was made at this stage and immunotherapy was scheduled (Fig. 1B). Intravenous methylprednisolone and immunoglobulin were sequentially administered, which alleviated the seizure activity, thereby reducing the need for anesthetics. However, persistent seizure activity was noted on the EEG 3 days after the completion of intravenous methylprednisolone and immunoglobulin treatment (Fig. 1C). Rituximab was administered, and the seizure activity resolved completely on EEG 4 days after the first infusion, prompting discontinuation of anesthetic infusion. He regained consciousness and could follow instructions 4 days after the discontinuation of anesthetics.

At this stage, the test results for the detection of autoimmune encephalitis antibodies (e.g., NMDAR, AMPA1, AMPA2, LGI1, CASPR2, and GABA-B) and paraneoplastic antibodies (e.g., Hu, Yo, Ri, Ma2, CV2/CRMP5, amphiphysin, recoverin, SOX1, and titin) in serum and CSF were negative. Follow-up brain MRI revealed an improvement in what was probably herpes encephalitis or limbic encephalitis compared to the earlier lesion on the baseline image (Fig. 1A, blue line). He completed a 4-week schedule of rituximab treatment and successfully returned to social activity after 2 months of hospitalization.

DISCUSSION

We described the favorable outcome of early-intensive immunotherapy for a 37-year-old man with RSE. Treatment was initiated immediately on suspicion of NORSE with a 5-day course of intravenous methylprednisolone and immunoglobulin, followed by the first infusion of rituximab within 2 weeks of immunotherapy. This drug regimen kept the patient seizure-free for a period of 1-month after hospitalization.

Although NORSE was initially defined as cryptogenic RSE, recent studies have suggested that autoimmune encephalitis may be a common etiology [4,5]. Therefore, immunotherapy has been recommended for NORSE, even in the absence of the detection of specific antibodies, after excluding infections from the differential diagnosis [6]. Furthermore, several recent systematic reviews have reported that early treatment is associated with improved outcomes in autoimmune encephalitis [5]. Therefore, earlier empirical immunotherapies such as steroid-pulse therapy, immunoglobulins, or plasmapheresis are often tried sequentially, depending on the clinical response.

Interestingly, although our patient exhibited improvement in the clinical course during initial immunotherapy (e.g., sequential treatment with intravenous methylprednisolone and immunoglobulin), which contributed to a dramatic decrease in the need for anesthetics, total discontinuation of anesthetics was possible with the subsequent administration of rituximab (for the management of RSE). Rituximab is a monoclonal antibody against CD20-positive B cells. It leads to B-cell depletion and therefore, suppression of autoimmune neurological disorders including autoimmune encephalitis, especially in patients that respond poorly or are unresponsive to empirical immunotherapy [7,8]. Rituximab does not affect the innate immune system, immunoglobulin, or T-cell activity, and is relatively safe in terms of infectious adverse events [9]. Therefore, rituximab can be considered to be an

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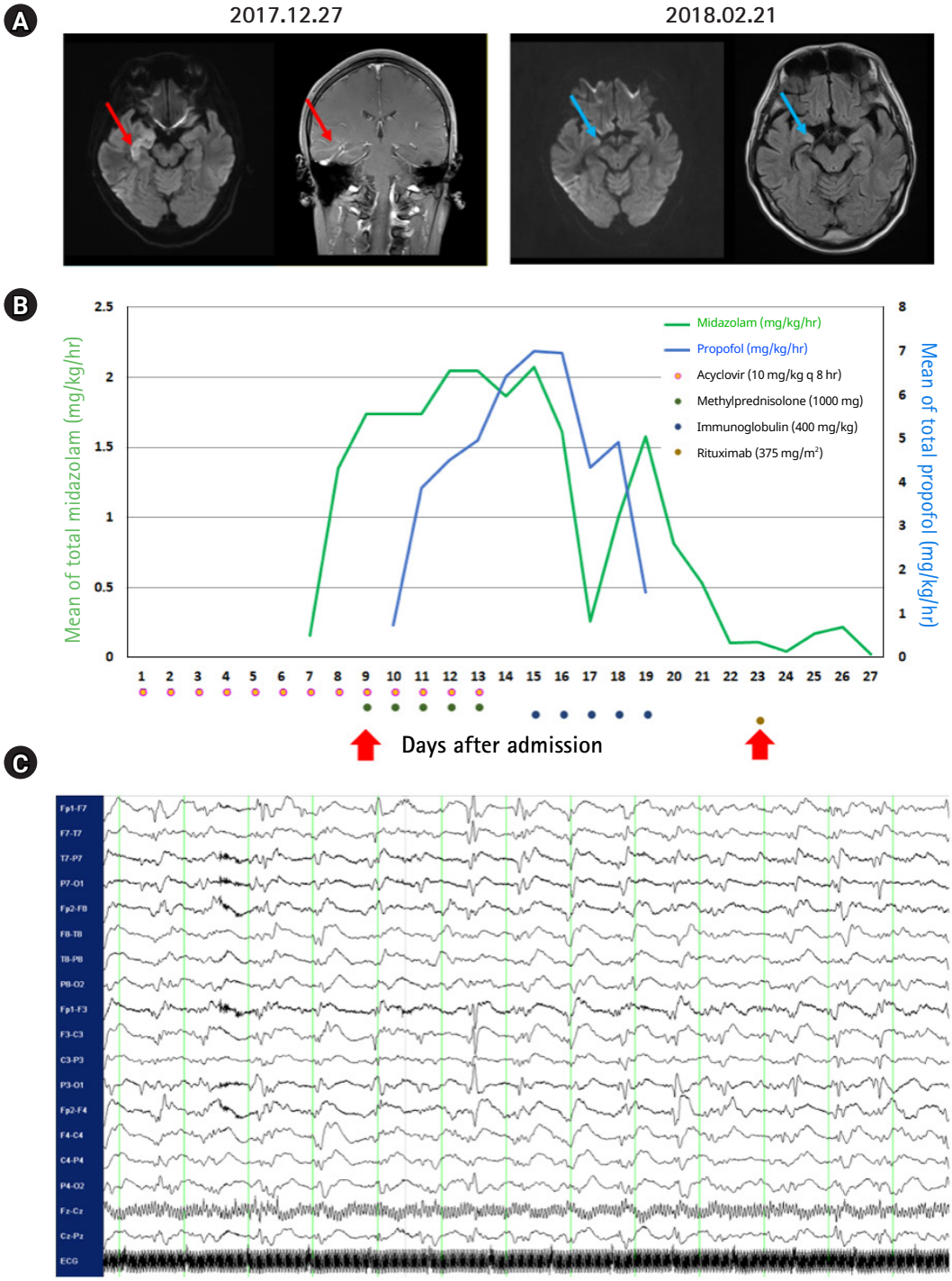

