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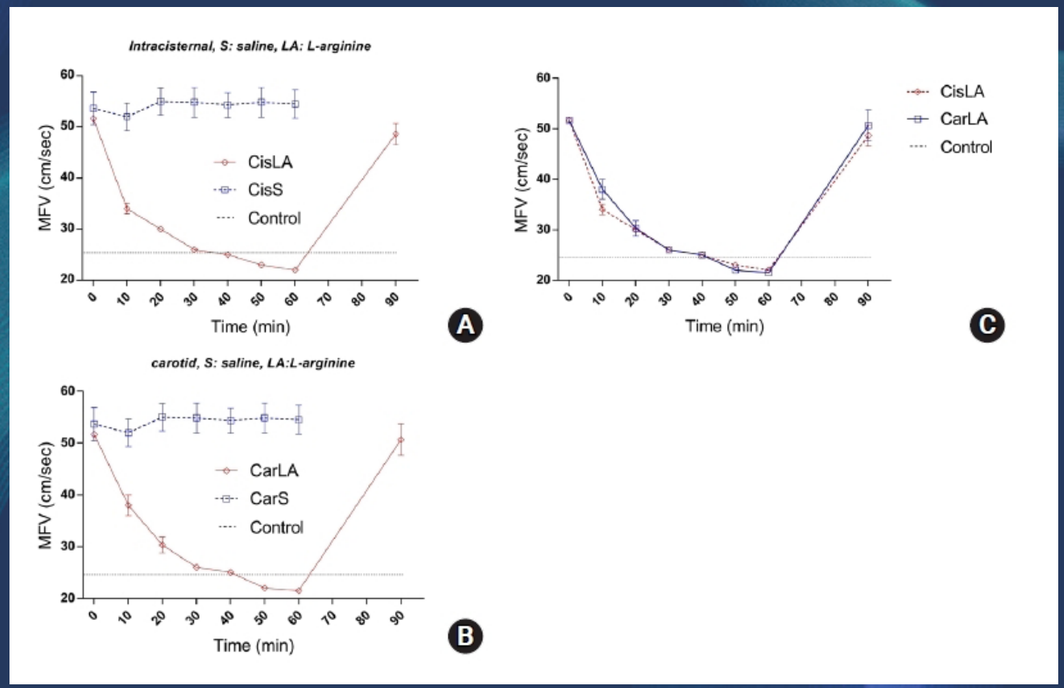

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Aims and Scope

Journal of Neurointensive Care (J Neurointensive Care, JNIC) is the official journal of the Korean Neurointensive Care Society and is published biannually (the last day of April and October). It is a peer reviewed, open access journal aimed at publishing all aspects of neurointensive care medicine, such as stroke, brain and spine trauma, perioperative neurosurgical intensive care, neuro-pediatric severe anormaly, CNS infection, seizure, myelitis and etc. It is intended for all neurointensive care providers as neurosurgeons, neurologists, anesthesiologists, emergency physicians, and critical care nurses treating patients with urgent neurologic disorders.

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Management of Chronic Subdural Hematoma a Challenge in Neurosurgical Practice

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Chronic subdural hematoma (CSDH) is a common neurosurgical disease encountered by neurologists, neurosurgeons, intensive care specialists, and emergency physicians in the emergency department. Although much has been published on CSDH, it remains a topic of active research, also a significant challenge in specific scenarios. The spectrum of clinical presentation varies from asymptomatic radiological entity to significant sensory-motor deterioration resulting in a comatose state. The majority of these cases have an underlying history of trivial trauma in one or the other form. More often, elderly individuals present with CSDH. Management of CSDH in elderly individuals presents specific challenges due to pre-existing comorbidities and medications which alter the pathophysiology. There exists a significant diversity in the treatment modality of CSDH amongst neurosurgeons. The treatment modality includes medical management as well as various forms of surgical manoeuvres intended to evacuate the hematoma and hence alleviate the mass effect over the surrounding brain matter. The treatment modality needs to be individualized for every case. The rationale selection of cases for medical and surgical intervention with robust follow-up results in a better prognostication of these cases.

Keywords: Chronic; Subdural hematoma; Traumatic brain injury; Subdural hygroma; Hemorrhage; Inflammation.

INTRODUCTION

The Chronic Subdural Hematoma (CSDH) is an encapsulated crescentic collection of fluid, blood, and blood degradation products layered between the dura and arachnoid covering the brain surface which is localized between the dural border cell layer oc-

curring 3 weeks or 21 days after a mild to moderate traumatic brain injury episode[1,2].

In general, intensive care unit (ICU) management, it is considered that the general condition of the patient is low, i.e., glasgow coma scale (GCS) ≤ 12. Briefly, management involves assessment for neurological deficits. Assessment of blood investigations like complete blood count, electrolytes, liver function test, and coagulation studies is mandatory if the GCS ≤ 8 endotracheal intubation is warranted[3]. Reversal of Coagulopathy, if there is one. If the patient has active cerebral herniation temporary use of hyperosmotic or hypertonic agents before surgery will be beneficial to reduce the ICP [Intra cerebral pressure]. Antiepileptic medications are started keeping in mind that a new onset seizure can increase morbidity and mortality of the patient[4]. The routine use of corticosteroids is generally not recommended as there is no solid evidence.

EPIDEMIOLOGY

The incidence of CSDH is not well established, Yang & Huang indicate in their study that its incidence has been increasing in recent years[5]. According to a 2017 study report, CSDH incidence was estimated between 3.4 to 58 persons per 100,000 person-years (considering that the value might change depending on the population age), the median age of 63 years old the average for suffering from CSDH but the population aged the median age from suffering will too (follow accordingly)[2]. The prevalence and relation between males and females are 3:1[2]. In the elderly population, the CSDH has been referred to as a sentinel event related to a concomitant systemic pathology and 1-year mortality[2,6].

AETIOLOGY

The specific formation of CSDH is not well-established, according to some literature, CSDH might be caused by the chronic usage of anticoagulant and antiplatelet combined especially in the eldest population, and by inflammatory responses, a pressure increment between the hematoma and blood vessels, chronic alcohol consumption due to the associated brain volume reduction), and as previously mentioned, head trauma antecedent [2,6]. Also, according to some recent studies, acute SDH (aSDH) leads to multiple physiologic sequelae (angiogenesis, vascular permeability factor release, and growth factor release) that will develop the CSDH[7]. CSDH might be developed after an acute subdural hematoma (due to the incomplete blood product resorption) or a subdural hygroma and the inflammatory response that leads to neovascularization due to the angiogenic factors of the inflammation process. In both cases, a substantial inflammatory response seeps into the subdural space. This inflammation includes angiogenic factors that lead to the formation of new blood vessels. Although these fragile capillaries are forming, they experience microbleeds, which can lead to SDH. Enclosed chronic subdural haemorrhage cavity prevents clearance of fibrinolytic enzymes inflammatory cytokines and angiogenic factors. This initiates a cascade of inflammation, fibrinolysis, angiogenesis, and rebleeding (Fig. 1)[2].

Theories for chronic subdural haemorrhage

Dural border cell theory

First proposed by Inglis in 1947[8]. These are layers of flattened elongated cells connected by desmosomes with extracellular matrix and extracellular fibres. Chronic subdural haemorrhage is formed between dural border cells which is confirmed by electron microscopic studies[9]. The new membrane formation is due to inflammation and pro collagens type one and type 3 collagens. Inflammation causes pro-angiogenic cells which produce new leaky blood vessels which cause microhemorrhages and fluid exudates into the newly formed sub-dural membrane (Fig. 2).

Colloid osmotic theory

Chronic subdural haemorrhage is more hyperosmolar than cerebrospinal fluid [due to increased protein content by liquefaction of hematoma][10]. However, this theory was disproved by Weir, who demonstrated that the osmolality of the hematoma fluid was identical to that of blood and cerebrospinal fluid[11]. This concept was further substantiated by Taguchi et al. in their study of the resorption of CSDH fluid after surgery. In that study, the authors found that the attenuation rates of radioactivity (due to 111-In-DTPA in-

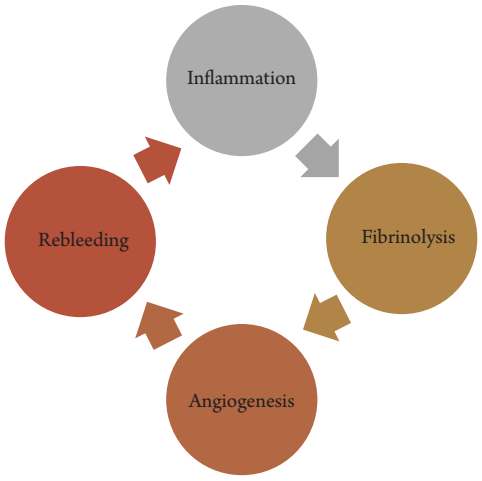


Fig. 1. Schematic diagram representing the events leading to the formation of Chronic subdural hematoma

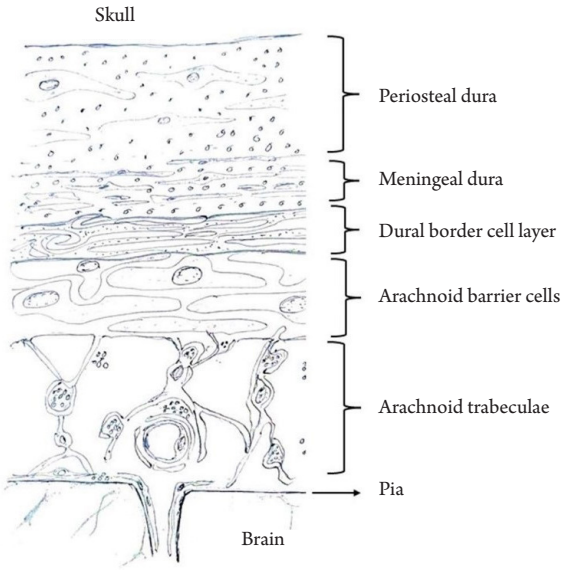


Fig. 2. Illustrative diagram showing the various layers of the skull and meningeal coverings of the brain.

stallation in subdural space) were faster after the surgery[12]. As the osmotic pressure is the same for the CSDH hematoma fluid, blood, and cerebrospinal fluid, the osmotic pressure difference alone cannot explain the faster attenuation rate after surgery. The hematoma gets absorbed in the sinusoidal channel layer and therefore the colloid osmotic pressure explains the phenomena better.

Traumatic brain injury theory

In the place where Bridging veins travel from the cortex into the subarachnoid space, it is thicker. Just before its entrance to the Dural border cells and inside the Dural border cells these veins become very thin. And inside the dural border cell layer, these veins have a single layer of endothelium and a single layer of collagen, and no surrounding arachnoid trabeculae. This is the place where the tearing of veins happens[13].

Inflammation theory

First reported by Virchow in 1857 as "pachymeningitis hemorrhagic interna" a- cytokines induced by inflammation (interleukin-1,6,8,10)[14] b- chemokines

The membrane of CSDH is composed of an outer and inner layer. The outer layer of the membrane which is toward the inner side of the dura is composed of vascularized granulation tissue[15]. This layer can be 1 cm thick and is found to be composed of inflammatory tissue consisting of fibroblasts, collagen, and endothelial cells with fenestration and gap junctions[16].In contrast to this, the inner membrane is relatively avascular and is more like the arachnoid membrane[17]. Hong et al. found that inflammation plays a role in the propagation of CSDH based on their findings of increased interleukin-6, vascular endothelial growth factor, and basic fibroblast growth factor in the recurrence of CSDH[18].

Risk factors

Elderly, male sex, epilepsy, decreased intracranial pressure states, hemodialysis, chronic alcohol consumption (or abuse), therapeutical interventions (e.g. ventricular shunting, lumbar puncture, spinal anaesthesia, spinal surgery with dural tear and CSF leak), falls and trivial head trauma (especially in the eldest population), and anticoagulant and antiplatelet usage[7]. Diseases related to brain atrophy- Alzheimer's, systemic diseases like liver and kidney diseases.

Clinical presentation

The CSDH can present stroke or progressive dementia signs that can confuse the diagnosis[19], due to this unspecific clinical presentation is known as "the great imitator", as well, its symptoms can onset many weeks before its presentation[2]. Patients might present seizures, memory disturbances, headaches, speech and gait disturbances, cognitive decline, confusion, hemiparesis, falls and altered mental status that can range from acute confusion deteriorating to even coma[1].

DIAGNOSTIC IMAGING MODALITIES

Computed tomography scan

The computed Tomography Scan (CT-Scan) is the main imaging modality for CSDH diagnosis; however, Magnetic Resonance Imaging (MRI) is also useful but not preferred[1]. On the CT Scan, the CSDH appears as a crescent-shaped hypodense collection distributed by the convexity of the brain (Table 1)[2]. The diagnosis of chronic subdural hematoma is made through neuroimaging, the study of choice is non-contrast computed tomography of the skull[1], given its high availability and non-invasive nature. The characteristic of the image obtained in this pathology is a crescent formation due to the collection of blood products in the subdural space, between the arachnoid and the dura mater; Radiodensity measured in Hounsfield units depends on the time of evolution of the lesion due to hemosiderin degradation. It is known that the density decreases by approximately 1.5 units per day[20], therefore, in CSH, it is expected to find a hypodense lesion, without ruling out being able to find isodense or mixed lesions (acute-on-chronic); Through this type of image, it is possible to assess the size, thickness, presence of subdural clots, their extension through the sutures (unlike epidural), if it generates a mass effect deviating the

midline[21], the presence of locations and/or membranes within the hematoma[22].

CT classification of chronic subdural haemorrhage

1. *Homogeneous*: Collections appear homogeneously isodense, hypodense, or hyperdense. Here the Risk of enlargement of hematoma and recurrence is 10 to 15% (Fig. 3)[23,24]

2. *Laminar* [mixed]- A thin high-density inner membrane and hypo or iso-dense collections lateral to that indicates the risk of enlargement and recurrence as same as homogeneous type[23,24].

3. *Layered* [separated or gradation]- 2 different density components were noted. A low-density component anteriorly and a high-density component posteriorly (Fig. 4) [23,24].

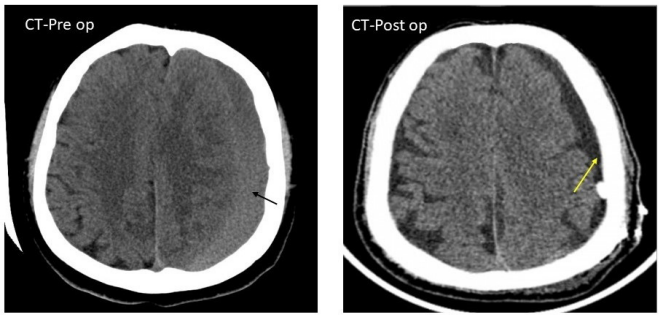


Fig. 3. Non-contrast pre and post-op CT scan head of a 55/male patient with homogenous, iso-dense chronic sural collection significant mass effect (black arrow). Note the reduction of chronic subdural hematoma collection in the post-op scan (yellow arrow). This patient underwent a single parietal burr hole with closed system drainage.

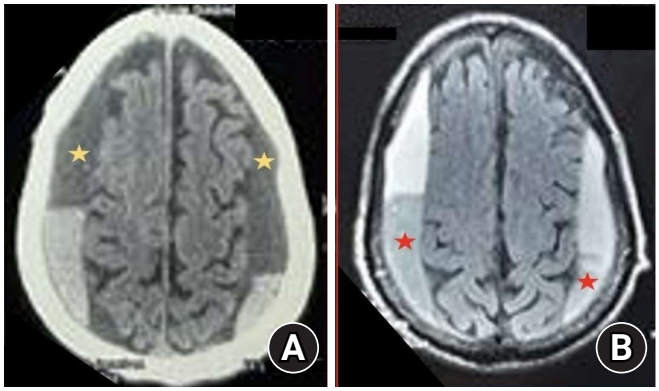


Fig. 4. Non-contrast CT scan head showing a bilateral collection of the layered type of subdural hematoma. (A) The yellow stars suggest chronic subdural hematoma. (B) The red stars in the FLAIR sequence of the MRI brain suggest the subacute nature of subdural hematoma which indicates a layered type of chronic subdural hematoma.

4. *Trabecular* [multilocular]- mixed density with high-density septations. Low risk of growth and recurrence (Fig. 5) [23,24]. Other less common forms of presentation of chronic subdural hematoma are bilateral ones, which generate a challenge to make the diagnosis by this means of imaging because although they can generate the effect of mass with a deviation of the midline when exerting opposing forces can neutralize, so this finding would not be as noticeable, a decrease in bilateral ventricular spaces can be found[21]. Likewise, the calcified or ossified subdural hematoma can be seen as an intracerebral subdural mass, composed of a hyperdense membrane that surrounds a hypodense centre in its internal and external parts[25], also known as "armoured brain", described as graded hematomas or bilateral hygromas[26], hematomas in the posterior fossa are less frequent, however, they can be distinguished in images of the cervical spine[20], Chronic subdural hematomas can present with associated infection, which can be seen in the tomographic image as regions of hyperintensity associated with the characteristic diagnostic isodensity[27].

MAGNETIC RESONANCE IMAGING

The use of nuclear magnetic resonance has increased over time due to its increased availability. Its use in this pathology is based on the study of possible differential pathologies. since for the diagnosis of chronic subdural hematoma the determination of age and diagnostic signs, it is more complex, and with less performance than tomography[20], especially by the variability of the progression of oxidation of blood products. In this type of image, it is expected to find hyperintensity in T1 and hypointensity in T2, due to the concentration of proteins, an aspect that allows differentiation with cerebrospinal fluid, hyperintensity in fluid attenuated inversion recovery, diffusion weighted imaging restriction is absent in most he-

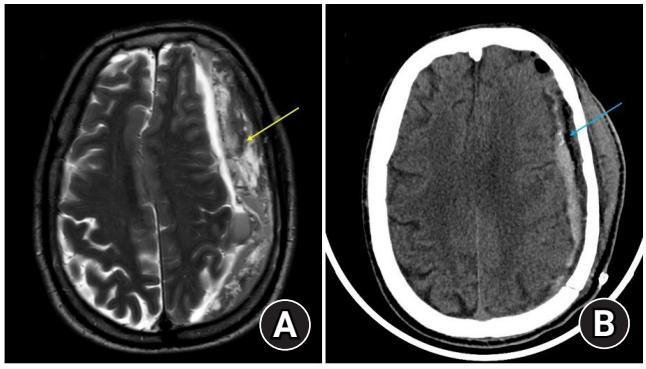


Fig. 5. Shows the MR I(A) and CT scan (B) head of a 70/ male who underwent craniotomy for the trabecular (multiloculated) type of chronic subdural hematoma collection with significant mass effect.

matomas, it can be found in infection or recent bleeding[28]. Likewise, in the presence of lesions of mixed densities, due to the risk of recurrence, the performance of NMR and the water diffusion variety has been evaluated, versus conventional tomography, regardless of availability, resonance has better performance than tomography for the detection of infarcts in recent stages, and prediction of treatment failure[29]. In the postoperative period, although the study of choice is still tomography, MRI is useful and should be considered initially in cases of suspected infarction or associated infection as possible complications depending on the clinical scenario[20]. As well, according to some studies, it is important to recall that the CT-Scan is a cost-effective method and preferred in daily clinical practice and can identify the size, thickness, midline shift, or even subdural clots, and the MRI can determine the internal anatomy and size of the CSDH[7].

Predictors of recurrence

The patients undergoing surgery have been studied with tomography, and different studies propose postoperative volume as the greatest predictor of recurrence, beyond clinical or other imaging predictors. the greatest predictor supported by the literature is volume. it is proposed by 40/40 rule, which is when the volume is less than 40 ml or a volume less than 40% of the initial volume of cSDH, there is decreased risk of recurrence[30], other studies propose a volume greater than 20 ml preoperatively as a risk factor for recurrence[31], associated with or without midline deviation, but it is believed that the increase in size may be due to decreased intracranial pressure due to atrophy in elderly patients[27]. Other predictors studied are the characteristics of the hematoma, according to the Sakaguchi classification, a complex structure or membrane formation has been described as a possible predictor of recurrence[27], hematoma density, and a direct relationship has been found between hyperintensity and mixed patterns with greater recurrence[27].

Differential diagnosis

Given the characteristics of this pathology, possible differentials are hygromas, defined as a collection of cerebrospinal fluid in the subdural space due to traumatic injury to the arachnoid or non-traumatic causes such as hypotension, dehydration, and atrophy, which cannot be easily distinguished from subdural hematomas. Since they are found as hypodense lesions in the subdural space, for which it is necessary to demonstrate the presence of blood products through images such as MRI[20]. Likewise, other differentials may be external hydrocephalus or the early postoperative period, lesions with similar characteristics but mostly isodense[21], from subarachnoid hematomas, it differs from the involvement of the subarachnoid spaces in cisterns and grooves[20]. With meningiomas and metastasis of prostate cancer, their location in the subdural space and the characteristic hypodensity make it difficult to differentiate with chronic subdural hematoma, so in these cases, it is considered whether there is diagnostic suspicion to carry out a contrast study to make the differentiation[32].

Management

As suggested by Ragland and Lee[2], the initial assessment must evaluate de ABC (airway, breathing, and circulation), the life-threatening hazards, the Glasgow Coma Scale (GCS) Score to identify the need for tracheal intubation, as well a clinical history of trauma, falls, antiplatelet or anticoagulant therapy usage should be clarified. If needed, laboratory studies should include the blood-cell count and coagulation test, electrolytes values, and liver function test.

In patients with minor symptoms (cSDH thickness < 10mm with no or mild mass effect) conservative trial is considered. Asymptomatic small cSDH may undergo spontaneous resolution. Several pharmacological therapies[33] have been tried as a part of the treatment regime as mentioned in Table 2. Symptomatic cSDH mostly land up in surgery, they very rarely undergo spontaneous resolution[2]. These patients need close clinical and radiological follow-up with prolonged discontinuation from anticoagulants and antiplatelets.

Surgical treatment is divided into preoperative, operative, and postoperative management.

Surgical treatment is recommended for symptomatic patients,

Table 1. Summarizes the advantages of two most commonly used pre op imaging

CT	MRI
•Most preferred for pre op and post op follow up	•More accurate delineating the extent and visualizing the Intra hematomal membranes
•Easily available and done quickly	•CSDH appears hyperintense in FLAIR (differentiates it from CSF) and has DWI restrictions
•Can appreciate size, thickness, consistency, and membranes (not well defined as in MRI)	•Unilateral isodense or rarely bilateral isodense CSDH are better viualized here

CT: Computed tomography, MRI: Magnetic resonance imaging, CSDH: Chronic subdural hematoma, FLAIR: fluid attenuated inversion recovery, DWI; diffusion weighted imaging.

Table 2. Pharmacological Treatment[7]

Anticoagulant or Antiplatelet reversal therapy	Cessation of the therapeutic agents is the first step.
	Prevent the hematoma expansion by giving reversal for anticoagulants thereby reduce operative risks when emergency neurosurgery is needed.
	Use of prothrombin complex concentrate, fresh frozen plasma, and Vitamin K is recommended for vitamin K antagonists.
	For newer oral anticoagulants [factor Xa inhibitors and direct thrombin inhibitors (Dabigatron)] there is no clear evidence for reversal of its effects. If there is no life-threatening condition or risk of hematoma expansion or need for urgent surgery then buying some time is the best form of reversal.
	For Dabigatran, FDA approved the usage of idarucizumab for its reversal.
	Antiplatelet effects last from 7 to 10 days so it is needed to wait for the replacement of the new and functional platelets but, when emergency surgery is needed- a platelet transfusion might be performed.
Intravenous therapy	It is used to generate an osmotic gradient between the plasma and the brain by decreasing the water in the brain to decrease intracranial pressure. Hypertonic Saline Solution is recommended as it has an effect that helps in the modulation of the inflammatory response in the brain by reducing its swelling and edema thus avoiding states of intracranial hypertension and its related complications[37].
Corticosteroids	Its usage has been related to a decreased rate of recurrence of the hematoma after surgical intervention. Generally not recommended due to lack of evidences, but there are ongoing trials Dex-CSDH, DECSA, and SUCRE[33] can provide answers on its usage.
Anti-seizure therapy	recommended for high risk cases (eg; alcohol abuse). Its routine use in all cases is still under debate[33]

Dex-CSDH: dexamethasone for Chronic subdural hematoma, DECSA: Ddexamethasone therapy versus surgery for chronic subdural hematoma, SUCRE: steroids in chronic subdural hematoma.

Table 3. Surgical indications[29]

Maximum thickness greater or equal to 1cm
Maximum thickness greater or equal to 0.5 cm of midline shift
Glasgow coma scale less or equal to 8 points with 2 points deterioration from the initial injury to the hospital presentation, herniation signs, or signs of elevated intracranial pressure.

Table 4. Summary of surgical treatment

Twist drill craniostomy	It is done in bed side under local anaesthesia, but carries high recurrence rate.
Burr hole craniostomy	This is the most commonly done treatment. Subdural collections are cleared with one frontal and parietal burr hole. Sometimes one parietal burr hole will suffice if the contents are homogenous and thin.
Craniotomy	It is done when there is significant acute component, recurrence and membranes.

even more, in those patients with neurological symptoms using burr-hole drainage (Table 3)[5]. It is usually recommended because, for some authors, as said by Vacca and Argento in their manuscript, its existence implies that the physiologic mechanisms are insufficient or unavailable to reabsorb the hematoma[19]. Even though, twist drill craniotomy and open craniotomy are also suggested for CSDH treatment[19]. Recent literature establishes that the usage of a drain after the CSDH drainage is associated with reduced recurrence and less mortality at a 6-month follow-up[7]. The CSDH is considered a reversible cause of dementia, drainage is related to independence of daily life activities and psychiatric function improvement, as well, early surgical interventions are most likely to be beneficial in the patient's prognosis[7].

The membranes of the CSDH removal are still controversial due to the risk of damage to the underlying arachnoid surface and the capillaries, still, when these are calcified or thick, their removal might allow the re-expansion of the brain after the hematoma drainage[7].

Three primary surgical techniques
1. Twist drill craniostomy
2. Burr hole craniostomy
3. Craniotomy

Burr hole craniotomy

Popularized by Mark Walder in 1981. It is the most common technique performed so far. Two burr holes are placed one in the frontal and the other in the parietal region. The distance between the 2 boreholes should be at least 7 centimetres. One burr hole can be considered if the collection is more localized.

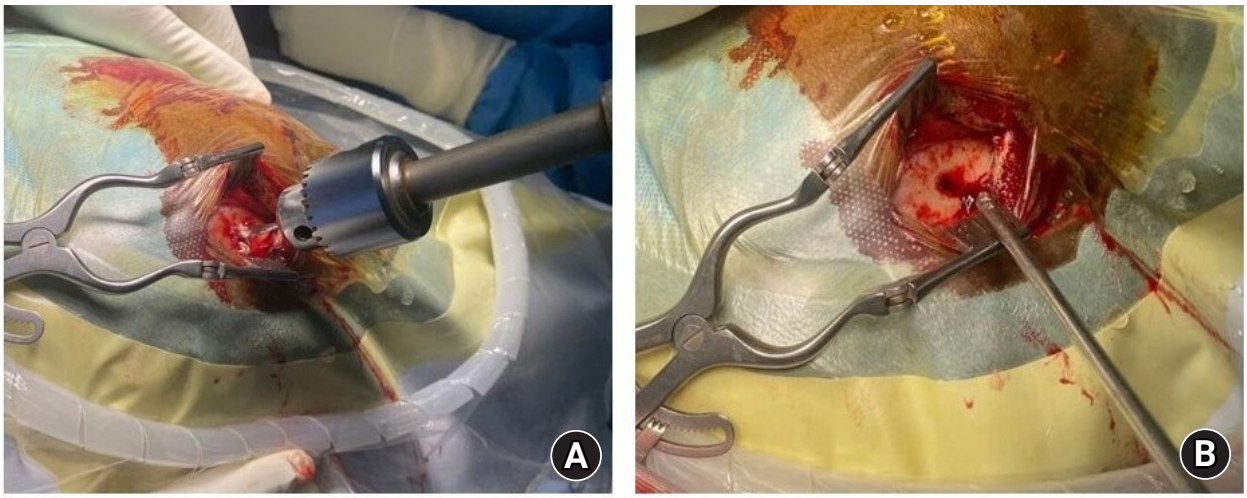
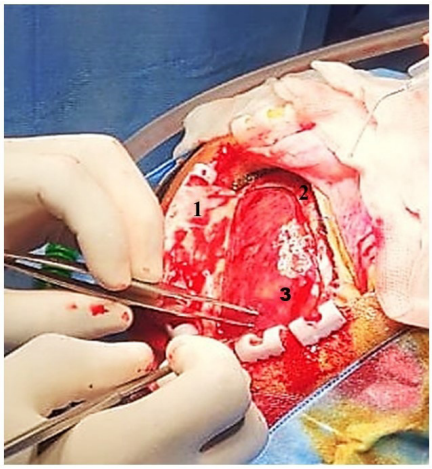


Fig. 6. (A) shows twist drill craniostomy procedure. (B) shows efflux of chronic subdural collections.

Twist drill craniostomy

Used in hypodense collections with no membranes. Done under local anaesthesia at bedside or ICU. Yagnik et al. presented the results of a systematic review and meta-analysis of 16 articles comparing twist drill craniostomy and Burr hole drainage and found that complications, cure, recovery, and mortality rates were similar in the two groups[34]. Though there was an increased risk of recurrence of CSDH in twist drill craniostomy results with closed suction drainage in twist drill craniostomy were similar to Burr hole drainage (Fig. 6).