Fig. 1. (A) Follow-up brain magnetic resonance imaging showing disappearance of the diffusion-restricted lesion with remnant fluid-attenuated inversion recovery changes in the right medial temporal lobe (blue lines), which previously showed an increased diffusion restriction and gadolinium enhancement (red lines). (B) Continuous infusion of multiple anesthetics including midazolam and propofol was increased sequentially for the management of refractory status epilepticus, but were tapered during sequential immunotherapy (methylprednisolone 1,000 mg for 5 days and intravenous immunoglobulin [IVIG] 0.4 g/kg for 5 days), followed by the first infusion of rituximab 375 mg/m^2 as booster immunotherapy (red arrow), after the maximum possible administration of multiple antiepileptic drugs including levetiracetam 1,500 mg, every 12 hours; valproic acid 800 mg, every 6 hours; phenytoin 300 mg, every 8 hours; phenobarbital 200 mg, every 8 hours; and topiramate 200 mg, every 12 hours. (C) Rituximab was started on day 23 of hospitalization, based on the findings of bilateral periodic lateralized epileptiform discharge on continuous electroencephalography monitoring even 3 days after the completion of initial immunotherapy, with a regimen of once a week for 4 weeks.

early immune booster for patients with NORSE, who are resistant to empirical immunotherapy, with or without proven autoantibodies. Prolonged seizure activity can aggravate epileptogenicity, which in turn leads to an increased risk of super-RSE by a kindling mechanism [10].

ARTICLE INFORMATION

Conflict of interest
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Instructions to Authors

Journal of Neurocritical Care

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  1. Kang J, Kang CH, Roh J, Yeom JA, Shim DH, Kim YS, et al. Feasibility, safety, and follow-up angiographic results of endovascular treatment for non-selected ruptured intracranial aneurysms under local anesthesia with conscious sedation. J Neurocrit Care 2018;11:93-101.
  2. van den Bent MJ, Keime-Guibert F, Brandes AA, Taphoorn MJ, Eskens FA, Delattre JY. Temozolomide chemotherapy in recurrent oligodendroglioma [abstract]. Neurology 2000;54(suppl 3):12.
  3. Di Luca DG, Mohney NJ, Kottapally M. Paroxysmal sympathetic hyperactivity with dystonia following non-traumatic bilateral thalamic and cerebellar hemorrhage. Neurocrit Care 2019 Feb 6 [Epub]. https://doi.org/10.1007/s12028-019-00677-9.

  - Book & book chapter

  4. Layon A. Textbook of neurointensive care. 1st ed. Amsterdam: Elsevier; 2003. p. 10-7.
  5. Rincon F, Mayer SA. Intracerebral hemorrhage. In: Lee K, editor. NeuroICU book. 2nd ed. New York, NY: McGraw-Hill; 2018. p. 36-51.

  - Online source

  6. Weinhouse GL, Young GB. Hypoxic-ischemic brain injury in adults: evaluation and prognosis [Internet]. Waltham, MA: UpToDate; c2019 [cited 2019 Feb 10]. Available from: https://www.uptodate.com/contents/hypoxic-ischemic-brain-injury-in-adults-evaluation-and-prognosis.

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