Subdural evacuating port system (SEPS™) is a unique, patented technology that requires a relatively smaller size burr hole craniostomy (5 mm). SEPS™ is placed under local anaesthesia, providing a closed system in the extradural space without the need for irrigation or aspiration. It is suitable not only for the treatment of chronic and subacute subdural hematomas but also for subdural hygromas.



1. Elevated dural flap
2. Cut edge of the dura
3. Thick outer membrane of CSDH cavity

Fig. 7. Shows the craniotomy procedure done for a chronic subdural hematoma. The thick outer membrane is demonstrated.
CSDH: chronic subdural hematoma.

Craniotomy/ mini craniotomy

A craniotomy of the size of 6 centimetres or more. Reserved for patients with a significant acute component, multiple membranes, and recurrent chronic subdural haemorrhage. Here dura and outer membrane of the chronic subdural cavity are open and irrigated generously with saline. (mini craniotomy is less than 6cm) (Fig. 7) [35].

In general, performing craniotomy has less recurrence rate but high morbidity. Performing twist drill craniostomy has a high recurrence rate but less morbidity. Performing borehole craniotomy gives a balance between efficacy and risk. One surgical technique may not be appropriate for all CSDHs. The selection of an ideal treatment strategy for an individual patient should be targeted based on individual factors[36].

Postoperative seizure prophylaxis is still discussed, however, it is sometimes recommended to use it for 7 days if the patient has an increased risk of seizures (alcohol consumption or traumatic brain injuries)[2]. According to some recent literature, from 11% to 19% of patients can present postoperative seizures, still, if the patient does not have a seizure history, it is not recommended the prophylaxis[19].

Middle meningeal artery embolization

Endovascular middle meningeal artery embolization with polyvinyl alcohol particles (PVA) is an emerging treatment for CSDH. It can be used for new or recurrent chronic SDH, or as prophylaxis

to reduce the risk of recurrence after surgery. It is based on the principle that by blocking the blood supply to the membrane which has neovascularization the leakiness and fragility of these vessels are controlled which eventually leads to the cessation of the process of further CSDH formation[37].

There is preliminary data to suggest that this minimally invasive therapy may be more efficacious and equally as safe compared to conventional, more invasive surgery[37]. In a case series by Link et al, 60 patients were treated with MMA embolization in which 41(91.1%) patients had stable or decrease in CSDH with avoidance of surgery and 4 (8.9%) patients had recurrence requiring surgical evacuation[38].

In a study done by Ban et al where he compared 72 patients treated by MMA embolization Vs 469 patients treated by conventional means (surgically treated). It has been found that the treatment failure rate was 1.4% in the embolized group and 27.5% in surgically treated patients and surgical rescue was needed for 1.4% patients in embolized patients and 18.8% in the surgically treated group[39].

In a meta-analysis conducted by Srivatsan et al among 9 studies published, it has been found that the recurrence rate of CSDH treated by embolization is 2.1%, but for surgical treatment, it was 27.7%[40].

Catapano et al.[41] did a retrospective propensity-adjusted comparison of MMAE Vs conventional treatment for 231 patients with CSDH. It has been found that MMAE is associated with good CSDH volume reduction and less treatment failure than conventional approaches.

Kan et al.[42]did a multicenter prospective trial among 138 patients with CSDH in which 154 MMAE was done. 70.8% of patients had a greater than 50% reduction in hematoma volume while only nine patients (6.5%) required surgery.

In a recent systematic review and meta-analysis done by analysing database from 1987 to 2020 and by analyzing 20 studies by Ironside et al.[43]it has been found that recurrence rate, surgical rescue and in-hospital complication was significantly low (718 MMAE Vs 698 conventionally treated patients).

This shows that MMA embolization is an emerging and promising minimally invasive treatment option for CSDH and may offer a safe and effective alternative to conventional surgery for specific patients, but it needs further randomized controlled trials for its definitive application.

Complications and prognosis

According to some studies, even if it is scarce the literature reports, a calcified CSDH has been reported, its inside is from 0.3 to 2.7% according to Snopko et al.[1]. Calcified CSH is the blood collection localized under the outer shell of the brain 3 weeks after the injury[1]. Calcified CSDH is characterized by neurological symptoms with slow progression and brain atrophy found in neuroimages. It is important to consider that the differential diagnosis of this entity is subdural empyema, arachnoid cyst, epidural hematoma, or even a meningioma[1]. The calcified CSDH aetiology has been related to vascular factors, poor circulation, intravascular thrombosis, metabolic function, and metabolic events[1]. According to some case reports, conservative treatment is indicated in those elderly patients that do not present neurological symptoms (especially if there is a Calcified Chronic Subdural Hematoma), however, if there is a clinical deterioration is important to perform a complete resection of the calcified lesion[1].

Another complication after the resection is the recurring haemorrhage of the subdural space, bleeding with brain compression, and adhered inner membrane dissection for the brain that will produce new neurological deficits. It is important to consider that patients could also present (in the 8% of cases according to the currently available literature, and as mentioned previously) acute-on-chronic SDH, this might be caused by head traumas and the clinical of the patient is characterized by the acute finding along with rapid neurologic deterioration. In the CT-Scan hyper and hypointensity are typical[7]. These patients have the worst outcome prognosis[6].

About 10% to 25% of the SDH might repeat after the surgical evacuation, especially in those patients with the previously referred risk factors[7]. Focal brain injury, intracranial haemorrhage, seizures, focal brain injury, empyema, or even pneumocephalus are post-op complications[19].

CONCLUSION

Chronic subdural hematoma represents a unique challenge to the treating neurosurgical team. The evolution of diverse modalities of treatment has not brought a significant difference in the overall outcome of this indolent condition. Understanding the basic pathology and close monitoring of patients with chronic subdural hematoma points toward a better prognosis.

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NOTES

Ethics statement

This study was a literature review of previously published studies

and was therefore exempt from institutional review board approval.

Author contributions

Conceptualization: GAQO. Data curation: GAQO, VPM, DCSZ, RM. Formal Analysis: VPM, DCSZ. Investigation: DCSZ, EGB. Methodology: GAQO, DCSZ, LRMS, RM. Project administration: GAQO, BD, DCSZ, TJ, RM. Resources: GAQO, BD, DCSZ, EGB, RM. Software: DCSZ, TJ, RM. Supervision: VPM, LRMS, RM. Validation: VPM, DCSZ, LRMS, RM. Visualization: VPM, RM. Writing- original draft: GAQO, VPM, DCSZ, TJ. Writing, review & editing: GAQO, VPM, TJ, LRMS, RM.

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There is no conflict of interest to disclose.

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Cerebellar Stroke: A Primer on Diagnostic Considerations and Therapeutic Options

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Cerebellar infarction is an infrequent pathology that represents only 3% of ischemic strokes with associated high morbidity and mortality. Immediate medical and surgical interventions are required for early and timely clinical management; making correct use of diagnostic images, the start of support measures that allow patient stabilization, and adequate surgical treatment to counteract the progression to catastrophic herniation.

Keywords: Cerebellum; Infarction; Ischemia; Diagnosis; Therapy; Decompression

INTRODUCTION

Cerebellar infarction accounts for 3% of all ischemic strokes in the United States, with 27,400 new cases diagnosed each year[1,2]. This pathology, although infrequent, has serious complications and repercussions. This is considered to be the most common cause of vascular vertigo[3-5]. This was first described in 1956 by Fairburne et al. as a pathology that compromised the circulation of the posterior fossa with edema and compression of the brain stem[6]. This pathology is mainly caused by the occlusion of the vascular flow or trauma to 3 main arteries of the vertebrobasilar system: the posterior inferior cerebellar artery (PICA-which is usually more frequently associated with this pathology), the anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA)[2,5,7]. The infarction in this vascular system generates edema related to ischemia and metabolic changes that modify the functioning of the tissue, thus leading to cellular swelling secondary to energy failure. This process causes the posterior fossa to undergo a mass effect caused by the edema ultimately obstructive hydrocephalus and herniation. This hydrocephalus is due to blockage of cerebrospinal fluid (CSF) passage in the fourth ventricle or the aqueduct of Sylvius, the latter is one of the greatest complications and leads to high mortality and morbidity[2,5].

This pathology usually manifests with vertigo, nausea, nystagmus, vomiting, uncoordinated gait, and headache. There are some important clinical characteristics: site-manifestation correlation, where, for example, Wallenberg syndrome or lateral spinal cord syndrome associated with PICA alteration, Foville syndrome with AICA alteration, and Mill syndrome with SCA alteration[2,5,7].

DIAGNOSTIC CONSIDERATIONS

Given the clinical suspicion of a cerebellar ischemic condition, an evaluation is carried out using brain images (Fig. 1)[8]. Computed axial tomography (CAT) without contrast of the skull is the first-line diagnostic test in the evaluation of patients with clinical suspicion of cerebellar infarction. It allows the exclusion of the presence of posterior fossa hemorrhage, and possible complications inherent to the infarction such as obstructive hydrocephalus. However, more than 25% of patients can have a normal computed tomography (CT) in the initial period[1,9]. CT scan of the brain in a stroke patient is usually done with a CT angiogram and CT perfusion. With a high clinical suspicion and early diagnosis of this stroke, a magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain without contrast is deemed prudent.

The CT angiogram of the head and neck allows the cause of the ischemic event to be identified, such as dissection or embolic occlusion, as well as looking for basilar artery occlusion. Compared to CT angiogram, head and neck magnetic resonance angiography provides better detail of the vasculature in the setting of severe blood vessel calcification[10]. MRI of the head detects abnormalities not identified by CT and provides details about the mechanism of infarction. However, its disadvantages include the longer time required to perform it, the risk of the patient's airway crisis, and the impossibility of its use in patients with electrical or metallic devices[1].

The transthoracic echocardiogram and the transesophageal echocardiogram, as diagnostic modalities, provide information about cardiac valvular vegetations or thrombi as a cause of posterior circulation embolic occlusions[1].

Transcranial doppler (TCD) allows evaluation of the existence of underlying vascular pathology and/or abnormality with the advantages in terms of availability, rapid speed, and lower monetary cost. The only major limitation is that the quality of testing is operator-dependent[2].

• ***Computed Tomography (CT):*** First choice, exclusion of bleed and/or complications. 25% without alteration in early stages
• ***CT angiogram:*** Provides detailed imaging of blood vessels, detects vascular abnormalities, and aids treatment decisions.
• ***MR angiogram:*** Provides detailed imaging of blood vessels, detects vascular abnormalities, and aids treatment decisions without involving any radiation exposure
• ***Magnetic resonance imaging:*** Detects abnormalities not seen on CT. Evaluate mechanism of infarction.
• ***Transthoracic/transesophageal echocardiogram:*** Detection of thrombi and/or valvular vegetations
• ***Transcranial Doppler:*** Detects vascular pathology. Optimal availability, speed, and cost. Operator dependent.

Fig. 1. Diagnostic images for suspected cerebellar infarction

Differential diagnosis

The differential diagnosis for cerebral ischemic stroke-like symptoms includes meningitis or other infectious diseases, syncope, neoplasm, seizure, hypoglycemia, cerebral hemorrhage, and electrolyte imbalance.

SUPPORT MEASURES AND INITIAL MANAGEMENT

The guidelines for the management and initial treatment in the context of the patient with cerebellar infarction are not specific exclusively for the cerebellar condition due to the lack of randomized trials and evidence in the scientific literature, which is why its management results from the existing information about acute cerebrovascular accident (CVA) in general. The "American Heart Association" (AHA) in its latest update on early stroke management provided a set of recommendations on general supportive care and emergency treatment[2,8].

Airway and oxygenation

Airway and ventilatory support are indicated in the context of a decreased state of consciousness and/or alteration at the bulbar level that can compromise the respiratory mechanism. Likewise, it is important to maintain oxygen saturation above 94% with the use of supplemental oxygen[8]. However, supplemental oxygen is not recommended in patients who do not present with hypoxia, likewise, the use of hyperbaric oxygen is not indicated unless the cause is air embolization[1,8].

Blood pressure

The range of blood pressure (BP) values to maintain is not yet established, however, it is important to correct hypotension and hypovolemia by reaching blood pressure levels that guarantee optimal tissue perfusion and adequate organ function[2,8]. A study by Wohlfahrt et al. found that patients with mean arterial pressure (MAP) less than 100 mmHg at admission had a higher risk of death than those with MAP between 100–110 and 110–121 mmHg. Similarly, a systolic blood pressure (SBP) lower than 120 mmHg showed a higher risk of death compared to patients with SBP between 120–130 and 130–141 mmHg. There is currently no evidence to guide the amount and duration of intravenous fluids[8,11].

Body temperature

Temperature elevation greater than 38°C or hyperthermia should be duly recorded and treated with antipyretic medications until a state of normothermia is reached. However, there is currently insufficient evidence to recommend the induction of hypothermia, which despite being known as a neuroprotective strategy is associated with an increase in infections[1,8,12].

Blood glucose

Hyperglycemia within the first 24 hours in the context of a cerebrovascular accident (CVA) is associated with worse results and clinical outcomes[1]. Therefore, it is important to maintain blood glucose between 140 and 180 mg/dL and constant monitoring to avoid a state of hypoglycemia[8].

Fibrinolytic therapy

The use of intravenous alteplase is recommended at a dose of 0.9 mg/kg (maximum dose of 90 mg) over 60 minutes, administering an initial bolus of 10% of the dose in 1 minute, within 3 hours of the onset of symptoms of stroke, and even within 3 to 4.5 hours according to the criteria established by the AHA[8,13]. Continuous observation during fibrinolytic therapy is essential because of possible adverse effects, such as hemorrhagic complications and angioedema that would lead to partial obstruction of the airway. In the scenario of patients with high BP and with eligibility criteria for treatment with alteplase, an SBP of less than 185 mmHg and a diastolic BP (DBP) of less than 110 mmHg are recommended before starting fibrinolytic therapy[8]. Evidence of cerebral microbleeds (> 10) on MRI and the initiation of alteplase treatment may be associated with an increased risk of symptomatic intracerebral hemorrhage[8].

Antiplatelet and anticoagulant therapy

Within the first 24 and 48 hours, administration of aspirin is indicated, however, in patients treated with alteplase/tenecteplase (TNK) (Table 1), its administration can be delayed up to 24 hours later. Treatment with dual antiplatelet therapy- aspirin and clopidogrel-started within the first 24 hours and continued for 21 days contributes substantially to the early prevention of secondary stroke, even up to 90 days after the episode. Anticoagulant therapy for the prevention of another ischemic attack or to improve the clinical condition of the patient is not recommended[8].

For a long time, acute ischemic stroke has been treated using intravenous thrombolytics, with tissue plasminogen activator (TPA) and TNK being the approved agents for the treatment of acute ischemic stroke. TPA is recommended for administration within 3 hours of symptom onset; however, studies suggest that it may be safe and beneficial if given as long as 4.5 hours later[14].

The use of TNK in acute stroke is recommended by guidelines from the American Heart Association/American Stroke Association for certain patients who meet specific criteria, such as those with large vessel occlusion and who can receive treatment within 4.5 hours of symptom onset. The EXTEND-IA TNK trial showed early reperfusion in 22% of patients who received TNK versus 10% of those who received alteplase[15].

SURGICAL MANAGEMENT

Surgical treatment of cerebellar infarction is external ventricular drainage (EVD), suboccipital decompressive craniotomy (SDC) with dural expansion, or a combination of the two. (two) Suboccipital decompressive craniotomy SDC is a safe procedure that is indicated if the initial medical treatment has not been favorable or the patient's condition deteriorates rapidly. The mortality of SDC is between 29.5% and has an 83% chance of not causing mild disability[16]. The purpose of this is to provide space for the edematous cerebellum, relieving compression of the fourth ventricle and the brainstem. If obstructive hydrocephalus occurs in addition to the cerebellar infarction, management with a ventriculostomy (EVD) added to a SDC is considered[1,17]. Several studies have indicated that EVD can be performed as initial management followed by SDC if no improvement is seen. However, the time that must elapse between the two procedures, EVD and SDC, has not been defined. Horwitz and Ludolph have given the option of perform-

Table 1. Medical management of cerebellar infarction

Name of Drug	Mechanism of action	Common adverse events
Aspirin	Inhibit thromboxane A2 production by platelets, which has an antithrombotic effect.	Heartburn, abdominal cramping, drowsiness.
Clopidogrel	prevents the activation of the glycoprotein GPIIb/IIIa complex by adenosine diphosphate (ADP) and its subsequent binding to the platelet P2Y12 receptor, which prevents platelet aggregation.	Headache, indigestion, nosebleed, dizziness.
Tissue plasminogen activator	The fibrin on the clot surface is where tPA binds. It activates the plasminogen which is attached to fibrin. The fibrin-associated plasminogen is then split apart to release the plasmin. The fibrin molecules are disassembled by plasmin, which also causes the clot to disintegrate.	Nose bleed, headache, internal bleeding.

ing SDC after a few hours, evidenced by the deterioration of the neurological condition after EVD placement[18].

The neurological signs looked for in patients are: a decreased level of consciousness, downward conjugate gaze or sunset eyes, gaze paresis, cranial nerve deficits, and long tract signs. The outcome has been associated with the patient's preoperative state of consciousness, regardless of the treatment that has been carried out, whether surgical or not[1,18].

Among the contraindications of SDC are clinical or radiological signs of severe or irreversible ischemia of the brain stem, severe comorbidity, or refusal to undergo the procedure[19].

External ventricular drainage

EVD is part of the first surgical measures that can be implanted in a patient who is stable in the initial stage of the cerebellar infarction, and who consequently has a mass effect secondary to tissue edema or obstruction of the flow of CSF in the posterior fossa, producing hydrocephalus and/or compression of the brain stem[5]. This therapeutic strategy has shown better results than medical treatment with significant positive results when evaluating neurological improvement with the Glasgow scale.

The EVD has been widely recommended in the literature due to its therapeutic value since with its application, improved inpatient survival[20,21]. In the literature, the use of EVD is recommended in hydrocephalus or brainstem compression secondary to cerebellar infarction, either as the only intervention or in conjunction with SDC. However, data suggest that EVD should be carried out alone and subsequent SDC if there is no improvement in neurological and clinical parameters found. There have been few studies comparing EVD intervention alone with EVD + SDC therapy, and although these do not show significant differences in survival, these do suggest that there is an improvement in long-term functional parameters[1,6-8,18,22-26]. However, the possibility of triggering a transtentorial herniation and additionally increased risk of ventriculitis and other neurologic infections have been attributed to EVD, for which clinical evaluation of the patient should be carried out regularly in search of signs and symptoms that may suggest the diagnosis[1,2,7,8].

CONCLUSION

Cerebellar infarction is a rare entity with serious consequences for the patient's health. It presents with unspecific clinical symptoms, however, the suspicion of this entity must be considered with signs of cerebellar dysfunction. CT of the head is the first-line image to carry out its imaging diagnosis. Initial management includes airway control, blood pressure, blood glucose, temperature, fibrinolytic, and antiplatelet/anticoagulant therapy. Likewise, surgical measures, such as EVD and SDC, are necessary to resolve complications of this entity.

NOTES

Ethics statement

We confirm that, for this work ethical guidelines, ethical approvals (institutional review board) and the use of informed consent were not applicable.

Author contributions

Writing – original draft: NA, GB, S, BOH,CMA, GHD. Writing – review & editing: TJ, MK, LFM.

Conflict of interest

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Neurocritical Care Nutrition: Unique Considerations and Strategies for Optimizing Energy Supply and Metabolic Support in Critically Ill Patients

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Neuro-critically ill patients face unique challenges in nutritional support due to varying metabolic and energy demands arising from clinical situations such as elevated intracranial pressure, trauma, stroke, epilepsy, targeted temperature management (TTM), and pharmacological interventions. Despite these challenges, there is a lack of systematic reviews addressing their specific needs. This study conducts a systematic review and narrative synthesis of the existing literature on nutritional support for neuro-critical patients, focusing on amino acids that act as neurotransmitters or their precursors. We examined nutritional requirements and timing in patients with stroke and traumatic brain injury, as well as energy and metabolic demands during TTM, a common therapeutic intervention in neuro-critical care. Our review aims to clarify uncertainties surrounding amino acid provision in neuro-critical patients and provide up-to-date recommendations on nutritional support for those with elevated intracranial pressure and undergoing TTM, serving as a foundation for future research and evidence-based guideline development. Key findings include the potential benefits of branched-chain amino acids (BCAAs) in neuro-critical care, the roles of methionine and serine, the significance of arginine in vascular constriction, the controversial role of glutamate in nutrition, and the potential benefits of selenium supplementation. We also discussed special considerations in nutritional support for neuro-critical patients, such as changes in energy demand, the influence of sedation on energy demand, and metabolism changes during TTM. Our review highlights the need for a better understanding of the unique metabolic requirements of neuro-critical patients and the development of evidence-based guidelines for optimal nutritional support in this population.

Keywords: Critical care; Nutritional status; Amino acids; Calorimetry; Intracranial hypertension

INTRODUCTION

The importance of nutrition in the management of critically ill patients has been increasingly recognized over the years. Recent research has actively explored various aspects of nutrition in septic patients, such as the timing of oral nutrition initiation, routes of nutrient delivery, and appropriate methods of administration. Neurocritical care patients differ from other critically ill patients with medical conditions in several aspects that warrant special consideration. These differences stem from the unique neurovascular supply, metabolic characteristics of neurons, and specific clinical situations and treatments in neurocritical care.

The brain, accounting for only 3-5% of body weight, demands a disproportionately high energy supply, contributing to 20% of the total metabolic rate. This high metabolic demand is met by an elevated cerebral blood flow via neurovascular coupling. Neurons in the cerebral cortex are situated at the outermost region of the brain and receive blood supply not directly from large arteries but rather through low-pressure terminal vessels. In cases of increased intracranial pressure, neuronal damage in brain regions receiving low-pressure blood supply (e.g., cerebral cortex, deep basal nuclei) is accelerated.

When cerebral perfusion is not maintained due to increased intracranial pressure or hypotension, neurons may face energy supply disruptions even from astrocytes. This leads to intracellular energy deficiency, impairing various electrolyte pumps (e.g., Na-K pump) and neurotransmitter functions and accelerating secondary neuronal damage. Furthermore, neurons possess a unique signaling system in the form of neurotransmitters, requiring a continuous supply of amino acids as precursors. However, the type of amino acids needed varies depending on the clinical situation in neurocritical care patients, and excessive administration can provoke side effects such as seizures. Thus, it is crucial to understand and provide the appropriate amino acid supply according to the clinical context. Recent advances in nutritional support for neurocritical care patients, revealed amino acids play a critical role in various metabolic and neurotransmitter pathways in the brain. This review aims to explore the potential benefits of amino acid supplementation in neurocritical care, focusing on branched-chain amino acids (BCAAs), methionine, serine, arginine, glutamate, and selenium. Current research has provided some evidence for the potential role of these amino acids in enhancing hippocampal function, regulating brain function and energy production, promoting neuronal survival, and modulating vascular relaxation in patients with neurological injuries. However, the direct relationship between amino acid supplementation and patient outcomes remains inconclusive, highlighting the need for further research in this area.

Collectively, neurons exhibit both unique nutritional requirements and vulnerability, making proper nutrient supply essential. In neurocritical care, patients with elevated intracranial pressure or undergoing therapeutic hypothermia may have specific nutritional requirements. Therefore, it is necessary to revisit the energy requirements, metabolic characteristics, nutritional instability of neurons, and the impact of neurocritical care treatment techniques on nutritional demands in neurocritical care patients.

METHODS

To systematically narrative review the recent updates in decompressive craniectomy and cranioplasty, we conducted a comprehensive literature search using the following electronic databases: MEDLINE, EMBASE, and Cochrane Library. The search terms included "neurocritical care," "nutrition," “amino acid,” "intracranial pressure," "metabolism," "hypothermia," "traumatic brain injury," “indirect calorimeter,” and "stroke." The search was limited to articles published between January 2010 and December 2022, and only articles written in English were considered for inclusion.

Two independent reviewers screened the search results by title and abstract. Articles were considered for full-text review if they were deemed relevant to the study's objectives. Any disagreements between the reviewers were resolved by consensus or consultation with a third reviewer. Full-text articles were reviewed to determine eligibility for inclusion in the systematic review.

We included studies that reported on physiological changes following decompressive craniectomy, indications for decompressive craniectomy, optimal size of decompressive craniectomy, optimal timing of cranioplasty, syndrome of trephined, and the necessity of suboccipital cranioplasty. Both randomized controlled trials and observational studies were considered for inclusion. Case reports, case series, and expert opinions were excluded.

A narrative synthesis of the findings from the included studies was conducted, focusing on the physiological effects, indications, complications, and management of decompressive craniectomy and cranioplasty. Due to the heterogeneity in study design and reported outcomes, a meta-analysis was not performed. Instead, we present a descriptive summary of the available evidence, including a discussion of the strengths and limitations of the reviewed studies, and provide recommendations for clinical practice and future research.

LITERATURE REVIEW

The role of amino acid supplementation in neurocritical care

Amino acids, the fundamental components of proteins, consist

of 20 different types. Although the body's proteins are incredibly diverse, encompassing hundreds of thousands of varieties, only 20 amino acids form their structure. These 20 amino acids are categorized into 9 essential amino acids (EAAs), 7 conditionally non-essential amino acids, and 4 non-essential amino acids. Essential amino acids cannot be synthesized within the body or are synthesized in inadequate amounts, necessitating their external supply to support physiological functions. Conditionally non-essential amino acids can be synthesized under normal circumstances, but their production may be impaired in specific situations, such as trauma, requiring an external supply. Non-essential amino acids are easily synthesized within the body.

Utilization of branched-chain amino acids in neurocritical care

Branched-chain amino acids (BCAAs), including valine, leucine, and isoleucine, have a tree branch-like structure, are hydrophobic, and promote protein synthesis (Fig. 1). BCAAs serve as precursors for the neurotransmitters glutamate and GABA (gamma-aminobutyric acid) and are essential components of the energy metabolism-related citric acid cycle (Krebs cycle)[1].Studies in animal models and clinical settings have confirmed decreased BCAA concentrations in the hippocampus and plasma following traumatic brain injury (TBI)[2,3].This observation has led to the hypothesis that BCAA supplementation after TBI may enhance hippocampal function by providing a source for the synthesis of glutamate and GABA.

In a mouse model of brain injury, a decrease in hippocampal BCAA concentrations was observed. Subsequent BCAA supplementation in the brain-injured subjects improved their conditioned fear responses to levels similar to those of the control group, while simultaneously increasing hippocampal BCAA concentrations[4]. Additionally, BCAA supplementation was advantageous in maintaining wakefulness. A study involving patients with TBI revealed significant decreases in BCAA and metabolite concentrations[3]. Plasma BCAA concentrations decreased following brain injury, with more severe injuries showing more significant reductions. These findings suggest that changes in BCAA metabolism after TBI may affect the pathophysiology of TBI by causing insufficient energy production and neurotransmitter synthesis. Researchers have found considerable associations between decreased blood concentrations of BCAA metabolites, such as propionylcarnitine, 2-methylbutyrylcarnitine, and 4-methyl-2-oxopentanoate, and increased intracranial pressure (Fig. 2).

The exact cause of reduced BCAA metabolism in traumatic brain injury remains unclear. However, it could be related to metabolic disorders of enzymes involved in BCAA metabolism, such as reversible transamination by branched-chain aminotransferase and irreversible dehydrogenation by branched-chain α-keto acid dehydrogenase. These enzymes play an inevitable role in the initial stages of BCAA metabolism, and their dysfunction may be linked to the observed decrease in BCAA metabolism following injury[5].

The association between bcaas levels and altered consciousness in neurocritical care patient

Although a definitive conclusion about the direct relationship between serum BCAA concentrations and brain function remains

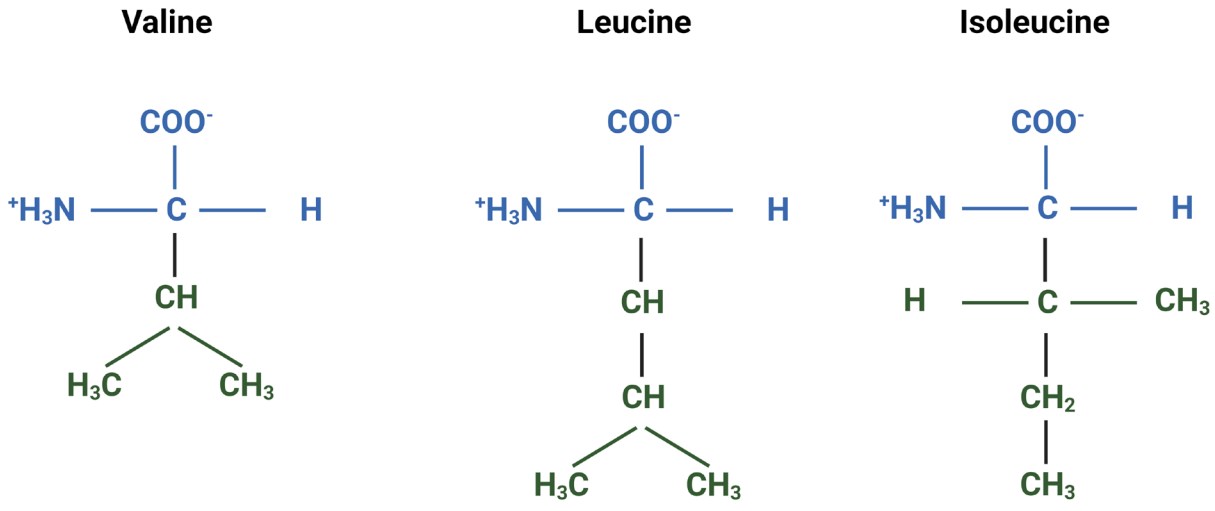

Fig. 1. Chemical structures of branched-chain amino acids (BCAAs): Valine, Leucine, and Isoleucine. This figure presents the molecular structures of the three BCAAs, which are essential amino acids that have been shown to maintain cognitive function and play a crucial role in the recovery of consciousness in neurocritical care patients.

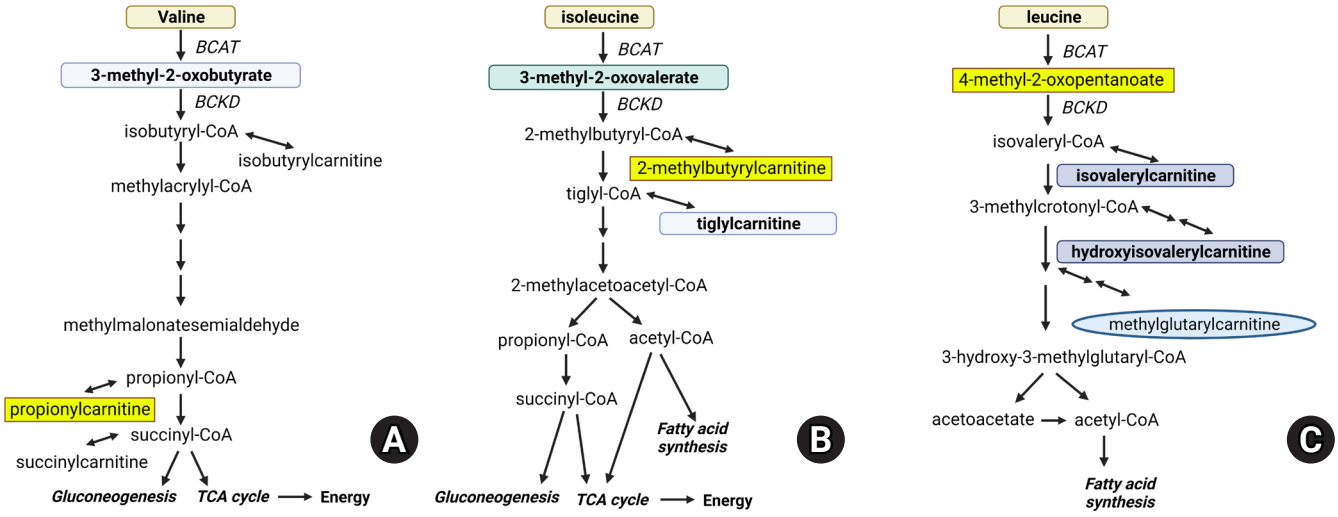

Fig. 2. Branched-chain amino acid (BCAA) metabolic pathway. This figure illustrates the major metabolites and enzymes involved in the metabolism of BCAAs: (A) Valine metabolism, highlighting key enzymes and metabolites. (B) Isoleucine metabolism, showcasing major metabolites. (C) Leucine metabolism and the changes in metabolite levels in traumatic brain injury patients compared to healthy volunteers. Metabolites in rectangles indicate a significant decrease, hexagons represent no change, and ovals signify a significant increase in plasma levels. Metabolites in gray were not measured in the study.
BCTA: Branched-chain amino acid aminotransferase, BCKD: Branched-chain keto acid dehydrogenase, TCA: The citric acid cycle.

elusive, there is evidence supporting this possibility. First, the glucogenic energy production of valine and isoleucine, as well as the ketogenic energy production of leucine and isoleucine, play a role in this connection[6]. BCAAs pass through the blood-brain barrier using energy-dependent transporters. In injured brains, blood flow alterations can lead to ATP deficiency (Fig. 3A). Consequently, leucine generates energy through the ketogenic pathway, replacing glucose in the brain, and increasing the secretion of its metabolic product, glutamate (Fig. 3B). Thus, the use of BCAAs as an energy source accelerates TBI-mediated glutamate excitotoxicity, leading to secondary neuronal damage (Fig. 3A).

The second line of evidence highlights the amino acid imbalance resulting from decreased BCAAs. In patients with long-standing brain injuries, serum BCAA levels decrease even further. Contrary to the previous discussion, a prolonged state of reduced leucine may lead to a decrease in excitatory neurotransmitter glutamate, resulting in diminished synaptic activity and neuroplasticity, ultimately causing cognitive and behavioral disorders[1]. Moreover, when BCAA serum concentrations decrease, large neutral amino acids (LNAAs, including tryptophan, tyrosine, and phenylalanine) are utilized instead. This substitution can increase serotonin and catecholamine concentrations, potentially leading to behavioral and cognitive abnormalities, such as bipolar disorder and schizophrenia, when present in excess[7,8].

Based on this evidence, the external supply of BCAAs has been proposed as a potential therapeutic approach. In fact, BCAA administration in patients with severe traumatic brain injury (TBI) has significantly aided cognitive recovery[9]. Other studies have reported that maintaining normal protein and caloric intake in patients with TBI may enhance cognitive recovery through nutritional BCAA supplementation[10].

The role of methionine and serine in cognitive function of neurocritical care patients

1) Methionine

Methionine serves as a methyl group donor during methylation. Its metabolite, S-adenosylmethionine (SAM), plays a crucial role in gene expression and cellular signaling (Fig. 4). Additionally, methionine is involved in the synthesis of glutathione, which protects cells from oxidative stress. The brain, with its high lipid content and metabolic activity, is particularly vulnerable to oxidative stress. Consequently, a decrease in glutathione levels due to brain injury may accelerate brain damage[11]. In cases of severe traumatic brain injury (TBI), methionine, SAM, and glutathione levels decline, leading to various cellular changes. These changes include reductions in protein synthesis, gene expression, and cellular protection via glutathione production. In fact, decreased serum concentrations of methionine, BCAAs, and histidine have been reported in patients with severe TBI[12]. However, no direct evidence currently supports the external supplementation of methionine to improve

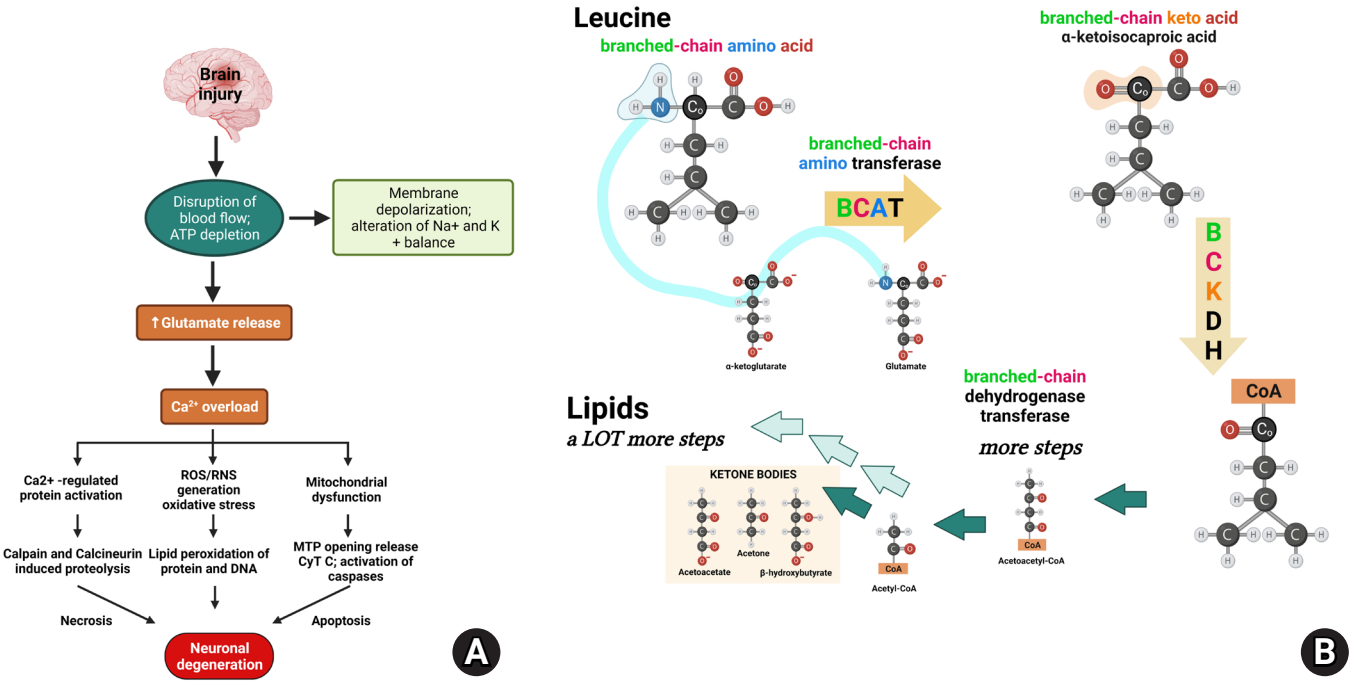

Fig. 3. Mechanisms of neuronal damage in traumatic brain injury and the involvement of essential amino acid metabolism. This figure illustrates the interconnected mechanisms contributing to neuronal damage following brain injury and the role of essential amino acid metabolism. (A) Sequential events in the cascade include: 1) brain injury triggering glutamate release, which leads to calcium overload, followed by activation of calcium-regulated proteins such as calpain and calcineurin, ultimately resulting in proteolysis and neuronal degeneration; 2) calcium overload causing oxidative stress and lipid peroxidation of proteins and DNA, which contribute to neuronal degeneration; 3) calcium overload inducing mitochondrial dysfunction, followed by MTP opening, cytochrome C release, apoptosis, and neuronal degeneration. (B) The metabolism of branched-chain amino acids (BCAAs) involves their conversion to branched-chain keto acids by the branched-chain dehydrogenase complex, and the subsequent formation of ketone bodies, which play a role in the overall mechanism of neuronal damage.

the prognosis of patients with severe TBI.

2) Serine

Serine is a non-essential amino acid that can be synthesized in the body using glycine as a precursor. Serine is metabolized into phosphatidylserine (PS). Serine crosses the blood-brain barrier via sodium-dependent neutral amino acid transporters and is present in cerebrospinal fluid at approximately 10% of plasma concentration. In neurons, serine is metabolized to PS. Neuron-derived PS is rich in docosahexaenoic acid (DHA), and the supply of DHA promotes the synthesis of PS. PS is a major phospholipid in the inner layer of cell membranes in neural tissues, accounting for 13-15% of the phospholipids in the cerebral cortex. Located in the neuronal cell membrane, PS regulates synaptic receptor expression and neurotransmitter release, thus participating in signal transduction related to neuronal survival, neurite growth, and synaptic genesis[13].

The clinical significance of serine supplementation is still under investigation. Ethanol has been shown in animal studies to reduce DHA levels and degrade PS in the hippocampus, impairing neuronal survival and function and causing apoptosis of hippocampal cells[14,15]. Patients with Alzheimer's dementia, who exhibit memory and cognitive decline, have been found to have decreased DHA and PS levels. Oral administration of serine in the form of PS has been reported to improve cognitive and verbal call functions in Alzheimer's patients. However, more research is needed to establish the potential benefits of serine supplementation in neurocritical care patients[16,17].

The role of arginine in cerebrovascular constriction and vasospasm

Arginine serves as a precursor for nitric oxide (NO), which functions as an endothelium-derived relaxing factor. NO is produced from arginine through the action of endothelial NO synthase (eNOS) in the cerebral endothelium and neuronal NOS (nNOS) in the adventitia. NO production is stimulated in response to shear stress, metabolic demands, and chemoregulation, leading to vasodilation[18].

In the context of subarachnoid hemorrhage (SAH), hemoglobin released into the subarachnoid space destroys nNOS-contacting

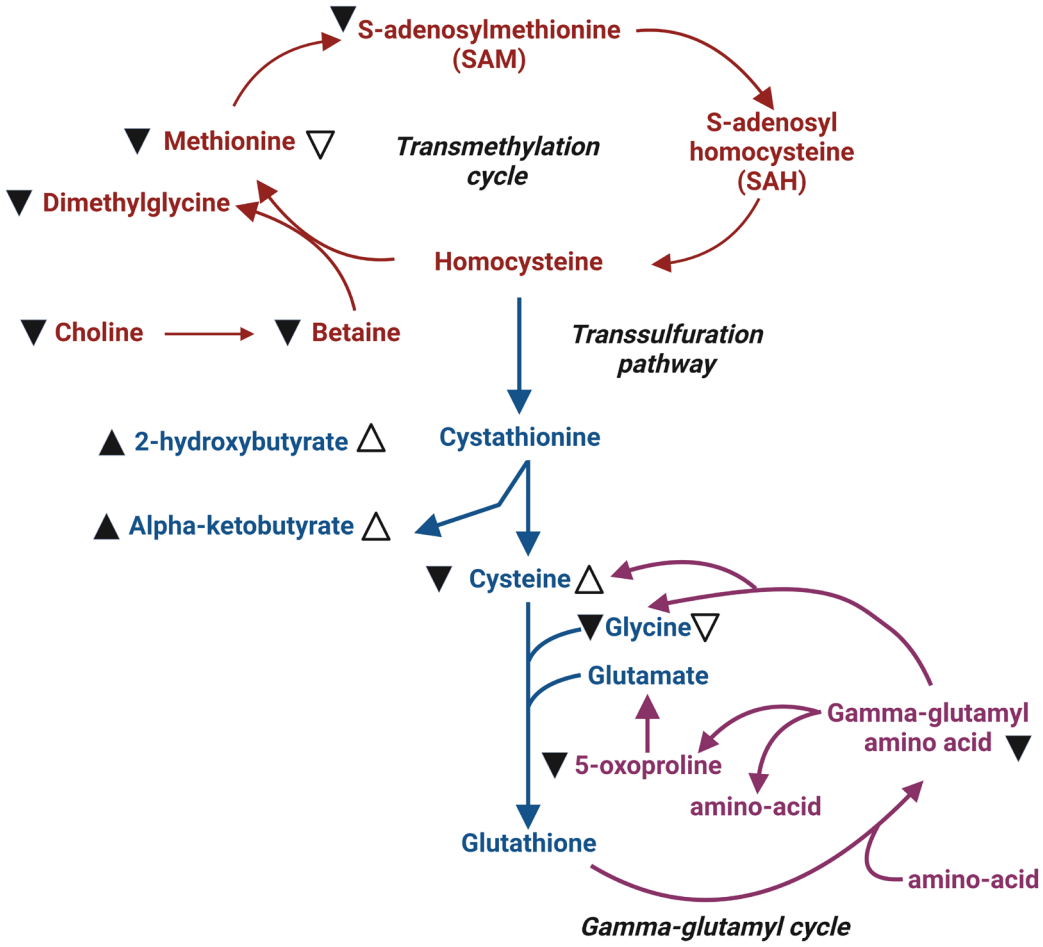

Fig. 4. Summary illustration of methionine metabolic pathways[11]. This figure provides an overview of the major pathways involved in methionine metabolism: the transmethylation pathway (indicated in red), the trans-sulfuration pathway (indicated in blue), and the gamma-glutamyl cycle (shown in green). Changes in metabolite levels in the plasma of severe traumatic brain injury (TBI) patients are denoted by black arrowheads (▲). Open arrows (△) represent significant changes observed in moderate TBI patients compared to healthy volunteers. Up arrowheads indicate increased levels, while down arrowheads (▼▽) signify decreased levels.

neurons, inhibiting NO synthesis and leading to cerebrovascular constriction. When vascular constriction occurs, eNOS activation induced by shear stress is counteracted by the activation of endogenous competitive NOS inhibitors such as asymmetric dimethylarginine (ADMA). During cerebrovascular constriction, the enzyme responsible for ADMA removal (dimethylarginine-dimethylaminohydrolase II, or DDAH II) is unable to function properly due to an immune response, resulting in increased cerebrospinal fluid ADMA levels and exacerbating cerebrovascular constriction[18] . Consequently, externally supplied arginine has been proposed as a potential treatment for cerebrovascular constriction by stimulating DDAH II and inhibiting L-arginine methylating enzyme[19].

Animal studies have demonstrated that the administration of L-arginine ameliorates cerebrovascular constriction. When administered intracarotidly, the degree of improvement in cerebrovascular constriction was assessed using transcranial Doppler (TCD) to evaluate mean flow velocity (Fig. 5)[20].In another study, an SAH vasospasm animal model showed that the administration of L-arginine, compared to saline, reduced the latency of motor evoked potentials and increased amplitude, resulting in improved clinical symptoms[21]. Another group directly observed changes in the vascular wall due to vasospasm and arginine administration using rat femoral artery samples[19]. Compared to the control group, the vasospastic vessels displayed increased wall thickness and non-intact endothelium. In the experimental group treated with L-arginine following vasospasm, an improvement in wall thickness and thinning was observed. These findings suggest that arginine adminis-

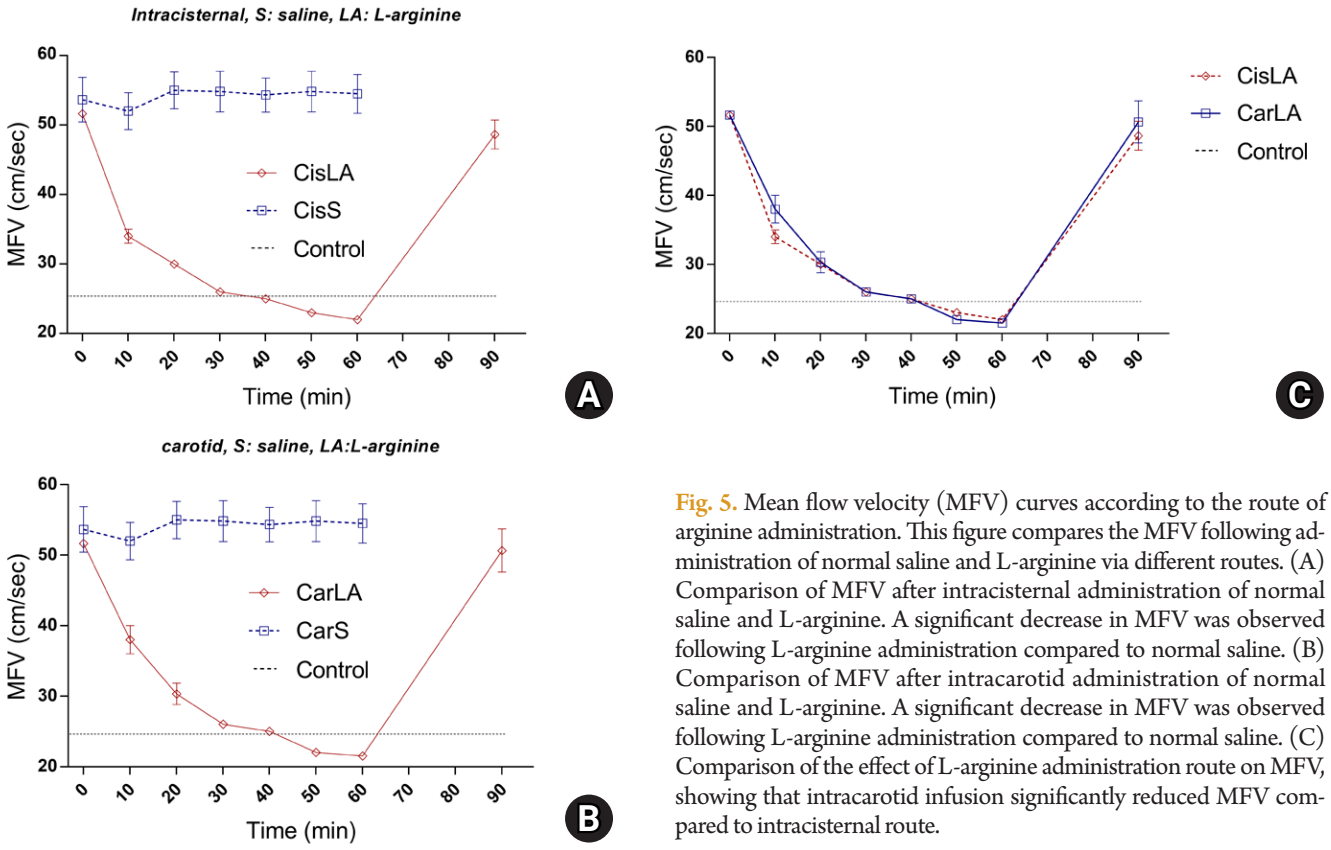

Fig. 5. Mean flow velocity (MFV) curves according to the route of arginine administration. This figure compares the MFV following administration of normal saline and L-arginine via different routes. (A) Comparison of MFV after intracisternal administration of normal saline and L-arginine. A significant decrease in MFV was observed following L-arginine administration compared to normal saline. (B) Comparison of MFV after intracarotid administration of normal saline and L-arginine. A significant decrease in MFV was observed following L-arginine administration compared to normal saline. (C) Comparison of the effect of L-arginine administration route on MFV, showing that intracarotid infusion significantly reduced MFV compared to intracisternal route.

tration may represent a novel therapeutic approach to treating cerebrovascular constriction in the context of subarachnoid hemorrhage.

Glutamate: to feed or not?

Glutamate is the most abundant free amino acid in the brain, and it serves as a neurotransmitter that transmits excitatory signals, is oxidized for energy production, and acts as a precursor for the synthesis of proteins, glutamine, GABA, and glutathione. Furthermore, it participates in cellular removal processes, thus playing a role in neural plasticity. Glutamate receptors are located on the surface of nerve cells, and excessive excitatory signals from glutamate can lead to cell death through a phenomenon called 'excitotoxicity.' Therefore, it is crucial for glutamate to be present in the appropriate concentration, location, and timing. A balance between glutamate transporter, which removes extracellular glutamate, and the blood-brain barrier, which prevents the movement of glutamate from the blood to the brain, is essential[22].

Glutamine is the most abundant amino acid in the human body and is primarily produced in muscles. It is a conditionally essential amino acid consumed in greater quantities during severe illness or following major surgery. Glutamine is responsible for more metabolic functions in the body than other amino acids. It can be converted into glucose to provide energy when needed, serves as a backbone for RNA/DNA synthesis, participates in ammonium production in the kidneys for acid-base balance, and is involved in the synthesis of the antioxidant glutathione[23-25]. In the central nervous system, glutamine acts as a precursor for neurotransmitters such as glutamate, aspartate, and GABA, and is synthesized in astrocytes through the glutamate-glutamine cycle. The synthesized glutamine is then transported to neurons and recycled as a precursor for glutamate and GABA (Fig. 6)[26,27].

One of the central nervous system disorders characterized by an imbalance in the glutamate-glutamine cycle is epilepsy. An imbalance in glutamatergic and GABA-ergic transmission results in insufficient glutamine synthesis, leading to a lack of GABA-ergic activity and hyperexcitation, which manifests clinically as epilepsy. External glutamine supply can reverse this process. However, since glutamine is metabolized in the liver, liver dysfunction or excessive glutamine administration can lead to brain edema, increased intracranial pressure, and neurological abnormalities. Therefore, liver function should be monitored concurrently with glutamine ad-

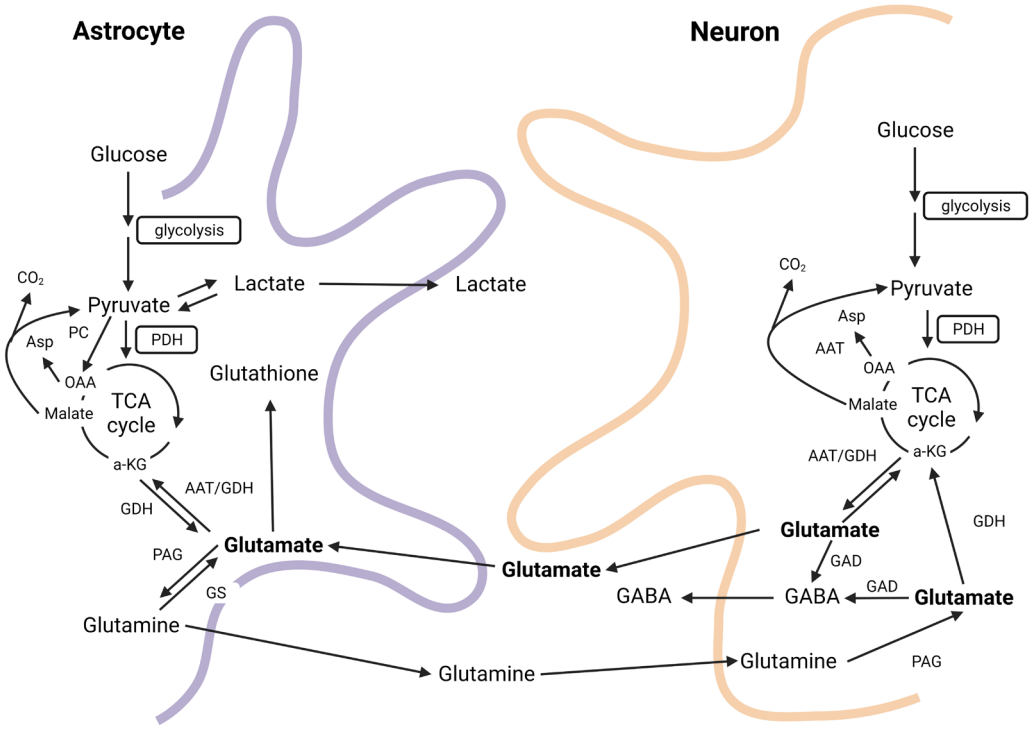

Fig. 6. Glutamate-Glutamine cycle in the brain[26]. This figure illustrates the Glutamate-Glutamine cycle, a crucial metabolic process in the central nervous system, which regulates the balance and recycling of neurotransmitters, particularly glutamate and glutamine, between neurons and astrocytes. The cycle plays a vital role in maintaining proper neuronal function and overall brain homeostasis.

ministration[22,23].

Glutamine is also involved in glutathione synthesis, protecting cells from oxidative stress, and a deficiency in glutamatergic neurotransmission may lead to emotional disorders and depression[28]. In animal models of stress-induced cognitive impairment, glutamine supplementation has shown significant positive results in recognition and location memory tests, suggesting its potential usefulness in preclinical settings[29]. In humans, increased mortality has been observed in critically ill patients with low blood glutamine levels, leading to ASPEN and ESPEN guidelines recommending glutamine administration with a level of evidence[30,31]. In cases of traumatic brain injury with blood-brain barrier damage, an appropriate external glutamine supply that does not increase glutamate concentration should be established to prevent exacerbation of excitotoxicity and brain edema[32,33]. Although a study in severe traumatic brain injury patients administering 0.34g/kg of glutamine within 20 hours showed a significant increase in glutamine levels without elevating glutamate levels, the clinical outcomes remain unclear, necessitating further research[34].

Considering this, it is advisable for each hospital to limit the administration of glutamate during the initial stages of brain injury when using amino acid preparations or total parenteral nutrition. This is due to the potential for intravenous nutrition containing glutamate to exacerbate brain injury during periods of rapid progression and uncontrolled brain edema caused by damage to the blood-brain barrier. Once hemodynamically stable and brain edema begins to be controlled, it is recommended to initiate enteral feeding and supplement with parenteral nutrition as needed.

Selenium: a beneficial element in neurocritical care?

Selenium exists in the human body in the form of 25 different selenoproteins and serves various functions. It is involved in numerous neural signal transmissions through neurotransmission. Selenium plays a role in maintaining motor function, coordination, memory, and cognition, and its deficiency can manifest as symptoms of Alzheimer's disease, Parkinson's disease, and epilepsy. In the cerebral cortex and hippocampus, it serves a GABA-ergic function, leading to refractory seizures in children when deficient. In the dopamine pathway, it exhibits both neurotoxic and neuroprotective properties depending on its concentration. It also participates in acetylcholine neurotransmission, contributing to the phosphorylation of antioxidant proteins and the maintenance of ion channel/calcium homeostasis at the molecular and cellular levels[35].

Under stress conditions, the stress hormone glucocorticoid affects the cerebral cortex and hippocampus, leading to memory and emotional disorders. Glucocorticoids suppress the expression of selenoprotein genes, but the administration of exogenous selenium can counteract this effect and inhibit oxidative damage (lipid peroxidation) caused by glucocorticoids[36,37]. Animal studies have shown that selenium supplementation enhances hippocampal neurogenesis by mediating the proliferation of neuronal precursor cells in response to physical activity stimulation, thereby improving cognitive decline associated with hippocampal injury and aging[38]. In actual traumatic brain injury patients, intravenous administration of selenium for up to 10 days (1000mcg q.d. for 5 days followed by 500mcg q.d. for the next 5 days) did not show a significant difference in mortality rates. However, functional outcomes at discharge and 6-month follow-up were significantly improved in the patient group receiving selenium[39]. In patients with non-abdominal trauma, supplementation of selenium resulted in significant reductions in mortality, ICU, and overall hospital stays[36]. A meta-analysis of critically ill patients did not yield significant positive results for overall hospital stays, pneumonia, or side effects of renal failure in the selenium treatment group. Although a significant statistical value was obtained for mortality, this was on the borderline[40]. Studies on the clinical outcomes of selenium supplementation in patients with systemic inflammatory response syndrome (SIRS) and sepsis have yielded inconsistent results[41]. Although the effects of selenium supplementation are not consistent, it is considered "not inferior" and warrants weak recommendation for administration.

Special considerations in nutritional support for neuro-critical patients

Changes in energy requirements in neuro-critical patients depending on clinical situations

There are several factors to consider in providing appropriate energy supply to neuro-critical patients. First, the brain accounts for a significant portion of the body's total energy requirements, so it is essential to consider metabolic changes in the brain due to brain injury. Second, brain metabolism varies depending on the cause of the brain injury (especially trauma, subarachnoid hemorrhage due to aneurysm rupture, and cerebral infarction), hormonal changes, accompanying injuries, sepsis, pneumonia, and inflammatory responses due to complications. Third, many treatments used in the management of neuro-critical patients, such as sedatives, muscle relaxants, and hypothermia, can induce changes in energy metabolism.

1) Increased intracranial pressure

Animal experiments have shown that anaerobic glycolysis occurs in the brain during increased intracranial pressure, leading to decreased pH, ATP, and phosphocreatine. Energy metabolism in the brain is preserved until cerebral perfusion pressure drops below 30 mmHg[42]. When intracranial pressure rises, immediate changes in energy metabolism appear in the brain, and glucose, lactate, and pyruvate in the extracellular fluid decrease rapidly[43]. This indicates that energy production becomes insufficient due to increased intracranial pressure. Conversely, when intracranial pressure is reduced rapidly, glucose, lactate, and pyruvate return to normal levels[42,43].

Although the degree of metabolic increase after brain injury is known to correlate with intracranial pressure, treatments for elevated intracranial pressure can also affect overall metabolic rate[44]. Since treatment aims to reduce intracranial pressure rapidly and avoid sustained elevated intracranial pressure, it is not easy to predict changes in energy requirements due to intracranial pressure fluctuations. Despite the theoretical expectation that thiopental should decrease $CMRO_2$ and thus reduce additional energy consumption, studies have shown that thiopental does not reduce additional energy consumption compared to fentanyl and midazolam sedation. This suggests that efforts to reduce brain metabolism may not be effective[45,46].

2) Trauma

It is well known that trauma triggers hypermetabolism and a catabolic state. In patients with head trauma, the metabolic rate is reported to increase by approximately 100-160%, although the extent varies in the literature[47]. In a study involving patients with traumatic brain injury, the basal metabolic rate was elevated compared to healthy individuals, with rates of 168 ± 53% for those with a Glasgow Coma Scale (GCS) score of 5 or below, 129 ± 31% for scores of 6-7, and 150 ± 49% for scores of 8 or above. The resting metabolic rate (RMR) during the stable phase increased by 45% for each 1-degree increase in body temperature in patients with GCS scores of 5 or below and by 15% in those with scores of 6-7. In patients with GCS scores of 8 or above, no correlation was found between RMR and body temperature[48]. Considering that patients with GCS scores of 5 or below showed posturing responses to pain and persistent rigid muscle tone, and those with GCS scores of 8 or above exhibited more agitation, the lowest basal rate observed in patients with GCS scores of 6-7 may suggest that muscle contraction has a greater influence than the severity of brain injury. In patients with traumatic brain injury, the energy metabolic rate is typically 120-250% higher than the basal energy expenditure calculated using the Harris-Benedict equation, and it ranges from

76-120% when sedatives, paralytics, or barbiturates are used. Therefore, providing 140% of the predicted basal energy expenditure (BEE) is necessary for patients without paralysis[49].

3) Stroke

The energy requirements for stroke patients have been reported variably in the literature. Stroke patients can be broadly categorized into ischemic stroke and hemorrhagic stroke.

In acute ischemic stroke patients, the total energy expenditure (TEE) is lower compared to other critically ill patients. When providing caloric supply to typical critically ill patients, there is a higher risk of overnutrition. The Harrison-Benedict equation (HBE) shows a relatively high correlation with the predicted TEE, so it is recommended to use HBE or indirect calorimetry to evaluate nutritional requirements[50].

In contrast, high-weight based energy calculations (30kcal/kg) are better predictors of resting energy expenditure (REE) in hemorrhagic stroke patients, while low-weight based energy calculations (25kcal/kg) are better predictors in acute ischemic stroke patients[51]. Hemorrhagic stroke patients had a basal energy expenditure (BEE) of 126% (101-170%) during the first week, which was not statistically different from the mean BEE of 147% (114-176%) in patients with severe traumatic brain injury. Therefore, similar to patients with traumatic brain injury, hemorrhagic stroke patients have an increased metabolic rate, and there is a risk of under-supplying nutrition compared to standard critically ill patients[52]. In a study of spontaneous intracerebral hemorrhage patients, the average REE increased by 117.5%, and the energy requirement peaked between 7-10 days as time progressed. In patients with aneurysmal subarachnoid hemorrhage, the energy requirement initially started close to 25kcal/kg but gradually increased, reaching above 30kcal/kg on the sixth day[53].

Influence of sedation and neuromuscular blockade on energy demand in neurocritical care patients

Many medications used in neurocritical care, particularly sedatives and muscle relaxants, have an impact on energy requirements. Although the reported effects vary in the literature, sedation with midazolam and fentanyl has been shown to decrease the average resting metabolic rate (RMR) by 6–33%, while neuromuscular blockers reduce it by 11–33%[54-57]. No significant difference in metabolic rate reduction was observed between propofol and midazolam[54], with some studies showing a decrease in energy requirements by an average of 25%.

Fever has been reported to increase energy consumption by 10% per 1°C, and sepsis raises energy consumption regardless of fever[46]. In sedated brain-injured patients, sepsis and body temperature have been reported as the main causes of changes in energy consumption. The relationship between sedation and energy consumption suggests that the deeper the sedation, the lower the energy consumption[55,56]. When sedation is deep enough to eliminate spontaneous movement, there seems to be little difference between drugs.

1) Propofol

Propofol is a widely used sedative in neurocritical care patients due to its effect on reducing intracranial pressure. Propofol is formulated as a 10% lipid emulsion of soybean oil, which itself provides 11 kcal/g (1.1 kcal/mL) of energy. If this is not considered, it can lead to an oversupply of calories, hypertriglyceridemia, and inappropriate protein provision[57]. When using commercial intravenous nutrition products simultaneously, lipid-free total parenteral nutrition (TPN) can be used, or if a fat-containing multi (3)-chamber bag is used, the fat-containing seal should not be opened, and only the catheter port of the dextrose and amino acid-containing chamber bag should be connected, allowing the administration of a lipid-free dextrose and amino acid solution.

Changes in energy requirements during targeted temperature management (ttm) in neurocritical care patients

Changes in body temperature are one of the main factors affecting energy requirements, with a 1°C change in temperature causing a 5-7% decrease in cerebral metabolic rate[58] and a 10-13% change in energy requirements[46]. Theoretically, when reducing the body temperature from 37°C to 33°C during TTM, at least a 40% reduction in energy requirements should occur, but in reality, a 20–30% reduction has been observed (Fig. 7)[59-61]. This difference is attributed to hypermetabolic states caused by shivering, infection, and trauma, which make accurate prediction of energy requirements challenging.

According to the POLAR-RCT study, which compared patients undergoing prophylactic TTM at 33°C for 3–7 days with traumatic brain injury patients maintaining a normal body temperature of 37°C, the average energy requirement on day 3 was 21 kcal/kg in the TTM group, a 20% reduction compared to the 27 kcal/kg in the normal body temperature group. On day 7, the TTM group's requirement was 25 kcal/kg, a 12% decrease compared to the normal group's 28 kcal/kg. After TTM, between days 8–14, a hypermetabolic state was confirmed with 33 kcal/kg[61]. In patients with cerebral infarction, energy requirements decreased by 29% during TTM at 33°C and increased to 116% after rewarming[59].

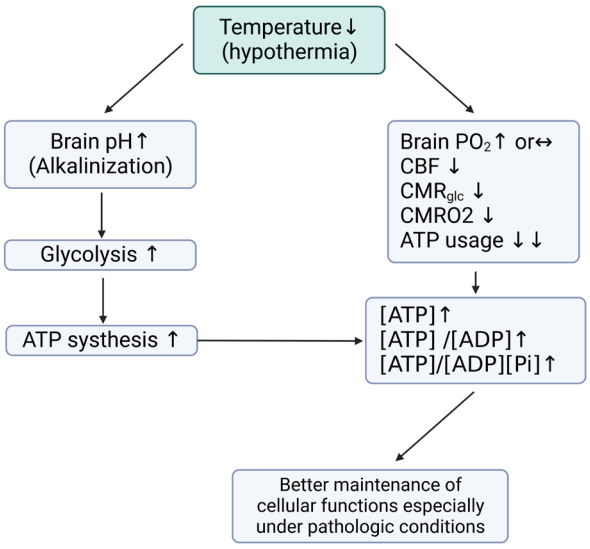

Fig. 7. Effects of hypothermia on brain energy metabolism and alkalization. This figure illustrates the sequential processes induced by hypothermia, which lead to brain alkalization and altered energy metabolism. Hypothermia results in brain alkalization, which in turn increases glycolysis and ATP production. Concurrently, hypothermia causes a decrease in cerebral blood flow (CBF), cerebral metabolic rate of glucose (CMR glucose), and cerebral metabolic rate of oxygen ($CMRO_2$), leading to reduced ATP consumption. These combined effects of hypothermia contribute to the maintenance of cellular function under pathologic conditions, such as ischemia or traumatic brain injury, by preserving energy balance and promoting neuroprotection.
$CMRO_2$: Cerebral metabolic rate of O_2, CMR: Cerebral metabolic rate of glucose, Pi: Inorganic phosphate.

Nutritional support in patients with targeted temperature management (ttm)

While early enteral nutrition is recommended for both general critically ill patients and those with severe head injuries, the appropriate nutritional support method for neurocritical care patients undergoing TTM remains unclear. Enteral nutrition should be approached with caution during TTM below 34°C due to the potential for paralytic ileus caused by reduced bowel motility and hemodynamic instability. It is often recommended to delay enteral nutrition until rewarming due to the risk of bowel ischemia or necrosis. ESICM recommends starting low-dose enteral nutrition early and increasing the supply after rewarming, although the evidence level is low (Grade 2D)[62,63].

Studies on the safety of enteral nutrition during TTM exist, and research results indicate that early enteral nutrition is safe during TTM at 33-34°C in cardiac arrest and hypoxic-ischemic encephalopathy patient groups[60,61,63-67]. An RCT study conducted in patients with traumatic brain injury showed that although the TTM group experienced more interruptions in enteral nutrition due to increased gastric residual volume, the reduced energy requirements due to TTM enabled them to better meet their energy needs compared to the normothermic group[61]. A study in patients with intracerebral hemorrhage found that enteral nutrition was delayed in TTM patients compared to the normothermic group, and the average caloric supply from days 0-3 was lower (398 kcal compared to 1006 kcal in the normothermic group). However, there was no association with adverse GI-related events or the occurrence of ventilator-associated pneumonia (VAP), indicating the feasibility of early enteral nutrition in TTM patients[64]. These studies are limited by small patient numbers and a focus on safety and meeting nutritional requirements during TTM in neurocritical care patients; no research has been conducted on improving outcomes, so caution is needed when interpreting the impact of nutrition on neurological outcomes.

Nevertheless, the benefits of enteral nutrition, including the preservation of intestinal mucosal function and maintenance of immune function, advocate for the implementation of early enteral nutrition even during targeted temperature management. It is recommended to monitor for gastrointestinal intolerance and adjust the dosage based on the patient's clinical presentation.

CONCLUSION

In conclusion, optimizing energy supply and metabolic support in neuro-critically ill patients requires a detailed understanding of the specific roles and interactions of various amino acids and micronutrients, such as branched-chain amino acids (BCAAs), methionine, serine, arginine, glutamate, and selenium. These elements are crucial in modulating neuronal function, energy metabolism, and neuroprotection, ultimately influencing patient outcomes.

BCAAs, comprising valine, leucine, and isoleucine, are precursors to the neurotransmitters glutamate and GABA, and serve as key components of the citric acid cycle. Methionine is essential for the synthesis of s-adenosylmethionine (SAM) and glutathione, both of which play pivotal roles in gene expression, cellular signaling, and protection from oxidative stress. Serine contributes to the formation of phosphatidylserine (PS), a crucial component of neuronal cell membranes that regulates synaptic receptor expression and neurotransmitter release. Arginine, a precursor to nitric oxide (NO), is involved in vascular relaxation and has been suggested as a potential therapeutic target for vascular constriction.

Understanding the complex relationship between BCAA levels and altered brain function, as well as the potential benefits of supplementing other amino acids and micronutrients, is imperative

for tailoring nutritional interventions for neuro-critical patients. Furthermore, special considerations in nutritional support encompass the assessment of energy demands, which may be influenced by the severity and etiology of brain injury, concomitant drug therapy (including sedatives and neuromuscular blockers), and targeted temperature management.

Future research should focus on elucidating the intricate relationships between these nutritional factors and their impact on neuro-critical patients, with the aim of establishing evidence-based guidelines to enhance metabolic support. By refining our understanding of these elements and tailoring nutritional interventions, we can ultimately contribute to improved patient outcomes and expedite recovery in this vulnerable population.

NOTES

Ethics statement

We confirm that, for this work ethical guidelines, ethical approvals (institutional review board) and the use of informed consent were not applicable.

Author contributions

Conceptualization: JHK, YHC, HWJ, MK, JWO, EJH, SL. Formal analysis: YBS, SHP, JHK, JOK. Writing – original draft: YHC, HK, SL. Writing – review & editing: SL.

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

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Anaesthetic Management of Systemic Injuries Requiring Surgical Intervention in Patients With Spinal Shock

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Spinal cord injury is a devastating event, and patients who have suffered a spinal cord injury may present to trauma emergency services in spinal shock. This subset of patients is likely to have concomitant systemic injuries, which may often require surgical interventions. All trauma patients should get sufficient pre-hospital care, including adequate measures to immobilize the spine. Because multiple organ systems are involved in these patients with spinal shock, anesthetic management for systemic injuries requiring surgery is challenging and necessitates a thorough understanding of the pathophysiology. The main goals of perioperative management are to provide oxygenation and maintain spinal cord perfusion to prevent secondary spinal cord injury while providing supportive care. Airway management invites a trained anesthesiologist to secure the airway while maintaining cervical spine immobilization. In this article, we review anesthetic considerations in managing spinal cord injury patients with systemic injuries in spinal shock requiring surgical interventions.

Keywords: Anesthesia; Spinal cord injury; Spinal shock

INTRODUCTION

During the year 1840, Hall coined the phrase "spinal shock"[1]. Sherrington went on to describe this as a transient cessation of reflexes below the level of spinal cord damage[2]. After an acute onset of spinal cord injury (SCI), there may be a sudden loss of reflexes and muscle tone below the level of injury. This condition is known as “spinal shock,” which can develop with SCI at any level[3]. Spinal shock should be distinguished from spinal neurogenic shock. The latter describes the symptoms of decreased systemic vascular resistance with hypotension, bradycardia, and hypothermia that develop following acute cervical and upper thoracic spinal cord damage when the regulation of the sympathetic nervous system on hemodynamic is disrupted. In this article, we want to review the anesthetic management of systemic injuries requiring surgical intervention in patients with spinal shock.

MANUSCRIPT BODY

Etiology

Spinal cord injury (SCI) can occur as a result of a variety of traumatic or non-traumatic causes. Motor vehicle collisions are the

most common traumatic cause of spinal cord injuries. Falls, violence, and sports-related injuries constitute other traumatic causes. Neoplastic, vascular, infectious, and hereditary-degenerative diseases are the common non-traumatic causes[4]. SCIs commonly affect the cervical spinal column, followed by the thoracolumbar junction[4].

Pathophysiology

The physiological function of the spinal cord will be temporarily interrupted in patients who have suffered a SCI and subsequent spinal shock. Mechanical force from bony fragments, joint dislocations, ligamentous tears, and herniated intervertebral discs usually results in cord compression and contusion during SCI, contributing to primary injury[5]. A critical fall in spinal cord perfusion due to vasospasm, injury to intramedullary arteries, and subsequent hemorrhage into gray matter causes secondary injury. Inflammation, ischemia, hypoxemia, hyperthermia, edema, and mediators from post-ischemic injury, free radical production, lipid peroxidation, ionic derangements and apoptosis of neurons are all associated with secondary damage. This underlying pathologic process causes further cord edema, which peaks 4-6 days following the damage[6,7]. The spinal cord below the level of the lesion is isolated from higher centers, and classic flaccid paralysis ensues. Early administration of high-dose methylprednisolone, as demonstrated by the National Acute Spinal Cord Injury Study (NASCIS) trials, is followed in many specialized spine centers to improve long-term neurological outcomes.

Diagnosis

Until otherwise demonstrated, the cervical spine is first assumed to be unstable in all trauma victims. The main objective of imaging is to quickly and precisely identify injuries to the spine that could endanger neural tissue. All trauma patients with risk factors for spinal cord or spine injury should have imaging done. These patients include those who have neck pain or tenderness, neurologic deficits, an impaired level of consciousness, intoxication, or painful distracting injuries. When all of these clinical risk factors are absent, a cervical spine injury can be ruled out with a high degree of confidence, according to several studies[8-10].

The antero-posterior, lateral, and odontoid views are included in standard cervical spine radiographs. Lateral films should be thoroughly examined for anomalies in vertebral alignment, bony structure, intervertebral space, and soft tissue thickening. A higher level of accuracy might be obtained by helical computed tomography (CT), which enables sagittal and three-dimensional reconstruction[11]. Magnetic resonance imaging (MRI) is the modality of choice for identifying acute cord injuries[12]. MRI also detects ligamentous injury, spinal cord edema and hemorrhage, and other non-osseous changes that may go undetected by other methods. SCI without radiographic abnormalities (SCIWORA) is the term used to describe patients with cord-induced deficits who do not have any spinal abnormality or injury that can be seen on plain radiographs or CT. It could happen in 2.8–3.8% of all spinal injuries[13,14]. Physical examinations should pay close attention to non-spinal cord injuries, which affect the head, chest, or abdomen most frequently in 20% to 60% of patients with SCI[5]. Abdominal ultrasound, CT, or diagnostic peritoneal lavage might help in ruling out intra-abdominal bleeding.

Anesthetic management

These systemic injuries may sometimes require simultaneous surgical management. Immediate resuscitation, stabilization of vital organ function, and prevention of secondary injury are the main components of the management of patients with SCI. The common systemic injuries that require emergency surgery may include, but are not limited to, any solid organ injuries, either in the thorax (lung or heart injuries leading to hemothorax) or abdomen (liver lacerations, spleen lacerations, intestinal perforations leading to hemoperitoneum, peritonitis), major vascular injuries, major pelvic injuries, and traumatic amputations of limbs.

Airway management

The place of airway management (trauma unit or operating room) is dictated by the condition of the patient. It is necessary to check the patency of the airway and, if required, support with a jaw thrust rather than a chin lift, as the former is associated with less cervical spine displacement. If the airway is patent, the patient should be given a trauma mask with high-flow oxygen. If not, it is best to intubate the trachea as soon as possible to maximize oxygen delivery and minimize hypoxic secondary injury to the injured spinal cord. Potential poor laryngoscopic view due to blood, debris, or distorted anatomy in concomitant facial trauma, immobilization of the cervical spine, and rapid sequence induction might contribute to the possibility of a difficult intubation[15].

Although cricoid pressure has been thought to dislocate the injured spine, a cadaver study using a lateral cervical spine x-ray revealed minimal spine movement when it is applied together with manual inline stabilization (MILS) [16]. MILS reduces but does not completely prevent cervical spine movement during laryngoscopy (Fig. 1) [17]. In patients under anesthesia, MILS reduces extension by 50% between the occipital bone and C1 and between C1 and C218). However, while using MILS, the laryngeal view during direct laryngoscopy may deteriorate, which could increase the chance of a failed tracheal intubation[19]. Additionally, it also in-

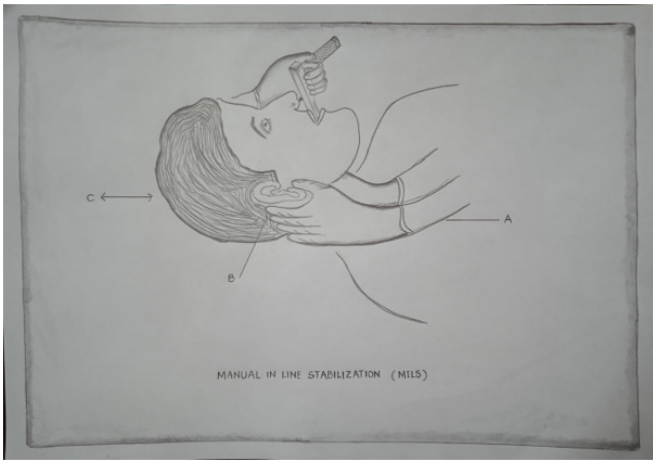

Fig. 1. Line diagram showing application of manual in-line stabilization (MILS) during direct laryngoscopy. A: rest forearms on the patient's chest; B: grasp the patient's mastoid processes and occiput with both hands; C: maintain neck alignment to limit as much movement of the head and cervical spine as possible without traction or counter-traction during laryngoscopy.

creases the maximum force transferred during direct laryngoscopy[20]. During direct laryngoscopic intubation, the gum elastic bougie is a key adjuvant to prevent displacement of the fractured spine[21]. It permits higher-grade laryngoscopy views of the vocal cords, thus reducing the forces transmitted to the spine. We have never encountered a failed intubation due to MILS. Despite higher grades of laryngoscopic views with MILS, it is routine practice in our institute to use either anterior laryngeal pressure or gum elastic bougie to facilitate tracheal intubation.

In patients with cervical spine immobilization, video laryngoscopes reduce intubation difficulty. In a cadaveric study comparing three different types of video laryngoscopes (GlideScope; C-MAC D-Blade; and McGrath MAC X-blade) with Macintosh blade, the authors concluded that all of the video laryngoscopes induced similar amounts of displacement at all cervical spine segments (C1-C6), which was much less than what was observed with the Macintosh laryngoscope[22]. There was no difference between the change in space available for cord with a Macintosh blade and the Airtraq video laryngoscope in cadaveric models of C3/C4 injury and type-2 odontoid peg fracture[23-25]. However, the King Vision aBlade did result in a lower change in space available for cord compared to a Macintosh blade in a cadaveric model of atlanto-occipital instability[26].

The choice of intubation strategy is determined by specific airway characteristics, the level of the patient's cooperation, and the operator's expertise[27]. The latter two are crucial for the success of the awake intubation. Elective airway management facilitates awake fiberoptic intubation and allows for unhurried airway topicalization. Flexible bronchoscope-guided tracheal intubation is regarded as the gold standard for patients with cervical spine injuries. This is partly because it could be done while the patient is conscious, allowing for a neurological evaluation following tracheal intubation and before general anesthesia is induced[19]. It is also a desirable choice as immobilizing devices do not need to be removed, and displacement of the spine is minimal in expert hands. However, unwanted neck movement may occur if the local airway anesthesia is ineffective. No single strategy of airway management has been proven to be superior to others. When MILS is ensured during intubation, there is no evidence to show an association between the technique of intubation and neurological decline. As a result, the operator should be able to secure the airway using the approach that they are familiar with without worrying about damaging the cord. Epistaxis, laryngospasm, and oesophageal intubation are some of the complications associated with blind nasal intubation. Less cervical spine movement is produced during intubating LMA insertion than during direct laryngoscopy[28].

Direct laryngoscopy combined with MILS is an acceptable and safe procedure. Most centers recommend rapid sequence induction with thiopentone and succinylcholine. Succinylcholine can be used safely until 48 h post-injury, after which a hyperkalemic response due to denervation hypersensitivity should be anticipated[29]. Gentle mask ventilation can be considered if the benefit of hypoxemia correction outweighs the risk of aspiration, as proper preoxygenation in the setting of emergency intubations is not always possible. The attending anesthesiologist has the option to select the anesthetic medications, and this decision is frequently influenced by the patient's clinical condition, drug availability, and institutional policies. MILS application requires additional, trained anesthesia personnel. The back of the rigid cervical collar is left in place to prevent movement of the injured cervical spine by cricoid pressure. If not, a bimanual approach with one hand under the neck, counteracting the downward pressure on the cricoid cartilage, should be used.

Monitoring

Along with standard American Society of Anesthesiologists monitors, invasive blood pressure monitoring is almost always required. It aids in beat-to-beat monitoring and facilitates sampling for arterial blood gas analysis. It is always useful to have central venous access for guiding fluid resuscitation and for the administration of a possible vasopressor or inotropic infusion. Monitoring systemic vascular resistance is advised since it is lower in patients with spinal shock. A pulmonary artery catheter or trans-oesophageal doppler may be needed in more complex cases. Ascending

sensory pathways in the posterior columns are evaluated by somatosensory evoked potentials (SSEP), whereas descending corticospinal tracts are assessed by motor evoked potentials (MEP)[30,31]. Multimodal intraoperative neuromonitoring (MEP and SSEP) may alert the operating team to any deterioration in spinal cord function and provide an opportunity to address the contributing factors during surgery. These factors include the patient's position (such as neck or shoulder position), hypotension, hypothermia, and surgical aspects of the operative procedure.

Role of immobilization

The main aim of immobilization is to prevent or restrict further secondary neurologic injury in patients with unstable spines following SCI. Because spinal injury can occur at multiple non-contiguous levels, the entire spine should be immobilized until the appropriate physical examination and imaging have ruled out injury. The proper technique of immobilization includes placement of a rigid cervical collar of suitable size, sandbags on either side of the head, attachment of adhesive tape across the forehead to each side of the trolley, transport of the patient on a hard spine board, and log-rolling wherever indicated, maintaining vertebral column alignment. However, immobilization is not without complications. More than half of the patients may develop pain, pressure sores, or diminished chest wall motion. The risk of airway compromise, difficult intubation, aspiration, and raised intracranial pressure may also increase with neck immobilization[32].

Role of steroids

In cases of acute SCI, methyl prednisolone reduces the release of interleukins, prostaglandins, and thromboxanes through its anti-inflammatory and cell membrane stabilization properties. It helps in reducing spinal cord edema and increasing perfusion to the injured cord. Methyl prednisolone (30 mg/kg IV followed by 5.4 mg/kg/h for 23 hours) and naloxone (5.4 mg/kg IV followed by 4.0 mg/kg/h for 23 hours) were compared in the NASCIS-II trail[33]. Motor function significantly improved when methylprednisolone was given within 8 hours of the injury at both 6 months and 1 year. However, the improvement was not functionally significant. In the NASCIS-III trial, further benefit was achieved by extending the administration of methyl prednisolone up to 48 h in patients who presented between 3 and 8 h after SCI. Adverse effects of steroid administration like increased blood glucose levels, myelopathy, wound infections, and gastrointestinal bleeding should be managed.

Intra operative considerations

General anesthesia is nearly always required for these surgical patients with SCI and spinal shock. Slow anesthetic induction is recommended as they are more sensitive to the hypotensive effects of anesthetic drugs on the background of relative hypovolemia and reduced sympathetic output. Additionally, positive pressure ventilation will also put them at risk of hypotension. Intraoperative fluid management for these patients with systemic injuries requiring surgical intervention can be challenging. The ideal fluid therapy for these patients remains unclear. However, it is better to avoid hypotonic crystalloids like D5W and 0.45% normal saline, which may worsen spinal cord edema. Isotonic crystalloid fluid boluses should be used to treat profound hypotension. However, repetitive fluid boluses are not advised if hypotension is found to be caused by spinal shock (as opposed to volume loss from hemorrhage caused by other injuries), and the patient should be given inotropes or vasopressors to maintain mean arterial blood pressure.

An agent having inotropic, chronotropic, and vasoconstrictive properties is required for injuries at the cervical and upper thoracic levels. Dopamine, norepinephrine, or epinephrine are substances that meet these criteria[34]. Due to its effect on vasodilation and potential for reflex bradycardia, dobutamine only has a limited role as an inotropic drug in this subset of patients[34,35]. Norepinephrine was found to be better than dopamine or phenylephrine at improving spinal cord perfusion with fewer side effects[36]. Strategies like the use of antifibrinolytic agents and recombinant factor VIIa have been shown to reduce intraoperative blood loss in these patients undergoing spine surgeries[4]. Emergency hemorrhage panel, which includes hematocrit, prothrombin time, fibrinogen and platelet count, has been developed with quick results that could guide the transfusion decisions in these patients[37].

In the prone position, pressure points need to be meticulously protected. Overzealous fluid administration in the prone position may be associated with airway edema, cardiac failure, electrolyte abnormalities and prolonged intensive care unit stay[38]. Changes in position may have major hemodynamic effects; abrupt adoption of the head-up position may cause severe hypotension through venous pooling of blood, whereas the head-down position may result in cardiac failure. A thoracotomy may be required for some injuries, and in that case, we may need to provide one-lung ventilation to facilitate surgery.

MEP monitoring necessitates total intravenous anesthesia (TIVA), which is the main impact of electrophysiologic monitoring on anesthesia practice. Inhalational anesthetics at a dose of less than 1 minimum alveolar concentration (MAC) can be used when SSEPs are being monitored. During MEP monitoring, it is recommended to avoid volatile anesthetics and nitrous oxide and use TIVA without muscle relaxation[39]. Starting at low concentrations, volatile anesthetics elicit a dose-dependent reduction in MEP signal amplitude. Opioids have no effect on evoked potential moni-

toring. Dexmedetomidine has been commonly used to reduce the dosage of propofol during the administration of TIVA[40,41]. The MAC of volatile inhalational anesthetics is unaffected by decerebration or cervical cord transection, suggesting that the site of action for the anesthetic effects is at the cord level for noxious stimuli under general anesthesia[42]. Thiopental may have a neuroprotective impact on the spinal cord[43].

Hypotensive anesthesia as a means of blood conservation is not a choice for patients with pre-existing SCI. Avoiding hypotension or hypovolemia is advised, and the mean arterial blood pressure should be kept above 80 to 85 mm Hg. This might necessitate the administration of blood and/or vasopressors. Vagal stimulation during tracheal suctioning might precipitate bradycardia and sometimes asystole. As a result, having vagolytic medications on hand and performing adequate oxygenation before attempting tracheal suction in these patients is critical. It is necessary to take the usual precautions to protect all pressure points during positioning. SCI worsens when the neck is hyperextended during positioning. Heated humidifiers and forced air warming devices will help in preventing hypothermia. Deepening the plane of anesthesia during surgery can be an effective way to address complications like autonomic dysreflexia and muscle spasms. Severe factors like type of surgery, duration of surgery, intraoperative positioning, intraoperative complications, hemodynamic stability, ease of intubation, etc. should be considered before planning extubation at the conclusion of surgery.

SPECIFIC CONSIDERATIONS

Respiratory considerations

In patients with cervical SCI, significant changes in respiratory mechanics, breathing patterns, ventilatory control, and bronchial reactivity can be observed[44]. Reduced pulmonary and chest wall compliance increases the work of breathing[45]. Rapid, shallow breathing with a restrictive pattern of pulmonary function testing is not uncommon[46]. The degree of respiratory support required in this subset of patients is determined by the level of SCI. Complete SCI above the level of C3 results in apneic respiratory arrest and death in the absence of prompt ventilatory support. Various levels of respiratory failure are linked to a C3-C5 injury. Less severe ventilatory impairment is associated with injuries below the C5 vertebra, but patients are still at risk for pulmonary complications.

Cardiovascular considerations

Systemic hypotension and reduced spinal cord perfusion pressure are typical complications of traumatic SCI[47]. They subsequently exacerbate secondary neurologic damage. Interruption of cardiac accelerator fibres (T1-T4) is proposed as the cause of bradycardia and decreased myocardial contractility. This cardiovascular depression in some of these patients may be preceded by a brief episode of acute hypertension that is assumed to be caused by the enormous, simultaneous discharge of sympathetic neurons. The subendocardial myocardial injury and neurogenic pulmonary edema that have been noted after SCI and other types of central nervous system injury may be caused by this hyperadrenergic response[48]. High SCIs can occasionally be accompanied by ECG abnormalities, including signs of subendocardial ischaemia and arrhythmias. In the presence of myocardial depression, which is common following SCI, pulmonary edema develops as a result of overzealous fluid administration to correct spinal shock.

Deep venous thrombosis

Venous thromboembolism is a specific risk for people with spinal injuries. For those who do not get prophylaxis, the incidence of deep venous thrombosis (DVT) ranges from 39% to 100%[47]. In patients with SCI, low molecular weight heparin or low-dose unfractionated heparin, combined with nonpharmacologic devices (like pneumatic compression devices and graduated compression stockings), was found to be effective for antithrombotic prophylaxis. Inferior vena cava filters should not be used as the primary thromboprophylaxis in these patients[49].

Gastrointestinal considerations

In patients with acute SCI, the risk of stress ulcers and upper gastrointestinal bleeds is increased. This is exacerbated in patients who are on mechanical ventilation and receiving high-dose steroid treatment. The risk of aspiration and subsequent postoperative pulmonary complications is also increased in this subset of the population because of gastric ileus and delayed gastric emptying. So, placing a nasogastric tube is necessary.

Neuropsychiatric considerations

A spinal cord injury is a catastrophic event and these patients may have significant psychological discomfort. Depression, anxiety disorders, substance-related disorders, and suicidal tendencies are mentioned in the literature among patients with SCI[50,51]. A humane and empathetic approach and good communication are crucial.

Autonomic dysreflexia

The most significant and pertinent SCI consequence for anesthesiologists is Autonomic dysreflexia (ADR). Symptoms can appear weeks or years after the initial injury. It is a clinical emergency with a cluster of symptoms characterized by a severe, disrupted au-

tonomic response to particular stimuli below the level of the spinal cord lesion[52]. Distension of hollow viscera (bladder, bowel, uterus, and gallbladder), cutaneous stimulation, and surgical procedures often involving pelvic organs or the lower extremities are the common triggering events[30,52]. It occurs after spinal reflexes have returned, usually after 4-6 weeks of injury. Adrenergic receptor up-regulation and abnormal synaptic connections due to postinjury sprouting are the other suggested pathophysiological mechanisms. The clinical manifestations include: an increase in blood pressure of at least 20%, headache, nausea, blurred vision, flushing, sweating, chills, nasal congestion, conjunctival congestion, pallor, and piloerection. Make the patient comfortable, remove any restrictive clothing, and look for and rule out bladder distension and constipation. Blocked urinary catheters or impacted feces must be addressed. Every effort should be made to search for the cause, and the priority of management should be the removal of the precipitating stimulus for ADR.

Follow up rehabilitation

After addressing the systemic injuries and weaning off spinal shock, all SCI patients need rehabilitation in a neuro-intensive care unit[53]. The purpose of SCI rehabilitation is to treat all compromised systems in order to help the patient regain as much independence as possible. In order to prevent pneumonia and atelectasis, the pulmonary system needs to be carefully monitored with frequent mobilization and deep inspirometry. Patients who are unable to turn themselves in bed require regular turning every two hours and the use of air mattresses to reduce pressure on these areas. Teaching patients to perform frequent self-catheterizations is part of genitourinary treatment. Suppositories and stool softeners should be used with bowel training. For the patient to adjust psychologically, support and counseling are necessary. A long-term stay of 3-6 months is usually required at specialized SCI rehabilitation facilities to achieve these objectives.

CONCLUSION

Anaesthetic management for various systemic injuries requiring surgery in SCI patients with spinal shock is challenging. A thorough understanding of the patients' cardiovascular and respiratory physiology is critical for preventing or limiting secondary SCI and improving postoperative outcomes. A skilled anesthesiologist with a proper plan for airway management while maintaining spinal alignment is crucial. A multidisciplinary team approach, along with good communication among the operative team and neuromonitoring team members, is warranted for the successful management of these patients.

NOTES

Ethics statement

This study was a literature review of previously published studies and was therefore exempt from institutional review board approval.

Author contributions

Conceptualization, Formal analysis: Sri Rama Ananta Nagabhushanam Padala, Vaishali Waindeskar, Jai Prakash Sharma, Amit Agrawal, Seema. Data curation: All authors. Writing – original draft: Sri Rama Ananta Nagabhushanam Padala, Molli Kiran, Vaishali Waindeskar, Amit Agrawal, Seema. Writing – review & editing: Molli Kiran, Jai Prakash Sharma, Amit Agrawal, Seema.

Conflict of interest

There is no conflict of interest to disclose.

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Impact of Critical Care Registered Dietitian on Clinical Outcomes of Neurocritically Ill Patients

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Background
To investigate the impact of early nutrition intervention and a critical care registered dietitian on the outcomes of neurocritically ill patients.

Methods
Among neurosurgical patients admitted to the intensive care unit (ICU) in a tertiary hospital from January 2015 to December 2019, A critical care registered dietitian co-management was initiated on May 1, 2017. The primary endpoint was ICU mortality. Propensity score matching (PSM) was used to control selection bias and confounding factors.

Results
In this study, 1,386 patients were included. In the overall study population, nutrition was provided to 719 (51.9%) patients under the supervision of a registered dietitian. Early nutrition was performed for 356 (25.7%) patients. In the overall study population and the PSM adjusted population, rates of early parenteral nutrition (EPN) were higher in the groups managed by a registered dietitian than in the group without a registered dietitian (both $p<0.001$). In the overall and PSM adjusted population, the rates of ICU mortality, 28-day mortality, and in-hospital mortality were not significant different between two groups (all $p>0.05$), but the group managed by a registered dietitian had a shorter hospital stay than the group without a registered dietitian (both $p<0.02$). In the multivariable analysis of the overall population and PSM adjusted population, EPN showed an association with ICU mortality.

Conclusion
The rate of EPN utilization increased after the implementation of co-management with a critical care registered dietitian, and the use of EPN was associated with lower ICU mortality in neurocritically ill patients.

Keywords: Enteral feeding; Prognosis; Neurosurgery; Intensive care unit

INTRODUCTION

Nutrition is a vital aspect of patient care, particularly for critically ill patients. Adequate nutrition support is essential for these patients to maintain their energy balance and achieve optimal outcomes[1-3]. In the neurocritical care setting, where patients often

suffer from severe neurological injuries and require prolonged hospitalization, nutrition management becomes even more critical[4-6]. Studies have shown that early initiation of enteral nutrition and the involvement of a registered dietitian in the care team can improve clinical outcomes in critically ill patients[7-9].

However, despite the potential benefits, there is still a significant variability in the delivery of nutrition therapy for critically ill patients, even among specialized units such as neurocritical care units[10]. The reasons for this variability are complex and multifactorial, but they may include differences in clinical practice patterns, staff knowledge and training, and resource availability[5,11]. Given the complexity of the factors that affect nutrition management in the neurocritical care setting, a multidisciplinary team approach that involves close collaboration between healthcare professionals with different expertise, such as neurosurgeons, neurointensivists, nurses, and dietitians, may be necessary to optimize nutrition management for these patients.

Therefore, in this study, we aimed to investigate the impact of early nutrition intervention and multidisciplinary team care that includes a critical care registered dietitian on the outcomes of neurocritically ill patients. We hypothesized that the involvement of a critical care registered dietitian in the neurocritical care team and the early initiation of enteral or parenteral nutrition would improve the clinical outcomes of neurocritically ill patients. We used propensity score matching to control for selection bias and confounding factors, and we assessed the outcomes of interest, including mortality, and length of hospital stay.

METHODS

Study population

The study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (No. SMC 2020-09-082) and patients' records were reviewed and published in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived by the IRB. We included patients who were hospitalized in the neurosurgical ICU for the management of neurocritical illness or for postoperative care after neurosurgery, as well as those who were hospitalized in the ICU for more than 3 days. Patients who had insufficient medical records, 'do not resuscitate' orders, were admitted to departments other than neurosurgery, or were transferred to other hospitals or had unknown prognoses were excluded from the study (Fig. 1).

Definitions and endpoints

In this study, baseline characteristics such as comorbidities, behavioral risk factors, ICU management, and laboratory data were collected retrospectively using Clinical Data Warehouse. Our center constructed a "Clinical Data Warehouse Darwin-C" designed for investigators to search and retrieve de-identified medical records from electronic archives.

A critical care registered dietitian co-management was initiated on May 1, 2017. The registered dietitian attended the weekly neurocritical care team meetings in person, and on days when not attending the meeting, she provided advice to the neurocritical care team on nutritional issues by phone after morning rounds. Patients who started enteral nutrition or parenteral nutrition within 72 hours of ICU admission were categorized as the early nutrition group. Early enteral nutrition (EEN) or early parenteral nutrition (EPN) was defined as the initiation of enteral nutrition or parenteral nutrition within 72 hours after ICU admission. The primary endpoint was ICU mortality. Secondary endpoint were 28-day mortality, in-hospital mortality and length of hospital stay.

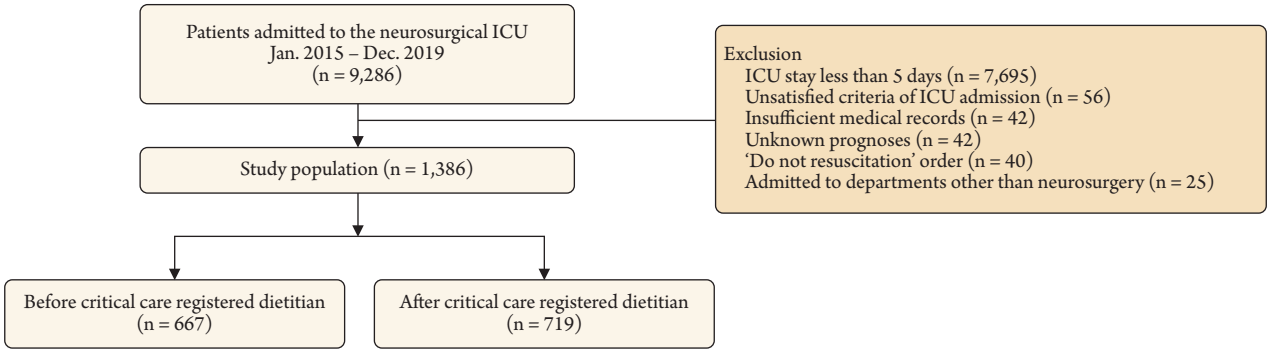

Fig. 1. Study flow chart.
ICU: Intensive care unit.

Statistical analyses

Continuous variables are presented as means ± standard deviations, while categorical variables are presented as frequencies and proportions. Data were compared using Student's t-test for continuous variables and either the chi-square test or Fisher's exact test for categorical variables. To control for selection bias and confounding factors detected in this observational study, we employed several analysis methods, including propensity score matching (PSM)[13]. In the PSM analysis, each patient was matched with one control patient using the nearest neighbor matching method within calipers determined by the propensity score. A caliper width of 0.2 of the standard deviation of the logit of the propensity score was used for the matching[14]. We compared the balance of baseline covariates between nutrition groups by calculating the standardized mean difference (SMD)[15]. If PSM analysis successfully balanced the exposure groups, the standardized mean difference (SMD) should approach zero[16]. Therefore, SMDs less than 10% were considered appropriate for achieving balance between the two groups in this study. To evaluate whether there were differences in ICU mortality according to clinical variables, we performed multiple logistic regression with stepwise variable selection in the overall population and PSM population. We aimed to obtain results that corrected confounding through regression adjustment in the overall population. Furthermore, we performed doubly robust estimation to correct any potential biases that may still exist after PSM. All tests were two-sided and p values of less than 0.05 were considered statistically significant. All statistical analyses were performed with R Statistical Software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 9,286 patients were admitted to the neurosurgical ICU during the study period and 1,386 patients were included in the final analysis. In the overall study population, nutrition was provided to 719 (51.9%) patients under the supervision of a clinical dietitian (Fig. 1). Early nutrition was performed for 356 (25.7%) patients. Malignancy (61.8%) and hypertension (34.7%) were the most common comorbidities. Brain tumors (44.6%) and intracerebral hemorrhage (15.2%) were the most common reasons for ICU admission (Table 1). There were no significant differences between before and after clinical dietitian co-management except hypertension, APACHE2 score, and use of continuous renal replacement therapy, glycerin, and vasopressor (Table 1). In PSM adjusted population, there were no significant differences of clinical variables between two groups (Table 2).

Clinical outcomes and early nutrition

In the overall study population, early nutrition was at a similar frequency in both groups (28.1 % vs. 23.5%, p = 0.068). However, the group managed by a registered dietitian had higher rate of EPN than the group without a registered dietitian (17.1% vs. 10.0%, p < 0.001). In the PSM adjusted population, rate of EPN was also higher in the group managed by a registered dietitian than in the group without a registered dietitian (17.9% vs. 10.1%, p < 0.001). In the overall study population and PSM adjusted population, the rates of ICU mortality, 28-day mortality, and in-hospital mortality were not significant different between two groups (all p > 0.05), but the group managed by a registered dietitian had a shorter hospital stay than the group without a registered dietitian (both p < 0.02) (Tables 1, 2).

In the multivariable analysis of the overall population, EEN (adjusted OR: 0.27, 95% CI: 0.09–0.68) and EPN (adjusted OR: 0.40, 95% CI: 0.18 – 0.82) showed an association with ICU mortality, whereas the presence of a registered dietitian (adjusted OR: 1.23, 95% CI: 0.76–2.00) did not demonstrate any significant association. Similar to the findings in the overall population, EPN was found to be significantly associated with ICU mortality (adjusted OR: 0.35, 95% CI: 0.12–0.86) in PSM adjusted population. However, neither EEN nor co-management with a registered dietitian showed any significant association with ICU mortality in PSM adjusted population (Table 3). In the PSM-adjusted population with a GCS below 13, there was no significant change in in-hospital mortality among those who received dietitian consultations (p = 0.497). However, a significant reduction in the incidence of infections (p = 0.007) and an enhanced early nutritional support (p = 0.018) were observed.

DISCUSSION

In this study, we investigated the impact of early nutrition intervention and multidisciplinary team care that includes a critical care registered dietitian on the outcomes of neurocritically ill patients. Major findings of this study were as follows. First, approximately one-fourth of neurocritically ill patients received early nutrition, with about one-seventh of these patients receiving support in the form of EPN. Second, following the initiation of co-management with a critical care registered dietitian, there was an increase in the rate of EPN utilization. Third, the group that received management from a registered dietitian had a shorter hospital stay compared to the group that did not receive this service. Finally, in both the overall population and the population adjusted by PSM, multivariable analysis indicated a significant association between EPN and ICU mortality.

Table 1. Baseline characteristics and clinical outcomes according to co-management of critical care registered dietitian

	Overall study population			
	Before (n = 667)	After (n = 719)	p value	SMD
Patient demographics				
Age (year)	49.2 ± 23.82	49.1 ± 24.0	0.964	0.002
Sex, male	322 (48.3)	380 (52.9)	0.099	0.092
Comorbidities				
Malignancy	396 (59.4)	449 (62.4)	0.263	0.063
Hypertension	250 (37.5)	231 (32.1)	0.042	0.113
Diabetes mellitus	95 (14.2)	102 (14.2)	0.999	0.002
Chronic kidney disease	38 (5.7)	50 (7.0)	0.396	0.052
Cardiovascular disease	24 (3.6)	23 (3.2)	0.793	0.022
Chronic liver disease	23 (3.4)	19 (2.6)	0.473	0.047
Behavioral risk factors				
Current alcohol consumption	119 (17.8)	154 (21.4)	0.108	0.09
Current smoking	60 (9.0)	74 (10.3)	0.468	0.044
Cause of ICU admission			0.028	0.224
Brain tumor	292 (43.8)	326 (45.3)		
Intracerebral hemorrhage	86 (12.9)	125 (17.4)		
Traumatic brain injury	82 (12.3)	65 (9.0)		
Subarachnoid hemorrhage	81 (12.1)	82 (11.4)		
Elective vascular surgery	58 (8.7)	65 (9.0)		
Spinal surgery	18 (2.7)	16 (2.2)		
Central nervous system infection	14 (2.1)	16 (2.2)		
Cerebral infarction	9 (1.3)	13 (1.8)		
Others	27 (4.0)	11 (1.5)		
APACHE II score on ICU admission	6.6 ± 6.4	5.9 ± 5.8	0.048	0.106
Glasgow coma scale on ICU admission	13.2 ± 3.5	13.5 ± 3.1	0.084	0.093
ICU management				
Mechanical ventilation	357 (53.5)	382 (53.1)	0.926	0.008
Continuous renal replacement therapy	22 (3.3)	9 (1.3)	0.017	0.138
ICP monitoring	279 (41.8)	279 (38.8)	0.275	0.062
Use of mannitol*	290 (43.5)	336 (46.7)	0.245	0.065
Use of glycerin*	200 (30.0)	289 (40.2)	<0.001	0.215
Use of vasopressors	52 (7.8)	178 (24.8)	<0.001	0.472
Early nutrition†	157 (23.5)	202 (28.1)	0.068	
Early enteral nutrition	90 (13.5)	79 (11.0)	0.179	
Early parenteral nutrition	67 (10.0)	123 (17.1)	<0.001	
Clinical outcomes†				
In-hospital mortality	121 (18.1)	127 (17.7)	0.872	
28-day mortality	108 (16.2)	125 (17.4)	0.602	
ICU mortality	93 (13.9)	106 (14.7)	0.728	
ICU length of stay (hour)	257.2 ± 768.7	198.4 ± 206.5	0.049	
Hospital length of stay (day)	80.1 ± 284.0	45.5 ± 134.4	0.003	

Data are presented as numbers (%) or means ± standard deviations.
*Some patients received more than one hyperosmolar agent.
†Variables are not retained in propensity score matching.
SMD: Standardized mean difference, APACHE II: Acute Physiology and Chronic Health Evaluation, ICP: Intracranial pressure, ICU: Intensive care unit, ICP: Intracranial pressure.

Registered dietitians are healthcare professionals specialized in nutrition and dietetics, possessing the credentials to assess, diagnose, and treat nutritional problems[17]. Their role encompasses a broad range of responsibilities, including the planning and implementation of medically recommended diets, patient education, and monitoring the effectiveness of dietary interventions[17]. In the neurocritical care area, the role of registered dietitians is particularly pivotal[18]. Neurological patients, whether due to traumatic brain

Table 2. Baseline characteristics and clinical outcomes according to co-management of critical care registered dietitian in propensity score-match adjusted papulation

	PSM adjusted population			
	Before (n = 542)	After (n = 542)	p value	SMD
Patient demographics				
Age (year)	46.4 ± 24.3	47.6 ± 25.0	0.423	0.049
Sex, male	274 (50.6)	268 (49.4)	0.761	0.022
Comorbidities				
Malignancy	353 (65.1)	342 (63.1)	0.527	0.042
Hypertension	177 (32.7)	184 (33.9)	0.699	0.027
Diabetes mellitus	70 (12.9)	78 (14.4)	0.536	0.043
Chronic kidney disease	28 (5.2)	29 (5.4)	0.999	0.008
Cardiovascular disease	14 (2.6)	16 (3.0)	0.853	0.022
Chronic liver disease	14 (2.6)	17 (3.1)	0.716	0.033
Behavioral risk factors				
Current alcohol consumption	105 (19.4)	107 (19.7)	0.939	0.009
Current smoking	51 (9.4)	50 (9.2)	0.999	0.006
Cause of ICU admission			0.996	0.067
Brain tumor	273 (50.4)	261 (48.2)		
Intracerebral hemorrhage	73 (13.5)	76 (14.0)		
Traumatic brain injury	46 (8.5)	52 (9.6)		
Subarachnoid hemorrhage	54 (10.0)	57 (10.5)		
Elective vascular surgery	53 (9.8)	51 (9.4)		
Spinal surgery	13 (2.4)	15 (2.8)		
Central nervous system infection	12 (2.2)	14 (2.6)		
Cerebral infarction	8 (1.5)	7 (1.3)		
Others	10 (1.8)	9 (1.7)		
APACHE II score on ICU admission	5.8 ± 5.6	6.3 ± 6.1	0.158	0.086
Glasgow coma scale on ICU admission	13.6 ± 3.0	13.6 ± 2.9	0.951	0.004
ICU management				
Mechanical ventilation	259 (47.8)	271 (50.0)	0.504	0.044
Continuous renal replacement therapy	6 (1.1)	7 (1.3)	0.999	0.017
ICP monitoring	239 (44.1)	234 (43.2)	0.806	0.019
Use of mannitol*	238 (43.9)	228 (42.1)	0.581	0.037
Use of glycerin*	182 (33.6)	183 (33.8)	0.999	0.004
Use of vasopressors	51 (9.4)	60 (11.1)	0.423	0.055
Early nutrition†	135 (24.9)	162 (29.9)	0.088	
Early enteral nutrition	80 (14.8)	65 (12.0)	0.212	
Early parenteral nutrition	55 (10.1)	97 (17.9)	<0.001	
Clinical outcomes†				
In-hospital mortality	76 (14.0)	79 (14.6)	0.862	
28-day mortality	68 (12.5)	79 (14.6)	0.375	
ICU mortality	56 (10.3)	63 (11.6)	0.560	
ICU length of stay (hour)	264.4 ± 838.6	194.7 ± 213.0	0.061	
Hospital length of stay (day)	63.6 ± 154.0	42.9 ± 116.82	0.013	

Data are presented as numbers (%) or means ± standard deviations.
*Some patients received more than one hyperosmolar agent.
†Variables are not retained in propensity score matching.
SMD: Standardized mean difference, APACHE II: Acute Physiology and Chronic Health Evaluation, ICP: Intracranial pressure, ICU: Intensive care unit, ICP: Intracranial pressure, PSM: Propensity score-match.

injuries, strokes, or other neurodegenerative diseases, often present with unique nutritional challenges. These can include dysphagia, altered metabolic rates, and specific nutrient requirements or restrictions[19]. A registered dietitian in this context plays a critical role in ensuring that these patients receive adequate and appropriate nutrition to support brain health, promote recovery, and prevent

Table 3. The relationship between critical care registered dietitian, EEN, EPN, and ICU mortality

	Adjusted Odds Ratio (95% CI)[a]	p value
Overall population		
Critical care registered dietitian	1.23 (0.76 – 2.00)	0.409
EEN	0.27 (0.09 – 0.68)	0.011
EPN	0.40 (0.18 – 0.82)	0.018
Propensity score-matched population		
Critical care registered dietitian	1.35 (0.77 – 2.37)	0.295
EEN	0.32 (0.09 – 0.90)	0.051
EPN	0.35 (0.12 – 0.86)	0.034

[a]Adjusted for age, sex, comorbidities, cause of ICU admission, utilization of organ support modalities, use of invasive ICP monitoring device, hyperosmolar therapy, and APACHE II score on ICU admission.
CI: Confidence interval, APACHE: Acute Physiology and Chronic Health Evaluation, ICP: Intracranial pressure, ICU: Intensive care unit, EEN: Early enteral feeding, EPN, Early parental feeding.

further complications. Their expertise is crucial in designing individualized nutritional plans that account for the complex interplay between neurological status, metabolic demands, and nutrient availability. Thus, the collaboration between neurocritical care teams and registered dietitians can significantly enhance patient outcomes by addressing the intricate nutritional needs inherent in this population[18].

In the management of neurocritically ill patients, the role of registered dietitian is particularly important[20]. Neurological disorders can lead to dysphagia, which can result in malnutrition and dehydration. In addition, these patients often require specialized diets to manage their conditions and prevent further complications[21]. Critical care registered dietitian can work closely with the neurocritical care team to assess the nutritional status of these patients, develop personalized nutrition plans, and monitor their response to nutrition therapy. Critical care registered dietitian can also provide recommendations for feeding modalities, such as enteral or parenteral nutrition, and work to prevent complications such as refeeding syndrome. The timely initiation of nutrition has been shown to improve patient outcomes, and registered dietitian can play an important role in developing and implementing personalized nutrition plans for neurocritically ill patients[21]. Overall, the involvement of registered dietitian in the care of critically ill neurological patients can improve outcomes, reduce complications, and ultimately contribute to their recovery.

In early stages of neurocritically ill patients, providing adequate nutritional support is crucial due to the hypermetabolic response that often follows brain injury[12,22]. Increased intracranial pressure can lead to sympathetic hyperactivation, which may have an impact on gastrointestinal dysfunction[23-25]. Furthermore, EEN on in neurocritically ill patients can elevate the risk of complications such as high gastric residual volume, delayed gastric emptying, and aspiration pneumonia[11]. Despite ongoing discussions about the ideal timing and method of feeding, a recent meta-analysis has demonstrated that EPN is more effective than EEN in reducing mortality rates and infectious complications, as well as improving outcomes in patients with traumatic brain injury during the acute gut-intolerant phase[5,26].

This study is subject to several limitations, including the fact that it relied on a retrospective review of medical records and utilized data extracted from a Clinical Data Warehouse. The use of nonrandomized registry data in this study may have introduced selection bias into the results. This study is a type of before-and-after study, so when the registered dietitian initially began working with the neurocritical care team, there may have been a window period that should have been excluded from the analysis in order to minimize the risk of bias in the study. Nutritional support for neurocritically ill patients was occasionally administered using non-protocol methods. Finally, the distribution of neurosurgical diseases in our study population differed from that typically seen in a general neurosurgical ICU, with a particularly high proportion of patients with brain tumors.

CONCLUSION

Neurocritically ill patients can face challenges in receiving appropriate nutritional support due to issues like decreased consciousness, elevated intracranial pressure, and gastrointestinal dysfunction caused by excessive sympathetic nerve activity, distinguishing them from general intensive care patients. A critical care registered dietitian considers these unique characteristics of neurocritically ill patients to provide suitable nutritional support. This tailored approach could potentially improve the overall prognosis for these patients.

NOTES

Ethics statement

The study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (No. SMC 2020-09-082) and patients' records were reviewed and published in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived by the IRB.

Author contributions

Conceptualization: HK, HJK, JAR. Methodology: HJK, JAR. Data curation: HK, JAR, Writing – original draft: HK, JAR. Formal analysis: All authors.

Conflict of interest
There is no conflict of interest to disclose.

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Data availability
None.

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Clinical Characteristics, Risk Factor and Outcome of Brain Abscess: A Retrospective Analysis During a 10-year Period

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Background
This study aimed to collect and analyze the information of patients diagnosed with primary brain abscess at our hospital over the last 10 years to determine the predisposing risk factors, clinical characteristics, and predictors of outcome.

Methods
The retrospective study evaluated hospital records and radiology data of patients diagnosed with and treated for brain abscess in our hospital from 2013 to 2022. A total of 25 patients were included in this study. Clinical characteristics of patients diagnosed with brain abscess were identified, and the surgical group and the non-surgical group were compared and the risk factors for poor prognosis were investigated. In addition, the excision and aspiration groups were compared among patients who underwent surgical treatment.

Results
Seventeen patients (68%) underwent surgery, and the remaining eight patients (32%) underwent conservative treatment. Of the 17 patients who underwent surgery, nine patients (52.94%) underwent stereotactic drainage, and eight (47.05%) underwent craniotomy, and excision. At discharge, nine patients (36%) had poor outcomes (modified Rankin Scale score 3-6), including one (5.88%) who died, and the remaining 16 (68%) had good outcomes (mRS score 0-2).

Conclusion
The most common comorbidity in the patients with brain abscess was diabetes mellitus, and Gram-positive Staphylococcus was the most common pathogen. Headache and confusion are also associated with poor outcomes. In addition, aspiration and excision had no significant differences in terms of outcomes

Keywords: Brain abscess; Aspiration; Excision

INTRODUCTION

Brain abscess is an intraparenchymal accumulation of pus. It begins with localized areas of cerebritis in the parenchyma and evolves into collections of pus enclosed in a well-vascularized capsule. It may occur as a result of spread from a contiguous focus of infection or may be of unknown origin. The reasons why brain abscess occurs include predisposing factors, such as underlying dis-

ease, a history of immunosuppressive drugs, disruption of the protective barrier surrounding the brain (e.g., neurosurgical procedure, head trauma), or a systemic source of infection (endocarditis or bacteremia)[1]. To manage patients with cerebral abscesses successfully, the infectious process is to be eliminated with an appropriate antimicrobial agent and the mass effect should be reduced using drainage or excisional procedures, thus avoiding or minimizing secondary cerebral injury and neurological deficit. Surgical excision or aspiration combined with prolonged antimicrobial therapy remains the treatment of choice. However, some factors should be considered when choosing the appropriate treatment. This study aimed to collect and analyze the information of patients diagnosed with primary brain abscess at our hospital over the last 10 years to determine the predisposing risk factors, clinical characteristics, and predictors of outcome.

MATERIALS AND METHODS

The retrospective study evaluated hospital records and radiology data of patients diagnosed with and treated for brain abscess in our hospital from 2013 to 2022. The study was approved by the Institutional Review Board (IRB) of Konyang University Hospital (No.2023-03-029). Patients who met at least one of the following criteria were included: (1) evidence of infection in brain specimens collected from surgical aspiration or excision and (2) brain magnetic resonance imaging (MRI) and/or computed tomography (CT) findings of brain abscess and reversal of brain lesions with antibiotic therapy. Patients with intracranial empyema, including those with subdural and epidural abscess, were excluded. The following factors were analyzed in all patients: age, sex, predisposing factors, location and volume of the brain abscess, initial neurological status, biological organisms, surgical procedures, duration and type of antibiotic therapy, and neurological outcomes. The neurological status of the patients was assessed on admission via physical examination. Brain abscess volume (mm^3) was calculated using the formula $0.5 \times X \times Y \times Z$, where X, Y, and Z are the largest diameters of the abscess in the X-, Y-, and Z-axes, respectively. If multiple brain abscesses were present, the largest was measured.

We conducted standard laboratory tests, including complete blood counts, c-reactive protein levels, blood and cerebrospinal fluid (CSF) cultures, and serum chemistry. Imaging diagnostic tools include enhanced CT and MRI. Stereotactic navigation-guided aspiration and resection via craniotomy were performed under general anesthesia. Empirical antibiotic treatment was initiated after diagnosis in all cases. All patients were administered intravenous antibiotics for 4–8 weeks. Factors, such as predisposing conditions, result of antibiotic susceptibility test, patient treatment response, as noted clinically and radiologically, and inflammatory laboratory parameters, were the main determinants of antibiotics. Follow-up CT imaging was performed within 24 h of the surgical procedure and weekly as part of therapeutic monitoring. At these time intervals, white and red blood cell counts and C-reactive protein levels were also monitored. Outcomes were assessed in all patients according to modified Rankin Score scores. A score of 3–6 was regarded as a poor outcome, and a score of 0–2 was regarded as a good outcome, indicating that the patient was independent in daily life.

Statistical analyses were performed using IBM SPSS 22.0. Continuous data were expressed as means ± standard deviation or median and were analyzed using the independent t-test or Mann–Whitney U test. Categorical data were analyzed using the Chi-squared test. Multivariate logistic regression analysis was performed to identify factors affecting the outcome. Statistical significance was set at $p < 0.05$.

RESULTS

Clinical characteristics

Twenty-five patients were diagnosed with brain abscess during the study period (Table 1). The mean age was 66.32 ± 13.05 years (range 34–93). Sixteen patients (64%) were males, and nine patients (36%) were females. The mean duration of hospitalization was 50.48 ± 12.3 days, and the median symptom duration at admission was 8 days. The patients' symptoms at admission included headache (n = 13, 52%), hemiplegia (10) (40%), fever (7) (28%), confusion (7) (28%), nausea and vomiting (3) (12%), seizure (3) (12 %), aphasia (5) (20%), dizziness (4) (16%), neck stiffness (2) (8%), and sore throat (1) (4%). At the time of hospitalization, fifteen patients (60%) were Good (mRS ≤ 2), eight patients (40%) were poor (mRS > 2). Sixteen patients (64%) showed improvement in mRS Score by more than 2 points at the time of discharge, and nine patients (36%) showed deterioration, including one death.

Predisposing factors and comorbidities

The most common predisposing factor in our cohort was the neurosurgical procedure (n = 8, 32%) (Table 1). Other predisposing factors included hematogenous infections, such as pneumonia, upper respiratory infection, urinary tract infection, liver abscess, viral infection (6, 24%), and adjacent infections, such as dental infection and sinusitis (5, 20%). Head trauma history (4, 16%), periodic injection drug (2, 8%), and immunosuppression, (1, 4%) were also investigated. The patients' comorbidities included immuno-

Table 1. Demographic characteristics of patients treated for brain abscess

Characteristics	Number of patients (%) (n=25)
Sex	
Male	16 (64)
Female	9 (36)
Age	
<65	14 (56)
≥65	11 (44)
Comorbidities	
Diabetes mellitus	10 (40)
Hypertension	9 (36)
Malignancy	2 (8)
Human immunodeficiency virus	1 (4)
Old stroke	1 (4)
Liver cirrhosis	1 (4)
Others	10 (40)
Predisposing factors	
Neurosurgical procedure	8 (32)
Hematogenous infection	6 (24)
Contiguous spread	5 (20)
Head trauma	4 (16)
Periodic injection drug	2 (8)
Immunosuppression	1 (4)
Symptoms and signs.	
Headache	13 (52)
Fever	5 (20)
Confusion	7 (28)
Hemiplegia	8 (32)
Nausea and vomiting	2 (8)
Seizure	2 (8)
Dysarthria	5 (20)
White blood cell count	
$<10.8 \times 10^3$ /uL	11 (44)
$\geq 10.8 \times 10^3$ /uL	14 (56)
C-reactive protein	
≥0.5 mg/dL	15 (60)
<0.5 mg/dL	10 (40)
Number of abscess	
Solitary	20 (80)
Multiple	5 (20)
Location of abscess	
Frontal lobe	7 (28)
Temporal lobe	6 (24)
Parietal lobe	7 (28)
Occipital lobe	1 (4)
Basal ganglia	2 (8)
Brain stem	1 (4)
Volume of abscess	
<1 cm^3	2 (8)
1-10 cm^3	10 (40)
>10 cm^3	1

M: Male, F: Female.

compromising diseases, such as diabetes mellitus (10, 40%), hypertension (9, 36%), Malignancy (2, 8%), liver cirrhosis (1, 4%), stroke (1, 4%), and human immunodeficiency virus (1, 4%).

Laboratory findings

Fourteen patients (56%) had elevated white blood cell counts ($>10.8 \times 10^3$ /uL), and fifteen patients (60%) had shown c-reactive protein elevation (>0.5mg/dL) on peripheral blood testing. Blood cultures were performed in eight patients (32%), and positive results were obtained in two (8%) of them; in addition, bacteria of the streptococcus anginosus and Enterococcus faecalis were isolated from each patient. Lumbar puncture was performed in 10 patients (40%), and an increased cell count ($>5 \times 10^6$ cells/L) was observed in the CSF of 7 patients (70%). Eight patients showed CSF protein levels greater than 50mg/dL. CSF culture was performed in 10 patients (40%), and positive results were obtained in two of them (20%); in addition, Staphylococcus aureus and E. faecalis were isolated from each patient. Culture of the intracerebral specimens obtained during surgery was performed in 17 patients (68%), and positive results were obtained in 10 of them (58.82%). Organisms from brain abscess material cultures are shown in Table 2.

Neuroimaging findings

Twenty patients (80%) had a single abscess, and five patients (20%) had multiple abscesses. The abscess was located in the frontal lobe in nine patients (36%), the parietal lobe in eight patients (32%), the temporal lobe in five patients (20%), the occipital lobe in one patient (4%), the basal ganglia in three patients (12%), and brainstem in one patient (4%). The median abscess volume was 15.24 cm^3 (95% confidence interval 10.37–19.52 with small (<1 cm^3), medium (1–10 cm^3), and large (>10 cm^3) lesions in two (8 %), ten (20%), and thirteen (52%) patients, respectively.

Treatment and outcome

Initial empirical antibiotic therapy included ceftriaxone, metronidazole, vancomycin, or a combination of these drugs, and was adjusted according to the results of sensitivity testing. The mean duration of antibiotic therapy was 46.34 ± 12.31 days. Surgical treatment was performed if there was a signature mass effect exerted by lesion or poor neurological deficit due to increased intracranial pressure. Seventeen patients (68%) underwent surgery, and the remaining eight patients (32%) underwent conservative treatment. Table 3 shows the comparison of patients with and without surgery, and significant differences in abscess volume ($p=0.016$) and some symptoms at admission, including headache ($p=0.011$) or hemiplegia ($p=0.003$), were observed between the two groups.

Table 2. Organisms isolated from brain abscess culture specimens

Sex	Age	Culture specimen	Organism
M	67	Intracranial purulent material	Staphylococcus epidermis
M	60	Intracranial purulent material, blood	Streptococcus anginosus
F	86	Intracranial purulent material	Escherichia coli
M	47	Intracranial purulent material, blood, CSF	Enterococcus faecalis
M	88	Intracranial purulent material	Viridans streptococcus
F	87	Intracranial purulent material	Streptococcus milleri
M	60	Intracranial purulent material	Staphylococcus aureus
F	93	CSF	Staphylococcus aureus
M	54	Intracranial purulent material	Staphylococcus aureus
F	51	Intracranial purulent material	Streptococcus intermedius
M	53	Intracranial purulent material	Citrobacter koseri

M: Male, F: Female, CSF: Cerebrospinal fluid.

At discharge, eight patients (32%) had poor outcomes, including one (5.88%) who died, and the remaining 17 (68%) had good outcomes. Multivariate analysis was performed to identify factors associated with poor outcomes. Headache (p = 0.015, 95% Confidence Interval 1.774–88.069) and confusion (p = 0.006 95% Confidence Interval 1.722–63.558) are independently associated with poor outcomes (Table 4). Of the 17 patients who underwent surgery, nine patients (52.94%) underwent stereotactic drainage, and eight (47.05%) underwent craniotomy, and excision (Table 5).

DISCUSSION

The average age of the study participants was 66 years, and 44% of them were aged more than 65 years. This is inconsistent with

Table 3. Comparison of patients with or without surgery

	Surgery (%)		No surgery (%)		Total	p-value
No of Pts	17	(68.0)	8	(32.0)	25	
Sex						
M	12	(70.6)	4	(50.0)	16	0.394
F	5	(29.4)	4	(50.0)	9	
Age						
<65	10	(58.8)	4	(50.0)	14	1.000
≥65	7	(41.2)	4	(50.0)	11	
Comorbidities	11	(64.7)	5	(62.5)	16	1.000
Headache	12	(70.6)	1	(16.7)	13	0.011
fever	4	(23.5)	2	(33.3)	6	1.000
confusion	5	(29.4)	3	(50.0)	8	1.000
hemiplegia	6	(35.3)	3	(50.0)	9	0.003
Nausea, vomiting	3	(7.6)	0		3	0.527
seizure	2	(11.8)	1	(16.7)	3	1.000
dysarthria	4	(23.5)	1	(16.7)	5	1.000
White blood cell count						1.000
$<10.8 * 10^3$ /uL	7	(41.2)	3	(37.5)	10	
$\geq 10.8 * 10^3$ /uL	10	(58.8)	5	(62.5)	15	
Number of abscess						1.000
solitary	14	(82.4)	6	(75.0)	20	
multiple	3	(17.6)	2	(25.0)	5	
Location of abscess						0.734
frontal lobe	6	(35.3)	3	(37.5)	9	
temporal lobe	4	(23.5)	1	(12.5)	5	
parietal lobe	4	(23.5)	4	(50.0)	8	
occipital lobe	1	(5.9)	0		1	
basal ganglia	2	(11.8)	0		2	
brain stem	0		1	(12.5)	1	
Volume of abscess						0.016
$<1cm^3$	1	(5.9)	1	(12.5)	2	
1-10 cm^3	4	(23.5)	6	(75.0)	10	
$>10cm^3$	12	(70.6)	1	(12.5)	13	

M: Male, F: Female.

Table 4. Risk factors related to functional outcome in brain abscess patients

	good outcome (%)		Poor outcome (%)		Total No	P-value	P, Regression (OR*, 95% CI*)	
No of Pts	17		8		25			
Sex						0.071		
M	13	(76.5)	3	(37.5)	16			
F	4	(23.5)	5	(62.5)	9			
age						0.395		
<65	12	(70.6)	2	(25)	14			
≥65	5	(29.4)	6	(75)	11			
Comorbidities	11	(73.3)	5	(62.5)	16	0.657		
Headache	11	(78.6)	2	(25)	13	0.039	0.015	(12.359, 1.774-88.069)
fever	3	(21.4)	2	(25)	5	1		
confusion	1	(7.1)	6	(75)	7	0.002	0.006	(20.458, 1.722-63.558)
hemiplegia	5	(35.7)	3	(37.5)	8	1		
Nausea and vomiting	2	(14.3)	0		2	0.526		
seizure	1	(7.1)	1	(12.5)	2	1		
dysarthria	2	(14.3)	3	(37.5)	5	0.297		
White blood cell count						0.086		
$<10.8 * 10^3$ /uL	10	(53.3)	1	(12.5)	11			
$\geq 10.8 * 10^3$ /uL	7	(46.7)	7	(87.5)	14			
Number of abscess						0.103		
solitary	15	(93.3)	5	(62.5)	20			
multiple	2	(6.7)	3	(37.5)	5			
Location of abscess						0.59		
frontal lobe	5	(33.3)	2	(25)	7			
temporal lobe	5	(33.3)	1	(12.5)	6			
parietal lobe	3	(20)	4	(50)	7			
occipital lobe	1	(6.7)	0		1			
basal ganglia	1	(6.7)	1	(12.5)	2			
brain stem			1	(12.5)	1			
Volume of abscess						0.788		
$<1cm^3$	2	(11.8)	0	(37.5)	2			
1-10 cm^3	7	(41.2)	3	(62.5)	10			
$>10cm^3$	8	(47)	5	(75)	13			
Surgical treatment	11	(64.7)	6	(25)	17	0.331		
Conservative treatment	6	(35.3)	2		8			

M: Male, F: Female, OR: Odds Ratio, CI: Confidence interval.

previously published reports associated with the age predilection of brain abscess. Some studies showed that individuals older than 40 years are more susceptible to brain abscess[2,3,4], whereas others revealed that brain abscess occurs more often in individuals younger than 40 years[5,6]. The average age of participants in a meta-analysis conducted in 2014 was 33.6 years[7]. Therefore, it is considered difficult to determine the most affected age group.

Twenty-one (84%) patients suffering from brain abscess had some predisposing factors. The neurosurgical procedure was the most common predisposing factor. When the blood-brain barrier is damaged, the brain becomes extremely vulnerable to bacterial infections. Each of the five patients (20%) experienced infection in adjacent areas, such as sinusitis, chronic otitis media, and dental or hematogenous infection. Most patients with brain abscess have predisposing conditions, which may provide clues toward causative micro-organisms[8]. The contagious spread of bacteria occurs in half of the cases and can result from penetrating trauma, neurosurgery, or infections[1,8]. Comorbidities, including diabetes mellitus, hypertension, tumor, liver cirrhosis, and a history of stroke, were noted in 72% of the patients in our cohort. Diabetes mellitus was the most common comorbidity observed in this study. The relationship between diabetes mellitus and susceptibility to infection has been reported[9]. Impaired glucose control may affect host defense and increase the risk of brain abscess. Our study differs from the previous reports. Other reports explained that a history of stroke was reported to be a common comorbidity, as damaged brain tissues might be vulnerable to invasion by infectious organisms[10]. Other comorbidities, including human immunodeficiency

Table 5. Comparison of aspiration and excision groups in brain abscess patients

	aspiration (%)		Excision (%)		Total No	p-value
No of Pts	9		8		17	
Sex						
M	6	(66.7)	6	(75.0)	12	1.000
F	3	(33.3)	2	(25.0)	5	
Age						
<65	5	(55.6)	5	(62.5)	10	1.000
≥65	4	(44.4)	3	(37.5)	7	
Comorbidities	5	(55.6)	6	(75.0)	11	1.000
Headache	8	(88.9)	4	(50.0)	12	0.131
Fever	2	(22.2)	2	(25.0)	4	1.000
Confusion	3	(33.3)	2	(25.0)	5	1.000
Hemiplegia	3	(33.3)	3	(37.5)	6	1.000
Nausea and Vomiting	3	(33.3)	0		3	0.206
Seizure	2	(22.2)	0		2	0.471
Dysarthria	1	(11.1)	3	(37.5)	4	0.294
White blood cell count						1.000
$<10.8\times10^3$ /uL	4	(44.4)	3	(37.5)	7	
$\geq10.8\times10^3$ /uL	5	(55.6)	5	(62.5)	10	
Number of abscess						0.576
solitary	8	(88.9)	6	(75.0)	14	
multiple	1	(11.1)	2	(25.0)	3	
Location of abscess						0.101
Frontal lobe	2	(22.2)	4	(50.0)	6	
Temporal lobe	4	(44.4)	0		4	
Parietal lobe	2	(22.2)	2	(25.0)	4	
Occipital lobe	1	(11.1)	0		1	
Basal ganglia	0		2	(25.0)	2	
Brain stem	0		0			
Volume of abscess						0.050
$<1cm^3$	1	(11.1)	0		1	
1-10 cm^3	4	(44.4)	0		4	
$>10cm^3$	4	(44.4)	8	(100.0)	12	
Outcome						0.335
Good (mRS≤2)	7	(77.8)	4	(50.0)	11	
Poor (mRS>2)	2	(22.2)	4	(50.0)	6	
Duration of hospitalization (days)	53.4		51.8			0.464

M: Male, F: Female.

virus infection, autoimmune disease, and immunosuppressive therapy, were reported in a previous study[11]. However, only a few patients had these comorbidities.

The clinical presentation of brain abscess depends on the site, size, number of lesions, and any secondary cerebral injuries. Similar to previous study[12], our cases were also frequently presented with classical symptom triad of this disease, such as headache, fever, and hemiplegia in our study, occurring in 52%, 40%, and 28% of the patients, respectively. The symptoms were atypical, and the absence of this classical clinical triad decreased the likelihood of brain abscess being suspected on initial examination. In addition, the advancement of MR technology, including perfusion- and diffusion-weighted images and MR spectroscopy, has made a more accurate diagnosis of cerebral abscess and differentiation from other ring-enhancing lesions possible[13,14]. Sixty percent of the patients in this study had an elevated peripheral white blood cell count. Indicators of inflammation, such as white blood cell count and c-reactive protein level, were useful indicators of clinical response to treatment, but not helpful in diagnosing brain abscess or in predicting outcome due to another infection in which the patient is present[15]. An increased cell count in the CSF, which indicates leptomeningeal infection, was observed in 70% of the patients who underwent lumbar puncture in this study, and this finding helped us determine the nature of the brain lesion in those patients. However,

not all patients with brain abscess show leptomeningeal involvement, and the role of lumbar puncture in diagnosis is limited.

The rate of brain abscess purulent material culture positivity in our study was 48%, which is far lower than the previously reported rate of approximately 70%[7,16]. This may be because we initiated antibiotic therapy before obtaining samples for culture, and the standard culture protocol followed at our hospital may result in certain organisms being undetected. In addition, operations in the referral cases from other non-neurosurgical departments were delayed. In our study, gram-positive Staphylococcus was the most common pathogen observed in the material culture of brain abscesses. In previous studies, the most commonly observed bacteria in patients with brain abscesses were those of the Streptococcus species from 1952 to recent days[15]. With the development of culture techniques and microbiological analysis, the trend is toward a high incidence of infection with polymicrobial and gram-negative organisms in today's causative organism[17,18].

The most common brain abscess location in our study was the frontal lobe, followed by the parietal and parietal lobes. Most patients had single lesions. This result is consistent with a previous report[1,3]. However, another study found that the temporoparietal region is the most common brain abscess location[19]. The location of a brain abscess partly depends on the route of infection transmission[20]. Brain abscesses related to direct spread from sinus or odontogenic foci tend to be frontal and are caused by aerobic or anaerobic streptococci, Enterobacteriaceae, Staphylococcus aureus, and anaerobes. An abscess secondary to an otic infection is usually temporal or cerebellar, with mixed flora, including anaerobes and streptococci (aerobic and anaerobic), Enterobacteriaceae, and Pseudomonas aeruginosa.

The treatment of brain abscesses is aimed at reducing space-occupying activity, lowering intracranial pressure, and eradicating pathogenic microorganisms; thus, brain abscess is basically a surgical lesion. Surgery allows the immediate reduction of intracranial pressure from a mass effect and the identification of the causative organism. In addition, surgical treatment by aspiration or excision is more likely to lead to shorter treatment and decrease the possibility of serious clinical deterioration With intraventricular rupture. However, recently, there have been a few reports demonstrating successful non-operative treatment of brain abscess with antibiotics alone[12,15]. The cerebritis phase refers to abscesses in an early stage of formation, in which there is inward migration of leukocytes and significant secondary edema, but no well-formed fibrous capsule. Therefore, these abscesses are usually observed in the first 0–9 days of development[21,22], and because they are not encapsulated, antibiotic therapy is more likely to provide adequate therapy without surgery[23-25]. In our study, 68% of the patients underwent surgery. We observed a significant difference in abscess volume between patients with and without surgery; however, no difference was observed in the number of abscesses. A previous study showed that the number or size of abscesses or midline shifts may affect the decision for surgical therapy[10]. Patients with headaches or hemiplegia were significantly more likely to undergo surgery. When these symptoms are visible, families tend to make more surgical decisions to improve their quality of life.

In choosing between aspiration or excision, the choice of procedure remains controversial[26,27]. Several reports have advocated excision as the procedure of choice because it is often followed by a lower incidence of recurrence and shorter hospitalization[28-30]. Recently, based on their good treatment outcome with craniotomy and lesionectomy, they recommended that indication for early surgical excision of brain abscess are single, accessible, superficial, and larger lesion accompanying aggravated neurological deficit[31]. However, recent studies indicated that the stereotactic management of brain abscess allow both confirmation of the diagnosis and institution of therapy by the aspiration of its contents and identification of the offending organism, which has become primarily widespread with the introduction of CT-guided stereotaxy[6,29,32]. In our cohort study, there was no significant difference between the excision and aspiration groups (Table 5). A previous study found no difference in the effects, outcomes, and complications of these two surgical techniques[3]. Xiao et al.[15] also reported that favorable outcome was not significantly different between the patient treated by excision or aspiration. These varying results could be considered that the aspiration group may be associated with more multiple abscesses and poor general conditions, whereas the excision group may have a more favorable abscess position that can be completely removed by craniotomy and a good general condition.

Previous studies have reported inconsistent findings regarding the factors associated with outcomes. Age, immunosuppression, and hematogenous spread were found to be associated with a poor outcome in brain abscess patients[2]. Meanwhile, it was revealed that sex was associated with an unfavorable outcome[3]. Another study found that consciousness at presentation had prognostic value[19]. In our study, headache and confusion influenced outcomes. As a classical symptom of brain abscesses, headache indicates possible intracranial hypertension, which may lead to a poor outcome. A confused mentality can lead to a poor prognosis because it suggests high intracranial pressure. This study has several limitations. The sample size is small. In addition, this was a retrospective single-center study. Therefore, our findings may not be generalizable to patients in different regions, and some data could not be collected or analyzed. Multicenter studies with larger sample sizes are warranted.

CONCLUSION

The most common comorbidity in the patients with brain abscess included in this study for over 10 years was diabetes mellitus, and Gram-positive Staphylococcus was the most common pathogen. Headache and confusion are also associated with poor outcomes. In addition, aspiration and excision had no significant differences in terms of outcomes.

NOTES

Ethics statement

The study was approved by the Institutional Review Board (IRB) of Konyang University Hospital (No.2023-03-029).

Author contributions

Conceptualization, Methodology: All authors. Data curation, Formal analysis, Investigation, Resources, Writing – original draft: JSP. Supervision, Validation, Writing – review & editing: EGS.

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

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Evaluating the Prognostic Efficacy of Scoring Systems in Neurocritical and Neurosurgical Care: An Insight into APACHE II, SOFA, and GCS

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Background
To investigate the utility of established prognostic scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS), for patients admitted to a neurosurgical intensive care unit (ICU).

Methods
Among neurosurgical patients admitted to the neurosurgical ICU in a tertiary hospital from January 2015 and December 2022, only patients who had an ICU stay exceeding three days were included. The primary endpoint was in-hospital mortality.

Results
In this study, a total of 3,417 patients were enrolled in the study. Of these, 3,052 (89.3%) survived until hospital discharge. Both the APACHE II and SOFA scores were significantly higher in non-survivors than in survivors ($p<0.001$ for both). Conversely, GCS and GCS motor score (GCS M) were substantially lower in non-survivors ($p<0.001$). Among the commonly used scoring systems, the APACHE II score emerged as the most effective predictor of in-hospital mortality (C-statistic of 0.887, 95% confidence interval: 0.869–0.887). Remarkably, the GCS M proved to be equally effective as the SOFA score in predicting in-hospital mortality ($p=0.435$) and offered the additional advantage of being simpler to use.

Conclusion
Our findings indicate that these scoring systems offer valuable insights into the clinical prognosis of patients in the neurosurgical ICU. Moreover, the GCS M stands out as a feasible and reliable metric for predicting in-hospital mortality among neurosurgical ICU patients.

Keywords: APACHE; Organ dysfunction scores; Glasgow coma scale; Prognosis; Intensive care unit.

INTRODUCTION

The prognosis of critically ill patients remains an intricate yet crucial component in the management and decision-making processes within intensive care units (ICU)[1,2]. Several scoring systems like the Acute Physiology and Chronic Health Evaluation

(APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS) are often utilized to gauge the severity of a patient's condition and to predict clinical outcomes[3-5]. While these scores have proven valuable in general ICUs, they are not without limitations—especially when applied to specialized areas like neurointensive care.

The landscape of neurointensive care presents unique challenges and complexities, often demanding a specialized approach to both management and prognosis[6]. Neurocritically ill patients often suffer from a wide array of neurological injuries and diseases, ranging from traumatic brain injuries to strokes, each with distinct pathophysiologies and prognostic indicators[7,8]. Despite the growing body of research in critical care medicine, there is currently a paucity of scoring systems that are specifically tailored for predicting outcomes in neurointensive care settings. In addition, there is a limited body of research investigating the efficacy of established scoring systems like APACHE II score, SOFA score, and GCS in predicting outcomes specifically for patients in neurointensive care settings. Generally, these prognostic scoring systems have been commonly used for predicting clinical outcomes in critically ill patients. Therefore, the aim of this study was to assess the utility of established prognostic scoring systems, such as the APACHE II score, SOFA score, and GCS, for patients admitted to a neurosurgical ICU.

METHODS

This was a retrospective, single-center, observational study conducted on patients admitted to the neurosurgical intensive care unit (ICU) of a tertiary referral hospital (Samsung Medical Center, Seoul, Korea) between January 2015 and December 2022. The study received approval from the Institutional Review Board (IRB) of Samsung Medical Center (No. SMC 2020-09-082) and was carried out in compliance with the principles of the Declaration of Helsinki. Given the retrospective design of the study, the IRB waived the requirement for informed consent. Our study population consisted of patients who had been admitted to the Neurosurgical ICU for the management of neurocritical illnesses or for postoperative care following neurosurgical procedures. Furthermore, only patients who had an ICU stay exceeding three days were included. We excluded patients with incomplete medical records, those with 'Do Not Resuscitate' orders, those admitted to departments other than Neurosurgery, or those transferred to other facilities with unknown prognoses (Fig. 1).

Definitions and endpoints

In this study, we retrospectively collected baseline characteristics including comorbidities, behavioral risk factors, ICU management strategies, and laboratory data through our Clinical Data Warehouse, known as "Darwin-C." This platform was specifically designed to enable researchers to search and retrieve de-identified medical records from electronic archives. In this study, results of blood laboratory tests as well as APACHE II score, SOFA score, and GCS were automatically extracted from the medical records. The APACHE II score was calculated based on initial values from 12 routine physiological measurements, age, and pre-existing health conditions to provide a comprehensive measure of disease severity[9]. An increasing score, ranging from 0 to 71, was strongly correlated with the risk of subsequent in-hospital mortality[9]. The SOFA score was determined by evaluating individual components related to respiratory, coagulation, liver, cardiovascular, central nervous system, and renal functions, as described in a prior study[10]. Both the APACHE II and SOFA scores were computed using the worst values recorded during the initial 24 hours following ICU admission. For intubated patients, the verbal component of the GCS was estimated using eye and motor scores, in accordance with previously established methods[11]. Invasive intracranial pressure (ICP) monitoring was performed by neurosurgeons. The decision to initiate ICP monitoring was primarily based on brain imaging findings and the patient's clinical condition. Specifically, the presence of space-occupying lesions, such as brain tumors, abscesses, and intracranial hemorrhages (including epidural hematoma, subdural hematoma, and intraparenchymal hematoma), warranted monitoring when increased ICP was suspected. In cases presenting with cerebrospinal fluid flow obstruction due to hydrocephalus, an external ventricular drain was predominantly used. Furthermore, in instances of cerebral edema or when clinically suspected increased ICP was evident, invasive ICP monitoring was employed,

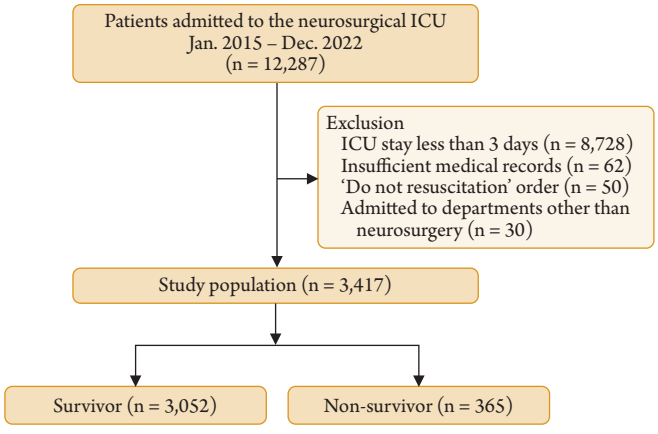

Fig. 1. Flowchart of the study.
ICU: intensive care unit.

contingent on the neurosurgeon's assessment, to facilitate neuromonitoring. The primary endpoint of this investigation was in-hospital mortality.

Statistical analysis

Continuous variables are presented as means with standard deviations, while categorical variables are shown as counts and corresponding percentages. Statistical comparisons were made using Student's t-test for continuous variables and either the chi-square test or Fisher's exact test for categorical ones. The predictive performance of each scoring system was assessed through the areas under the receiver operating characteristic (ROC) curves, with sensitivity plotted against 1-specificity. The areas under the curves (AUCs) were compared using DeLong et al.'s nonparametric approach for evaluating two correlated AUCs[12]. Clinically relevant variables—such as severity scoring systems, age, sex, comorbidities, behavioral risk factors, reasons for ICU admission, and ICU management practices—were subjected to multiple logistic regression analysis to identify statistically significant predictors. The adequacy of the prediction model was evaluated using the Hosmer-Lemeshow test, as well as the AUCs. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Data analysis was conducted using R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics and clinical outcome

A total of 3,417 patients were enrolled in the study. Of these, 3,052 (89.3%) survived until hospital discharge. The median age of the patients was 55.7 ± 17.0 years, and 1,779 (52.1%) were male. The most prevalent comorbidities among the study population were malignancy (72.1%) and cerebrovascular disease (31.0%). The leading cause of ICU admission was brain tumor, accounting for 62.1% of cases. Among patients with brain tumors, the most common reasons for ICU admission were post-operative care (39.5%) and neuromonitoring (17.2%). Interventions such as mechanical ventilation, intracranial pressure monitoring, the use of multiple hyperosmolar agents, and vasopressor and inotropic agent administration were more frequently observed in non-survivors. A comparative analysis of the baseline characteristics between survivors and non-survivors is presented in Table 1.

Relationship between APACHE II, SOFA, and GCS

A comparison of severity scoring systems between survivors and non-survivors is presented in Table 2. Both the APACHE II and SOFA scores were significantly higher in non-survivors than in survivors ($p < 0.001$ for both). Conversely, GCS and GCS M were substantially lower in non-survivors ($p < 0.001$). Multivariable analysis revealed that the APACHE II score (adjusted odds ratio [OR]: 1.19, 95% confidence interval [CI]: 1.15–1.23), SOFA score (adjusted OR: 1.13, 95% CI: 1.07–1.19), and GCS M (adjusted OR: 0.72, 95% CI: 0.64–0.81) were significant predictors of in-hospital mortality. Other variables, including malignancy (adjusted OR: 1.47, 95% CI: 1.09–2.01), mechanical ventilation (adjusted OR: 1.92, 95% CI: 1.33–2.80), continuous renal replacement therapy (adjusted OR: 2.79, 95% CI: 1.38–5.61), and ICP monitoring (adjusted OR: 0.61, 95% CI: 0.44–0.84) were also significantly associated with in-hospital mortality. The model demonstrated good fit with a Hosmer–Lemeshow Chi-squared value of 6.135 ($df = 8$, $p = 0.632$) and an AUC of 0.906 (95% CI 0.890–0.923) (Table 3).

In the ROC curve analysis for predicting in-hospital mortality, the APACHE II score demonstrated superior performance with a C-statistic of 0.887 (95% CI: 0.869–0.887), which was greater than that of the SOFA score (C-statistic: 0.783, 95% CI: 0.757–0.783), GCS (C-statistic: 0.833, 95% CI: 0.808–0.833), and GCS M (C-statistic: 0.796, 95% CI: 0.769–0.796) (all $p < 0.01$).

Moreover, the AUC for GCS was greater than those for the SOFA score and GCS M (both $p < 0.01$). However, there was no significant difference in predictive performance between the SOFA score and GCS M ($p = 0.435$) (Fig. 2).

DISCUSSION

In this study, we evaluated the utility of widely recognized prognostic scoring systems—namely, the APACHE II score, SOFA score, and GCS—in neurocritically ill and neurosurgical patients. Our major findings can be summarized as follows: First, statistically significant differences were observed in the APACHE II, SOFA, GCS, and GCS M scores between survivors and non-survivors. Second, multivariable analysis identified several variables, including APACHE II score, SOFA score, GCS M, malignancy, mechanical ventilation, continuous renal replacement therapy, and ICP monitoring, as significantly associated with in-hospital mortality. Among the commonly used scoring systems, the APACHE II score emerged as the most effective predictor of in-hospital mortality. Remarkably, the GCS M proved to be equally effective as the SOFA score in predicting in-hospital mortality and offered the additional advantage of being simpler to use. In conclusion, all the evaluated scoring systems, including the APACHE II score, SOFA score, GCS, and GCS M, demonstrated utility in predicting clinical outcomes in patients admitted to a neurosurgical ICU.

Table 1. Baseline characteristics according to in-hospital mortality

	Survivor (n = 3,052)	Non-survivor (n = 365)	P value
Patient demographics			
Age (year)	55.2 (17.0)	60.7 (16.2)	<0.001
Sex, male	1587 (52.0)	192 (52.6)	0.871
Comorbidities			
Malignancy	2261 (74.1)	204 (55.9)	<0.001
Cerebrovascular disease	871 (28.5)	188 (51.5)	<0.001
Hypertension	423 (13.9)	93 (25.5)	<0.001
Dyslipidemia	303 (9.9)	66 (18.1)	<0.001
Diabetes mellitus	230 (7.5)	56 (15.3)	<0.001
Chronic kidney disease	70 (2.3)	26 (7.1)	<0.001
Chronic liver disease	52 (1.7)	16 (4.4)	0.001
Cardiovascular disease	45 (1.5)	12 (3.3)	0.019
Behavioral risk factors			
Current alcohol consumption	591 (19.4)	70 (19.2)	0.988
Current smoking	308 (10.1)	34 (9.3)	0.708
Primary disease of ICU admission			<0.001
Brain tumor	1983 (65.0)	140 (38.4)	
Malignant brain tumor	733 (24.0)	29 (7.9)	
Benign brain tumor	494 (16.2)	17 (4.7)	
Brain metastasis	704 (23.1)	76 (20.8)	
Hematolymphoid tumor	52 (1.7)	18 (4.9)	
Intracerebral hemorrhage	217 (7.1)	61 (16.7)	
Traumatic brain injury	193 (6.3)	60 (16.4)	
Subarachnoid hemorrhage	201 (6.6)	43 (11.8)	
Elective vascular surgery	172 (5.6)	14 (3.8)	
Cerebral infarction	99 (3.2)	12 (3.3)	
Central nervous system infection	45 (1.5)	13 (3.6)	
Epilepsy	28 (0.9)	1 (0.3)	
Others	114 (3.7)	21 (5.8)	
Cause of ICU admission			0.036
Post-operative management	1955 (64.1)	202 (55.3)	
Neuromonitoring	846 (27.7)	129 (35.3)	
Respiratory failure	61 (2.0)	10 (2.7)	
Pre-operative management	27 (0.9)	4 (1.1)	
Cardiovascular disease	14 (0.5)	2 (0.5)	
Postcardiac arrest syndrome	14 (0.5)	0 (0.0)	
Post-procedural management	11 (0.4)	3 (0.8)	
Others	124 (4.1)	15 (4.1)	
ICU management			
Mechanical ventilation	1045 (34.2)	305 (83.6)	<0.001
Continuous renal replacement therapy	29 (1.0)	28 (7.7)	<0.001
ICP monitoring	745 (24.4)	107 (29.3)	0.047
Use of mannitol*	2294 (75.2)	248 (67.9)	0.003
Use of glycerin*	825 (27.0)	188 (51.5)	<0.001
Use of more than one hyperosmolar agent	2309 (75.7)	258 (70.7)	0.044
Use of vasopressors and inotropic agent	24 (0.8)	21 (5.8)	<0.001

Data are presented as numbers (%) or means ± standard deviations.
*Some patients received more than one hyperosmolar agent.
ICU: Intensive care unit, ICP:, Intracranial pressure.

Table 2. Severity scoring systems between survivors and non-survivors

	Survivor	Non-survivor	p value
APACHE II score	11.22 ± 5.22	21.70 ± 6.78	<0.001
SOFA score	1.97 ± 2.18	5.10 ± 3.38	<0.001
GCS	13.42 ± 2.64	8.05 ± 4.43	<0.001
GCS M	5.66 ± 0.88	3.61 ± 1.94	<0.001

Data are presented as means ± standard deviations.
APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, GCS M: motor score of GCS.

Table 3. Predicting factors for in-hospital mortality in neurocritically ill patients and neurosurgical patients assessed using logistic regression model

	Adjusted Odds Ratio[a] (95% CI)	p value
APACHE II score	1.19 (1.15 – 1.23)	<0.001
SOFA score	1.13 (1.07 – 1.19)	<0.001
GCS M	0.72 (0.64 – 0.81)	<0.001
Malignancy	1.47 (1.09 – 2.01)	0.014
Mechanical ventilation	1.92 (1.33 – 2.80)	0.001
Continuous renal replacement therapy	2.79 (1.38 – 5.61)	0.004
ICP monitoring	0.61 (0.44 – 0.84)	0.003

[a]Adjusted for severity scoring systems, age, sex, comorbidities, habitual risk factors, causes of intensive care unit (ICU) admission, and ICU management.
CI: Confidence interval, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, GCS M: Motor score of GCS, ICP: Intracranial pressure.

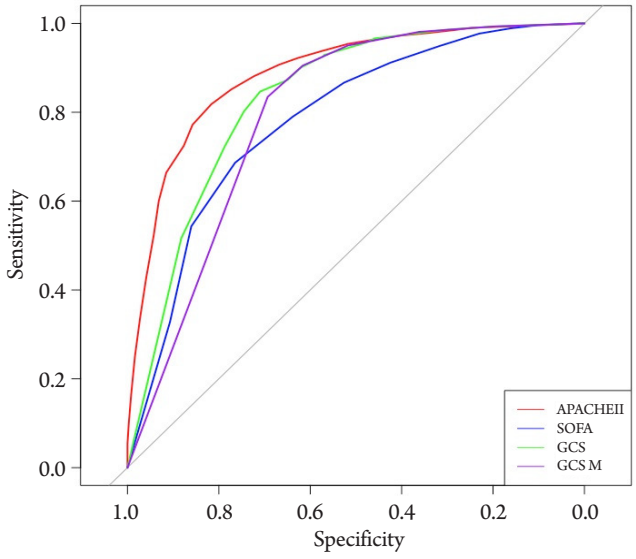

Fig. 2. Receiver operating characteristic curves for prediction of in-hospital mortality using Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale (GCS) and motor score of GCS (GCS M).
AUC: areas under the curve, CI: confidence interval.

In the complex and dynamic environment of the ICU, the utilization of validated scoring systems like the APACHE II and the SOFA score becomes imperative for several reasons. These scoring systems provide healthcare providers with a structured, evidence-based framework to assess the severity of illness, enabling timely and appropriate medical interventions[13]. By offering a quantitative measure of disease severity, these scores help in stratifying patients based on risk, thereby aiding in the allocation of vital resources and guiding clinical decision-making[14,15]. Additionally, they facilitate more transparent and data-driven discussions with family members about the potential prognosis and assist in cost-benefit analyses[14,15]. Importantly, they can also serve as valuable research tools, providing a standardized measure of patient severity that allows for meaningful comparisons across studies and settings. Despite their limitations and the need for periodic updates and revisions, the centrality of such scoring systems in optimizing patient outcomes in the ICU cannot be overstated. Generally, prognostic scoring systems are invaluable for assessing disease severity, conducting cost-benefit analyses, and informing clinical decision-making[3,5]. However, many of these systems are complicated and challenging to implement, particularly in critically ill patients[16]. Given these limitations, there is a need for simplified yet reliable scoring systems. In this context, the GCS M score emerges as a feasible and reliable metric for predicting in-hospital mortality among neurocritically ill and neurosurgical patients[17].

The APACHE II score may have advantages over other commonly used indices like the SOFA score or the GCS in certain contexts[9]. APACHE II not only incorporates a wide range of physiological variables but also considers age and pre-existing comorbidities, thus providing a comprehensive overview of a patient's condition[4]. This multidimensional approach potentially allows for a more nuanced risk stratification of ICU patients, which can be crucial for tailoring treatment strategies and resource allocation. Additionally, APACHE II's more extensive set of criteria might offer higher predictive validity for a broader spectrum of diseases and complications, making it a more versatile tool in diverse clinical settings[18]. While all of these scoring systems serve the essential function of aiding prognosis and guiding treatment, the unique features of APACHE II may render it particularly effective in capturing the complex interplay of factors that determine outcomes in critically ill patients. Therefore, in this study, the APACHE II score demonstrated greater predictive accuracy for clinical prognosis of patients in the neurosurgical ICU[19].

This study has several limitations. First, this was a retrospective review of medical records and data extracted from the Clinical Data Warehouse. The nonrandomized nature of registry data might have resulted in a selection bias. Second, in measuring the

GCS, we estimated the verbal score for intubated patients based on their eye and motor scores, following the methodology used in previous studies[11]. However, it should be acknowledged that this approach may not be entirely flawless. Third, in our study, unlike other ICU research, there was a disproportionately high prevalence of patients with malignancy and brain tumors. Although the present study provides valuable insights, prospective large-scale studies are needed to further confirm the usefulness of severity scoring systems in predicting clinical outcomes of neurocritically ill patients with evidence-based conclusions.

CONCLUSION

In this study, we explored the utility of well-established prognostic scoring systems, including the APACHE II score, SOFA score, and GCS, for assessing outcomes in neurocritically ill and neurosurgical patients. Our findings indicate that these scoring systems offer valuable insights into the clinical prognosis of patients in the neurosurgical ICU. Moreover, the GCS M stands out as a feasible and reliable metric for predicting in-hospital mortality among this patient population.

NOTES

Ethics statement

The study received approval from the Institutional Review Board (IRB) of Samsung Medical Center (No. SMC 2020-09-082) and was carried out in compliance with the principles of the Declaration of Helsinki. Given the retrospective design of the study, the IRB waived the requirement for informed consent.

Author contributions

Conceptualization: JAR. Data curation, Writing – original draft, Writing – review & editing: SC, JAR. Formal analysis, Statistical analysis: SC, HK.

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

Regarding data availability, our data are available on the Harvard Dataverse Network (http://dx.doi.org/10.7910/DVN/ZSFPUY) as recommended.

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Ultrasound-guided placement of Midline catheters performed by Neurosurgery resident as a substitute for conventional central venous catheter placement in Neurosurgical Intensive Care Unit patients

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Background
Midline catheters (MCs) and peripherally inserted central venous catheters (PICCs) are placed by a specialist or trained nurse to avoid the complications of conventional central venous catheters (CCVCs). The safety of MC placements by residents has not been evaluated. We investigated the safety of ultrasound-guided MC placement by neurosurgery residents as a substitute for CCVC placement in patients in the neurosurgical intensive care unit (ICU) requiring intravenous (IV) therapy ≤14 days.

Methods
Between July 2022 and June 2023, 57 MCs for 44 patients, 36 CCVCs for 35 patients, and 32 PICCs for 32 patients were placed during their ICU stay. One resident performed all MC placements under ultrasound guidance. The baseline and procedure-related parameters of the three catheter groups (MC, CCVC, and PICC) were analyzed, with focus on the comparison of complications between MC and CCVC.

Results
The first-attempt success rate was significantly higher (p=0.003) in the MC group (96.5%) than in the CCVC group (80%). Insertional injuries occurred more frequently in the CCVC group than in the MC group (13.3% vs 0%, p=0.012). The rate of completion of therapy was significantly higher (p=0.002) in the MC group (86.0%) than in the CCVC group (53.3%). The incidence of bloodstream infections did not differ significantly between the MC and CCVC groups (p=0.605).

Conclusion
MCs placed under ultrasound guidance by neurosurgery residents for neurosurgical ICU patients is safe and may be a substitute for CCVC indicated for IV therapy ≤14 days.

Keywords: Intensive care units; Central venous catheters; Intravenous infusions; Medical field training

INTRODUCTION

Most patients in neurointensive care need intravenous (IV) maintenance or resuscitation and medications to manage the increased intracranial pressure (IICP) or complications that may occur during hospitalization[1]. Therefore, establishing IV access, including central venous access, is imperative in these patients. Conventional central venous catheter (CCVC) placement has limitations of catheterization failure, central line-associated bloodstream infection (CLABSI), and mechanical injury, which can be fatal[2,3]. Mechanical complications occur in 1.5% and 8% of CCVCs and more common among catheter insertions performed by junior practitioners than by experienced physicians[4-6]. CCVC insertion under ultrasound guidance is safer but may be difficult for inexperienced operators[3,7,8]. Reduced resident working hours and the lack of easily accessible educational programs can worsen this problem.

A peripherally inserted central venous catheter (PICC) and a midline catheter (MC) can avoid the risk of insertion-related mechanical injury with an acceptable risk of catheter-related bloodstream infection (CRBSI)[9,10]. PICC is recommended for patients requiring IV therapy > 14 days[9]. Meanwhile, MC is an emerging device commonly used for short-term (≤ 14 days) IV therapy without a definite need for central venous access[9]. MCs are placed in a deep vein of the upper arm and the tip of the catheter is located in the axillary vein[9]. PICCs are also inserted in the same veins but its length is relatively long, sufficient to access the central veins[9]. Both PICC and MC insertions require surgical aseptic techniques and are usually performed by neurointensivists, specialists, or trained nurses[9,11]. However, these skilled personnel are not available at every time nor at every hospital. There is insufficient background or evidence for MC placement by neurosurgical residents. This study aimed to determines whether MC placement by residents could be a solution for the complications of CCVC catheterization performed by residents. We investigated the safety and efficacy of ultrasound-guided MC placement by neurosurgery residents in neurosurgical ICU patients who require IV therapy with an expected period of 14 days or less.

METHODS

This retrospective study evaluated adult neurosurgical patients (aged over 18 years) admitted to the neurosurgical ICU of our institution between July 2022 and June 2023. Patients who underwent central venous catheterization, including CCVC and PICC, and/or MC placement during their ICU stay were included. Catheterizations for hemodialysis (HD) were excluded because the purpose of the catheter was wholly different, and anesthesiologist or interventional radiologist placed all HD catheters during the study period. The institutional review board approved this study and the requirement for informed consent was waived because of the retrospective nature of the study.

Electronic medical records, neurosurgical department registry of catheter placements, and radiological data were retrospectively reviewed. Data on demographic characteristics, age, sex, and body mass index (BMI) were collected from the medical records. The Acute Physiology and Chronic Health Evaluation (APACHE) II score at the time of ICU admission, cause of ICU admission, comorbidities, and antithrombotic administration were also collected. Procedure-related characteristics including indications for catheter placement, Glasgow Coma Scale (GCS) score at the time of catheterization, use of ventilator/inotropics, whether the operator was a resident, application of ultrasound guidance, location of catheterization (ICU or others), coagulation study at the time of catheterization, whether the paretic arm was catheterized, veins of accessed and specifications of used catheters were also derived from medical records.

The placements were classified into three groups according to the catheter used (MC, CCVC, and PICC). And the patient characteristics and procedure related parameters were analyzed, with a focus on the comparison between MC and CCVC groups. The primary outcomes were procedure-related parameters including the success of the first attempt, procedure time, and insertion-related injuries. The secondary outcomes were the maintenance of catheters, specified as the completion of therapy, and complications that occurred during IV therapy. Completion of therapy was defined as catheter use untill the end of the intended purpose or for 14 days. Major complications were defined as serious insertional injuries, including pneumothorax, hemothorax, nerve injury, and bleeding, for which management was required beyond sandbag/ manual compression. CRBSI, including CLABSI and venous thromboembolism (VTE), were classified as major complications. Diagnosis of CRBSI was made based on the criteria from a previous study: (1) positive peripheral blood culture drawn with the presence of catheter or within 48 hours from the removal of the catheter; (2) detection of the same microorganism on catheter tip culture or a positive culture result of blood drawn via the catheter, which was obtained simultaneously with the peripheral blood sample; and (3) absence of any other suspicious source of bacteremia[11-13]. If the blood culture was positive, CRBSI was investigated in cooperation with our institution's Infectious Diseases Department and the Infection Prevention and Control Team. VTE was diagnosed by imaging confirmation (bedside ultrasound or computed tomography scan) of symptomatic deep venous thrombosis (DVT) in the relevant extremities or lungs, which was absent at

the time of catheterization[12]. Minor complications were defined as phlebitis, leakage of infusate into the soft tissue, dislodgement, and catheter occlusion. The criteria for minor complications were based on previous studies[12,14]. Insertion site bleeding as minor complications, that could be sufficiently managed with compression were also analyzed.

One postgraduate year (PGY)-3 resident performed all MC placements under strict surgical aseptic technique during the study period. One neurosurgical specialist (the corresponding author) provided an education program to the resident regarding MC placement using with a traditional method[15].

During the study period, the attending specialist selected the type of catheter to be used. However, if more than 2 weeks of IV therapy for any cause was anticipated, PICC was recommended by the operator (corresponding author) as appropriate. A 4-French (Fr) single-lumen Seldipur Smartmidline (Vygon, Ecouen, France) with 12cm length was used in all patients. All punctures were performed in the basilic, or brachial, or cephalic vein under ultrasound guidance and with the Seldinger technique. Meanwhile, CCVCs were placed by neurosurgical residents of PGY 3 and 4 neurosurgical residents, neurosurgical specialists, anesthesiologists, or interventional radiologist. The subclavian, or internal jugular, or femoral veins were accessed for CCVC placement with or without ultrasound guidance. A 7-Fr Arrowg+ard Blue® Two-lumen CVC (Arrow International, Inc., Everett MA, USA), 7-Fr Three-lumen CVC (Arrow International, Inc., Everett MA, USA), 7-Fr Prime-S Antimicrobial Double-lumen (Sungwon Medical, Cheongju, South Korea) or 7-Fr Prime-S Antimicrobial CVC Triple-lumen (Sungwon Medical, Cheongju South Korea) were used. All PICC procedures for neurosurgical patients have been performed by a single operator (corresponding author) with several years of experience in endovascular neurosurgery since 2018 until today. PowerPICC® Catheter 4(5,6) Fr single(dual, triple)-lumen (Bard, Salt Lake City, UT, USA) were used in all PICC cases. All catheter insertion sites were dressed every 7 days or when compromised.

Categorical values were presented as numbers (percentages) and a Fisher's exact test and chi-square test were used to analyze. Continuous variables were presented as the median (interquartile range [IQR]) and analyzed using the Mann– Whitney U test. All statistical analyses were performed using MedCalc (MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020). A p value of < 0.05 was considered significant.

RESULTS

There were 57 MC placements in 44 patients, 36 CCVC placements in 34 patients, and 32 PICC placements in 32 patients admitted to ICU. Considering the patients who received catheter exchange to other types, there were a total of 97 patients in this study. The baseline demographic characteristics of the patients are described in Table 1. Age, sex, BMI, incidence of comorbidities, and antithrombotic use did not show significant differences among the three groups. In total, 51 patients (52.6%) were male. The median age and BMI of the MC group were 75 years (IQR, 55.5-83.0, years) and 22.6 kg/m^2 (IQR, 21.3-26.9 kg/m^2), respectively. The most common cause of ICU admission was hemorrhagic stroke (53.5%), followed by traumatic brain injury (30.9%). The median APACHE II score was higher in the CCVC group (21.0) than in the other two groups (15.0 and 17.5, $p = 0.010$). The most common comorbidity was hypertension (62%).

MCs were more frequently placed than CCVCs and PICCs in patients with difficult peripheral IV access ($p < 0.001$). Meanwhile, CCVCs were more frequently placed than MCs and PICCs for intraoperative anesthetic management ($p < 0.001$). The rates of ventilator use and vasopressor administration were higher in the CCVC group than in the MC group ($p < 0.001$ and 0.005, respectively). The GCS score, coagulation studies at the time of catheterization were not significantly different among the three groups. The rate of catheter insertion in locations other than the ICU was higher in the CCVC group than in the MC group ($p < 0.001$), and this may reflect the tendency for CCVCs to be placed in the operation room. In the MC group, the basilic vein was the most common access site (70.0%). In the CCVC group, the most common access site was the subclavian vein (50%), followed by the femoral vein (44.4%). No patients underwent MC or PICC placement in the paretic arms (Table 2).

The procedure outcomes are presented in Table 3. Of the 36 CCVC placements, 30 were performed by neurosurgical residents and these were included in the outcome analysis. The first-attempt success rate was significantly higher in the MC group than in the CCVC group (96.5% vs 80%, $p = 0.003$). The ultrasound-guided technique was more frequently adopted in the MC group than in the CCVC group ($p < 0.001$). Insertional injury, limited as a major complication, was more commonly observed in the CCVC group (2 cases of pneumothorax) than in the MC group ($n = 0$), but the difference was not significant ($p = 0.147$). However, when hematoma (1 subclavian and one femoral) managed by 2-3 days of sandbag compression was included in the analysis, the rate of insertional injury was significantly higher in the CCVC group ($p = 0.012$).

There was no significant difference regarding the procedure time between the MC and the CCVC groups ($p = 0.332$). The catheter dwell time was the longest in the PICC group, with a median of

Table 1. Demographic characteristics

	MC (n = 44)	CCVC (n = 34)	PICC (n = 32)	p-value
Age (year), median (IQR)	75 (55.6–3.0)	69 (57.0–77.0)	69.5 (57.5–79.5)	0.188
Sex (male), n (%)	23 (52.3)	17 (50.0)	15 (46.9)	1.000
BMI (kg/m^2), median (IQR)	22.6 (21.3–26.9)	22.9 (21.2–24.7)	22.4 (20.6–25.1)	0.943
Diagnosis, n (%)				
Aneurysmal SAH	2 (4.5)	7 (20.6)	13 (40.6)	
Nonlesional ICH and/or IVH	22 (50.0)	8 (23.5)	8 (25.0)	
Traumatic brain injury	15 (34.1)	11 (32.4)	8 (25.0)	
Others	5 (11.4)	8 (23.5)	3 (9.4)	
APACHE II score, median (IQR)	15 (11.0–21.0)	21 (15.0–27.0)	17.5 (10.5–23.0)	0.010
Comorbidities, n (%)				
Diabetes mellitus	10 (22.7)	10 (29.4)	9 (28.1)	0.603
Hypertension	30 (68.2)	22 (64.7)	16 (50.0)	0.811
Malignancy	5 (11.4)	6 (17.6)	2 (6.3)	0.519
Chronic kidney disease	2 (4.5)	1 (2.9)	0 (0)	1.000
Atrial fibrillation	1 (2.3)	1 (2.9)	2 (6.3)	1.000
Coronary artery diseases	3 (6.8)	3 (8.8)	1 (3.1)	1.000
Hemorrhagic Stroke	2 (4.5)	0 (0)	1 (3.1)	0.501
Ischemic stroke	8 (18.2)	2 (5.9)	3 (9.4)	0.172
Venous thromboembolism	0 (0)	1 (2.9)	1 (3.1)	0.435
Use of anticoalgulants, n (%)	1 (2.3)	1 (2.9)	2 (6.3)	1.000
Use of antiplatelets, n (%)	16 (36.4)	8 (23.5)	6 (18.8)	0.323

MC: Midline catheter, CCVC: Conventional central venous catheter, PICC: Peripherally inserted central venous catheter, IQR: interquartile range; n(%): Number of patients (%), SAH: Subarachnoid hemorrhage, ICH: Intracerebral hemorrhage, IVH: Intraventricular hemorrhage, APACHE: Acute Physiology and Chronic Health Evaluation.

21.0 days (IQR: 15.0-29.0 days). And the median dwell time was longer in the MC group (11.0 days) than in the CCVC group (7.5 days); however, there was no significant difference (p = 0.114). The therapy completion rate was higher in the MC group than in the CCVC group (p = 0.002). Deaths before completion (n = 3), dislodgement (n = 2), CRBSI (n = 2), and phlebitis (n = 1) were the causes of catheter removal before completion of therapy in the MC group. For the CCVC group, all femoral vein catheters were changed to other catheters, even in the absence of complications, because they precluded ambulation, and there was concern that the longer the period of maintenance, the greater the risk of complications. The causes of CCVC removal that did not result from the completion of therapy were CRBSI (n = 2), phlebitis (n = 2), and dislodgement (n = 1). The incidence of CRBSI was higher in the CCVC group (6.7%) than in the MC group (3.5%); however, the difference was not significant (p = 0.606). The total complication rate (33.3%), including both major and minor complications, was higher in the CCVC group than in the MC group (p = 0.007).

DISCUSSION

CRBSI and catheter - related venous thrombosis in MCs and CCVCs

MC has replaced certain parts of traditional CCVC indications[10]. Emergence of MC use has attributed to the acceptable incidence of MC-related BSI documented by previous studies. In a systematic review comparing various IV catheters, MC-related infections occurred in 0.4% (0.2/1,000 catheter-days)[16]. This was lower than the infection rates of central venous (4.4%, 2.7/1,000 catheter-days) catheters[16]. CRBSI in the MC of our study was 3.5%, slightly higher than that in the above systematic review[16]. However, this is lower than the 6.7% incidence rate of CCVC-related CLABSI in our study. Although there is no significance, the lower rate of BSI in the MC group is consistent with previous findings.

The first-attempt success rate of MC placement in our study was higher than that reported previously (96.5% vs. 83.4%)[12]. The number of attempts is important for ensuring the safety of MC maintenance. In a previous study, when the first attempt of MC insertion was achieved, the rate of MC-related venous thrombosis was 4.5%, but when the attempts were repeated three times or more, the venous thrombosis rate was increased up to 9%[17]. DVT of the upper arm can the potentially cause fatal complications resulting from any IV catheters[10]. The target vein of the MC is usually smaller than that of central veins. Therefore, MCs have an inherently higher risk of DVT formation in the upper arm than CCVCs[18]. In our study, no DVT occurred in any of the catheter groups. The high first-success rate in our study may be attributable

Table 2. Baseline procedural characteristics

	MC (n=57)	CCVC (n=36)	PICC (n=32)	p-value
Indication, n (%)				
Difficult IV access*	24 (42.1)	3 (8.3)	0 (0)	< 0.001
IV fluid Maintenance	11 (19.3)	5 (13.9)	18 (56.3)	0.582
Infusion of drug	22 (38.6)	14 (38.9)	14 (43.8)	1.000
For operation	0 (0)	13 (36.1)	0 (0)	< 0.001
GCS score median (IQR)	12.5 (7.50–13.0)	9.5 (6.0–14.0)	8.5 (6.0–14.0)	0.626
Use of ventilator, n (%)	8 (14.0)	18 (50.0)	17 (53.1)	< 0.001
Use of vasopressor, n (%)	1 (1.8)	7 (19.4)	4 (12.5)	0.005
Operators, n (%)				
Residents	57 (100.0)	30 (83.3)	0 (0)	
Specialist	0 (0)	6† (16.7)	32 (100.0)	
Location, n (%)				
ICU	57 (100.0)	21 (58.3)	8 (25.0)	
Others	0 (0)	15 (41.7)	24 (75.0)	< 0.001
Paretic arm placement, n (%)	0 (0)	0 (0)	0 (0)	
Accessed vein, n (%)				
Basilic	40 (70.0)	0 (0)	22 (68.8)	
Brachial	14 (24.6)	0 (0)	9 (28.1)	
Cephalic	3 (5.3)	0 (0)	1 (3.1)	
Subclavian	0 (0)	18 (50.0)	0 (0)	
Jugular	0 (0)	2 (5.6)	0 (0)	
Femoral	0 (0)	16 (44.4)	0 (0)	
French of catheter, n (%)				
4	57 (100.0)	0 (0)	5 (15.6)	
5	0 (0)	0 (0)	25 (78.1)	
6	0 (0)	0 (0)	2 (6.3)	
7	0 (0)	36 (100.0)	0 (0)	
Lumen, N (%)				
1	57 (100.0)	0 (0)	5 (15.6)	
2	0 (0)	4 (11.1)	25 (78.1)	
3	0 (0)	32 (88.9)	2 (6.3)	
Laboratory parameters, median (IQR)				
Platelet ($\times 10^3/\mu L$)	207 (173.3–249.3)	231 (155.5–300.5)	179.5 (152.0–226.0)	0.322
PT-INR	1.08 (1.0–1.19)	1.09 (1.0–1.2)	1.09 (1.0–1.2)	0.335
aPTT (sec)	36.9 (33.6–45.2)	37.35 (31.9–46.8)	36 (33.4–40.2)	0.880

*Difficult peripheral intravenous access; †placement by specialist or anesthesiologist.
MC: Midline catheter, CCVC: Conventional central venous catheter, PICC: Peripherally inserted central venous catheter, IQR: Interquartile range, IV: Intravenous, GCS: Glasgow coma scale, PT: Prothrombin time, INR International normalized ratio, aPTT: activated partial thromboplastin time.

this favorable result. In addition, this result appears to be because, unlike previous studies, the study was conducted in an Asian population, which has a lower incidence of VTE than other races[19].

Potential of serious insertional injury with CCVC placement from lack of experienced personnel

In the guideline of IV catheter selection, CCVCs are the optimal choice for ICU patients who need central venous pressure (CVP) monitoring and when have an anticipated IV period of ≤ 14 days[9]. However, the benefit is only achieved when CCVC placement is performed by a skilled operator[9].

Subclavian vein catheterization has several advantages over other CCVCs. Subclavian catheters cause less discomfort to patients, and has a lower risk of thrombosis and CLABSI than internal jugular and femoral vein catheters[3,20-22]. Nonetheless, subclavian catheterization has safety issues, which are mostly related to technical difficulties for identifying the target vein and subsequent mispuncture. A prospective randomized study comparing ultrasound-guided subclavian catheterization with the landmark technique reported complications such as hematomas resulting from arterial puncture (5.4%), hemothorax (4.9%), pneumothorax (4.9%), nerve plexus injury (4.3%) and cardiac tamponade (0.5%) in the land-

Table 3. Procedural outcomes

	MC (n=57)	CCVC (n=30)	PICC (n=32)	p-value
Number of insertion attempts, n (%)				
1	55 (96.5)	24 (80.0)	28 (87.5)	
2	2 (3.5)	6 (20.0)	4 (12.5)	
More	0 (0)	0 (0)	0 (0)	
First attempt success rate	0.965	0.8	0.875	0.003
Procedure time, median (IQR)	10 (5.0–20.0)	13 (10.0–20.8)	17 (12.0–20.0)	0.332
Insertional injury, n (%)	0 (0)	4 (13.3)	0 (0)	0.012
Pneumothorax	0 (0)	2 (6.7)	0 (0)	0.147
Incision site bleeding	0 (0)	2 (6.7)	0 (0)	0.147
Other	0 (0)	0	0 (0)	
Ultrasound guided procedure	57	11	32	< 0.001
Dwell time (Days), median (IQR)	11 (7.0–14.0)	7.5 (2.0–15.0)	21 (15.0–29.0)	0.114
Cause of removal, n (%)				
Completion of therapy	49 (86.0)	16 (53.3)	25 (78.1)	0.002
Death before completion	3 (5.3)	1 (3.3)	3 (9.4)	
Death after completion	1 (1.8)	1 (3.3)	2 (6.3)	
Dislodgement	2 (3.5)	1 (3.3)	2 (6.3)	
CRBSI*	2 (3.5)	2 (6.7)	2 (6.3)	
Major complication, n (%)	2 (3.5)	4 (13.3)	2 (6.3)	0.177
Serious insertional injury	0 (0)	2 (6.7)	0 (0)	0.147
CRBSI	2 (3.5)	2 (6.7)	2 (6.3)	0.606
Symptomatic catheter related DVT	0 (0)	0 (0)	0 (0)	
Bleeding required beyond compression	0 (0)	0 (0)	0 (0)	
Minor complication, n (%)	3 (5)	6 (20.0)	3 (9.4)	
Insertion site bleeding	0 (0)	2 (6.7)	0 (0)	
Catheter dislodgement / occlusion	2 (3.5)	2 (6.7)	2 (6.3)	
Leakage	0 (0)	0 (0)	0 (0)	
Phlebitis	1 (1.8)	2 (6.7)	1 (3.1)	
Total complication	5 (8.8)	10 (33.3)	5 (15.7)	0.007

*CLABSI in cases of CCVC and PICC.
MC: Midline catheter, CCVC: Conventional central venous catheter, PICC: Peripherally inserted central venous catheter, IQR: Interquartile range, CRBSI: Catheter-related blood stream infection, DVT: Deep venous thrombosis.

mark-guided insertion group[23]. These complications occur more frequently among inexperienced practitioners[3,20,21]. Ultrasound-guided CCVC placement has become a solution to these complications and increase catheterization success rate; it has already become a standard practice[22,23].

However, ultrasound-guided catheterization is also difficult and unfamiliar to novice practitioners[23]. Appropriate simulation-based training and certification of techniques for ultrasound-guided vascular access have been suggested[24]. And the need for a training program with a consensus was also raised[24]. It is clear that appropriate training could reduce the complications of CVC catheterization[15,22]. However, whether such an educational program is well prepared at every institution is questionable. Furthermore, it seems difficult to become skilled while continuing clinical practice, considering the decrease in training time for the current residency program.

As an alternative method, puncture of the femoral or jugular vein with ultrasound guidance is much easier than puncture of the subclavian vein[3,20,21]. However, femoral vein catheterization has a higher risk of infection and thrombosis, which precludes maintenance for more than 4 days[22]. Jugular vein catheterization also has the disadvantage of strong patient discomfort, with a relatively high incidence of thrombosis and infection than subclavian catheterization[20-22]. The first-attempt success rate of MC insertion in our study was 96.5%. And no insertional injury was found in the MC group of our study. These outcomes which are superior to the CCVC group in our study, demonstrate the safety of MC placements with ultrasound-guided techniques even performed by residents.

Special consideration of IV infusates for neurosurgical ICU patients

Guideline recommend that infusates administered via MC should "ideally" be in the physiologic range of pH and osmolarity,

which are compatible for peripheral infusion[10]. However, a range of pH and osmolarity of infusates and the list of medications with absolute necessities for central venous catheter (CVC) administration is not clearly established and are changing[9]. Although this lack of evidence, guideline have been used as a clinical reference suggesting medications for CVC rather than peripheral IV catheter or MC[10]. Amiodarone > 2mg/mL as an acidic agent, dextrose > 20% in non-emergent situations, hypertonic saline, total parenteral nutrient, vesicants, calcium chloride, epoprostenol, potassium concentrate > 0.1mEq.mL and vasopressors require CVC infusion[10]. Other medications can be administered via MCs[10].

Mannitol is frequently administered for neurosurgical ICU patients. In our institution, we use 15% mannitol with an osmolarity of 823 mOsm/L (Baxter, Deerfield, IL, USA), which is lower than the 20% (1369 mOsm/L) osmolarity of definite irritants in a recent study[25]. Administration of hypertonic saline through a CVC is also preferred[10]. However, access may be limited in urgent situations for IICP control[25]. Recent studies have shown an acceptable safety profile for peripherally administered hypertonic saline even with bolus injection[26,27].

Vasopressors induce local vasoconstriction and elevation of hydrostatic pressure, especially in small veins, and subsequently disintegrate adjacent tissues[25]. This potential harm is particularly concerning with respect to the accumulation of drugs in peripheral IV administration because the venous flow in the peripheral vein is slower than that in the central vein[25]. A meta-analysis of adverse events resulting from peripheral infusion of vasopressors showed no significant difference in complications between peripheral IV and CVC[28]. However, when vasopressor infusion for ≥ 24 hours or a dose increase was anticipated, a switch to CVC was recommended[28]. In our study, only one patient underwent norepinephrine administration via the MC; however, this patient in a few days of end-of-life caused by massive intracranial hemorrhage. In our study, vasopressors use was significantly more in the CCVC group than in the MC group ($p = 0.005$). Antineoplastic agents classified as definite vesicants were not used in our study.

Minor complications of MC during the management period

Minor complications of MCs can result in loss of catheter function[12]. In a retrospective study of 411 MCs and 282 CVCs, the rate of loss of catheter function was higher in the MC group than in the CCVC group ($p = 0.03$)[29]. These minor complications are not uncommon in patients with MCs[12,14]. A retrospective study of 115 MC placements reported that minor complications including dislodgement, kinking, skin infiltration, catheter occlusion, and thrombophlebitis occurred in 23.5% of the patients[12]. Although minor complications are not fatal, they should not be ignored because they can induce device removal before the completion of therapy[12]. However, in our study, the minor complication rate was only 5%, markedly lower than that reported previously.

Suggested MC indications for neurosurgical ICU patients

MCs are now a widely accepted device for patients with difficult IV access who have need of 5 to 14 days of administration of peripherally compatible infusate with a simple regimen[10,14,30]. Central venous access has clear advantages such as the capabilities of infusion of all types of medications, large volumes of blood transfusion/fluid, CVP monitoring, and complex IV therapies[10]. However, inserting CVCs to all neurosurgical ICU patients may be considered overtreatment and expose patients to potential harm. CCVC placements should be performed on highly selected patients; critically ill patients requiring central venous pressure monitoring for unstable hemodynamic conditions, multiple IV lines and anticipated significant blood loss on major surgery are appropriate candidates. PICC has an exceptional IV maintenance period with most advantages of CCVCs[9]. PICC has a certain role in the care of neurosurgical ICU patients[11]. However, PICC is preferred to MC if the expected IV period is ≥ 15 days[9].

In our study, the total complication rate was significantly lower ($p = 0.007$) in the MC catheterizations performed by residents, and the rate of completion of therapy was significantly higher than that in CCVC catheters placed by residents ($p = 0.002$). These results ascertain that CCVC is not necessary for patients without the definitive indications described above considering the risk of CCVC-related complications.

Limitations

This study has inherent biases owing to its retrospective nature and the small sample size. In addition, the catheter type was selected by the attending physician and was not a protocol-based decision. The use of MC and PICC in neurosurgical ICU patients was initiated by an endovascular neurosurgeon not dedicated to neurocritical care. Further, not all attending staff participating in the study understood or agreed with the catheter selection rationale. The dressing methods or materials, which could have influenced the incidences of BSI and phlebitis, were not properly addressed and recorded. A well-established surveillance for DVT was not available during the study period. Our results on local practice with the above limitations may not be applicable to high-quality practice centers with experienced personnel and abundant equipment. However, our results of MC placements demonstrated a higher first-attempt success rate (96.5%) and a higher rate of therapy

completion (86.0%) compared to the results of a previous study (83.4% and 80.9%, respectively)[12]. Our study is noteworthy because to our best knowledge, this is the first study to show the acceptable safety and efficacy of ultrasound-guided MC placement by neurosurgical residents.

CONCLUSION

CCVC placement should be decided carefully and performed in patients with a definitive need for central venous access, especially when placement is performed by a resident. MC placement by a neurosurgical resident demonstrated a significantly lower complication rate than CCVC placement by neurosurgical residents. MC placement by a neurosurgical resident may be a substitute for CCVC in neurosurgical ICU patients with a requirement of 6 to 14 days of IV therapy with a simple regimen.

NOTES

Ethical approval

All study procedures involving human subjects were performed in accordance with the ethical standards of our Institutional Review Board (No. SGPAIK 2023-08-013) and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Author contributions

Conceptualization: SYC. Data curation: All authors. Formal analysis: SYC. Methodology: HJK, SYC. Project administration: SYC. Visualization: SYC. Supervision: SYC. Writing – original draft: HJK, SYC. Writing – review & editing: SYC.

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

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Hyaluronidase Injection to Reduce Periorbital Edema after Surgery for Unruptured Intracranial Aneurysms

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Background
In the era of endovascular treatment for intracranial aneurysms, microsurgical treatment might necessitate the minimization of postoperative discomforts such as headache, nausea, vomiting, and edema. The current study aimed to evaluate the effectiveness of hyaluronidase on the reduction of periorbital edema after clipping surgery for unruptured intracranial aneurysms.

Methods
From July 2016 to March 2018, the patients who underwent elective surgery for unruptured intracranial aneurysms were included. A mixture of 4500 IU hyaluronidase was injected subcutaneously on the sectional plane of the scalp incision. The photographs of patients' faces were obtained on postoperative day 1, 3, and 7. The degree of periorbital edema was judged on the grading system based on the vertical palpebral aperture. The thickness of the scalp, temporalis muscle, and soft tissue was measured on a preoperative computed tomography (CT) scan, and other variables (e.g., intraoperative input and output, serum albumin level) were analyzed retrospectively.

Results
A total of 60 patients were included in this study, and a hyaluronidase mixture was injected in 30 patients. The periorbital edema tended to resolve in 7 days after surgery, but notable differences between the two groups was observed at day three after surgery in this study. On the ordinal logistic regression analysis on the grade of periorbital edema, hyaluronidase injection is significantly associated with the reduction of periorbital edema throughout the postoperative period. (p value < 0.05)

Conclusion
Hyaluronidase injection might be helpful in reducing periorbital edema after surgery for unruptured intracranial aneurysms.

Keywords: Intracranial aneurysm; Hyaluronoglucosaminidase; Craniotomy; Edema; Postoperative care

INTRODUCTION

In Korea, the number of endovascular treatments for intracranial aneurysms has overwhelmed the number of microsurgical clipping since 2014, based on the data of the Health Insurance Review & Assessment Service (HIRA)[1]. This trend might result from the superiority in accessibility and recoverableness of the endovascular treatment over microsurgical clipping. Accordingly, several studies have been conducted to reduce postoperative headache, nausea, and vomiting, and to reduce postoperative edema after craniotomy[2-4]. Furthermore, these efforts might be the elements of Enhanced Recovery After Surgery (ERAS) strategies for craniotomy, which has been adopted more recently compared with other specialties[5].

Especially, periorbital edema after craniotomy is reported frequently during the postoperative period up to 79.5% and it might be accompanied by pain and ecchymosis[6]. Cryotherapy was reported as effective in reducing postoperative edema, but it might be applied in contact with skin postoperatively[3]. Hyaluronidase is known as a spreading factor and is reported to reduce periorbital edema after plastic procedures[7]. However, there has not been any study using hyaluronidase for periorbital edema in craniotomy. We expected the hyaluronidase might reduce periorbital edema after craniotomy based on the properties of which would promote the diffusion and dispersion of fluids and wound healing[8]. The current study aimed to evaluate the effectiveness of hyaluronidase on the reduction of periorbital edema after clipping surgery for unruptured intracranial aneurysms.

MATERIALS AND METHODS

Study design

After the authors had received approval from the Institutional Review Board, the retrospective analysis was performed on a total of 280 patients who were treated for unruptured aneurysms surgically between June 2016 and March 2018. Among 280 patients, 60 patients were included in the current study based on the following inclusion criteria.: 1) scheduled microsurgical clipping of unruptured aneurysms, located on anterior circulation 2) pterional approach or lateral supraorbital approach 3) available photograph of patient's face including both peri-orbital region on postoperative day 1, 3, and 7.

In addition to demographic data of included patients, the thickness of scalp and muscle was measured on preoperative computed tomography (CT) or magnetic resonance images (MRI), and intraoperative volume input and output (I/O), retraction time, pre-operative and post-operative serum albumin was collected, based on medical record. Moreover, it was identified whether the patient had surgical drains and whether the patient took streptokinase/streptodornase (Varidase TM, SK Chemicals, Korea) on postoperative day 1 or 2. Moreover, to identify the relation between periorbital edema and subjective pain, the first pain score immediately after the surgery and the maximum pain score of postoperative day 0, 1, 3, and 7 was collected using a numeric pain intensity scale (NPIS)[9].

Surgical procedures

Microsurgical clipping of unruptured aneurysm was undergone as a general principle. Before scalp closure, a mixture of hyaluronidase 3000 I.U. (H-lase inj, Kuhnil Pharmaceuticals, Korea), 1 milliliter (ml) of 1:10000 lidocaine/epinephrine and 10ml of normal saline was injected into the subcutaneous layer of the scalp flap along the incision line. During the procedure, retraction time was defined as the interval between making burr holes and re-approximating the bone flap, which was defined as operation time on the anesthesiologist's record. We usually utilized drainage catheters for the patients with conventional pterional approach otherwise we did not use them for the patients with mini-pterional approach or supraorbital approach.

Grading system of periorbital edema

Photographs of patients' faces were taken before wound dressing on postoperative day 1, 3, and 7. We made a grading system of periorbital edema based on the vertical palpebral aperture of the contralateral eye (Fig. 1). The grading system ranged from 1 to 5 and

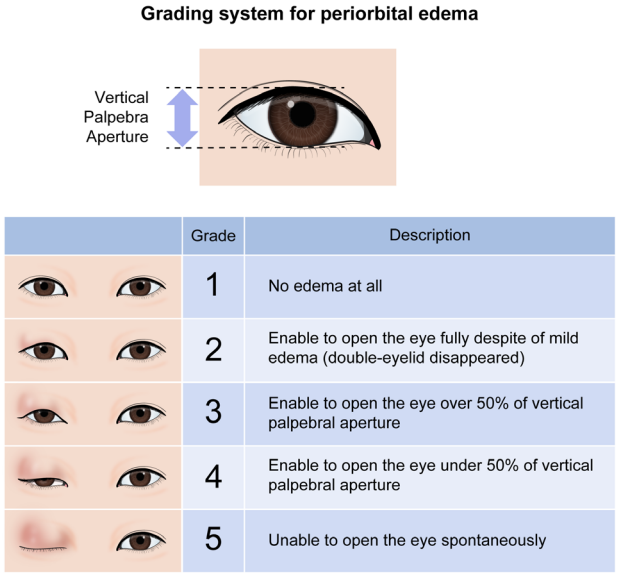

Fig. 1. Grading system for periorbital edema

the higher score means the more severe periorbital edema. Photographs were cropped and the bilateral periorbital region remained. Two physicians independently reported the grade of periorbital edema for the cropped photographs based on the grading system. In case of discrepancy of grades between two physicians (SY and CKJ), the final grading was decided with agreement among the authors (SY, CKJ, JJK).

Radiologic evaluation for muscle thickness

The thickness of the scalp was measured on the axial image of preoperative CT or MRI, at the level of just above ipsilateral orbital roof, which was thought mostly hinged during the surgery. Virtual line for measurement was made perpendicular to the long axis of temporalis muscle and it passed the tip of sphenoid ridge on axial image[10]. The measurement was performed in detail to evaluate the effect of muscle and soft tissue separately, such as bone-to-deep fascia, bone-to-superficial fascia, and soft tissue.

Statistical analysis

We dichotomized all included patients based on the use of hyaluronidase (HYAL), which are HYAL (+) group and HYAL (-) group. All demographic data was compared using chi-square test or Fischer's exact test for categorical variables and independent two-sample t-test for continuous variables. To evaluate efficacy of hyaluronidase and identification of predictors for reduction of periorbital edema, we compared ordinal grades of periorbital edema using the ordinal logistic regression model. Ultimately multivariate ordinal logistic regression analysis was performed for significant variables of univariate analysis (p-value < 0.05). We utilized linear mixed model – random intercept model to quantify the relationship of periorbital edema or subjective pain with use of hyaluronidase over time. P value < 0.05 was considered statistically significant in the analyses. SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

RESULTS

Patient demographics

A total of 60 patients were included in this study. There was no significant between HYAL (+) group and HYAL (-) group in baseline demographic and clinical characteristics (Table 1). 61.7% were female patients, and the median age was 57.1 ± 9.4 years. The mean volume of intraoperative I/O was larger in HYAL (+) group but was not significant.

Periorbital edema

The periorbital edema tended to be increased between postoperative day 1 and 3, and then decreased after postoperative day 3. On the spaghetti plot, the decline of the periorbital edema was identified as steeper in HYAL(-) group than in HYAL(+) group (Fig. 2). However, the decline in both groups was not significantly different with the linear mixed model – random intercept model, which compares the estimated slope of both groups along the time (p = 0.287).

On postoperative day 1, intraoperative I/O (OR 0.900; 95% CI 0.824–0.982; p = 0.018) and the use of hyaluronidase (OR 0.318; 95% CI 0.120–0.844; p = 0.021) were significantly correlated with reduction of the periorbital edema with univariate ordinal logistic regression analysis. On postoperative day 3, the use of hyaluronidase (OR 0.196; 95% CI 0.070–0.549; p = 0.002) significantly decreased the periorbital edema and the use of a drainage catheter (OR 3.188; 95% CI 1.133–8.967; p = 0.028) significantly increased the periorbital edema. On postoperative day 7, the use of hyaluronidase (OR 0.256; 95% CI 0.087-0.753; p = 0.013) significantly decreased the periorbital edema and the depth between bone and deep fascia of temporalis muscle (OR 1.329; 95% CI

Table 1. Patient demographics

	HYAL (+) (n=30)	HYAL (-) (n=30)	p value
Female	22 (73.3%)	16 (53.3%)	0.180
Age	57.8 ± 9.6	57.4 ± 8.6	0.855
Use of wound drainage	13 (43.3%)	6 (20.0%)	0.096
Scalp (mm)	13.8 ± 2.9	14.0 ± 3.6	0.807
Soft tissue (mm)	3.8 ± 1.1	4.0 ± 1.1	0.399
Superficial fascia (mm)	10.0 ± 2.6	10.0 ± 2.8	0.958
Deep fascia (mm)	7.9 ± 2.2	8.1 ± 2.4	0.657
Intraoperative input and output (ml)	639.2 ± 693.2	697.8 ± 525.8	0.713
Use of streptokinase	6 (20.0%)	4 (13.3%)	0.729
Preoperative albumin (g/dl)	4.4 ± 0.4	4.3 ± 0.3	0.152
Postoperative albumin (g/dl)	3.5 ± 0.4	3.5 ± 0.4	0.892

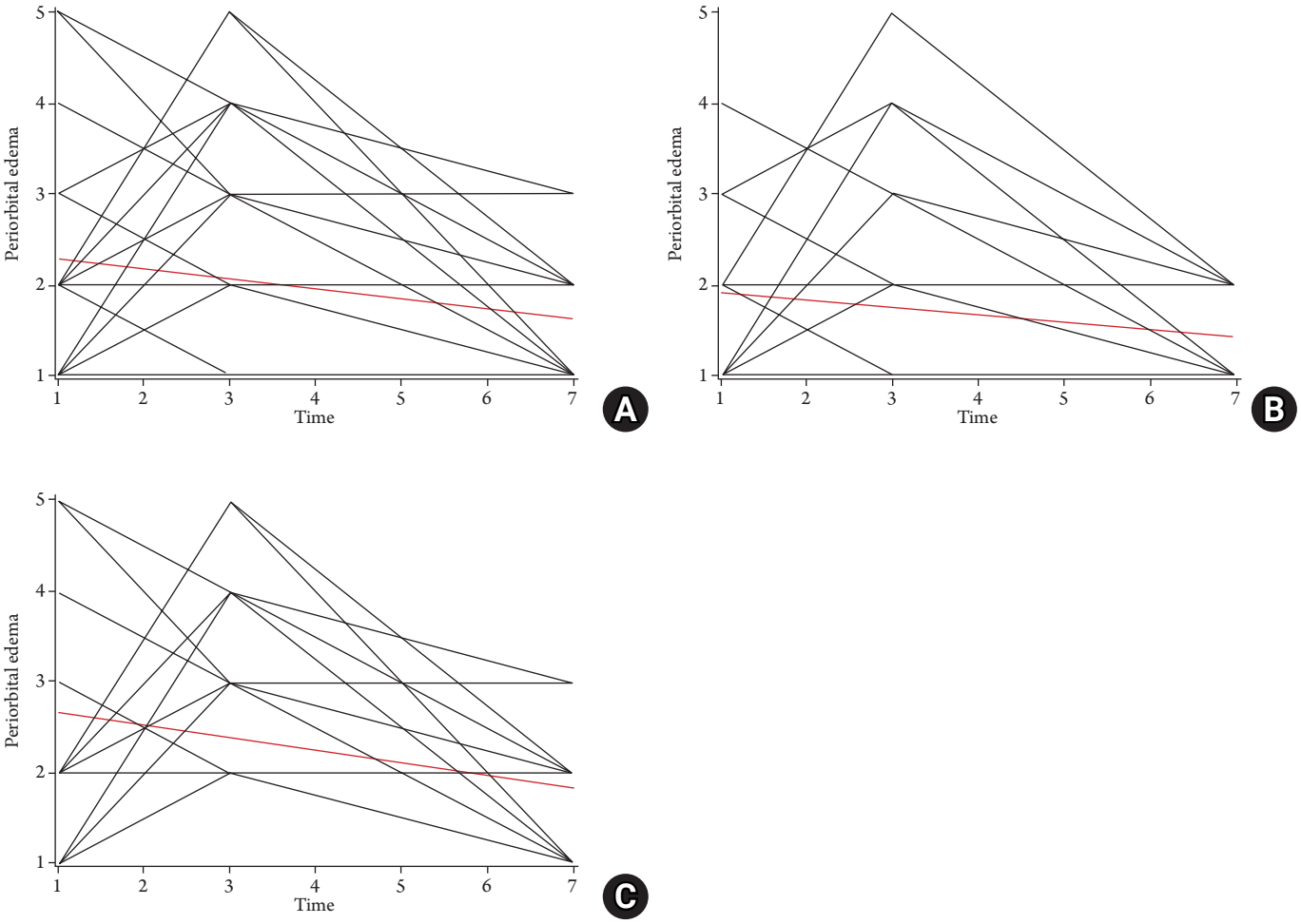

Fig. 2. Spaghetti Plot of Periorbital Edema and Postoperative Day. (A) Total population, (B) HYAL(-) group, (C) HYAL(+) group

1.045–1.689; p = 0.020) and postoperative level of serum albumin (OR 5.107; 95% CI 1.217–21.435; p = 0.026) significantly increased the periorbital edema with univariate ordinal logistic regression analysis (Table 2).

With multivariate ordinal logistic regression analysis including parameters of p-value 0.05, the use of hyaluronidase constantly showed a significant correlation with the reduction of periorbital edema on postoperative day 1 (OR 0.337; 95% CI 0.125–0.906; p = 0.031), 3 (OR 0.230; 95% CI 0.081–0.655; p = 0.006), and 7 (OR 0.160; 95% CI 0.046–0.553; p = 0.004).

Postoperative pain based on NPIS

The postoperative pain showed a decline over time and the slope of the decline was steeper in HYAL(+) group (estimated slope = –0.505; p < 0.0001) than in HYAL(-) group (estimated slope = –0.339) with linear mixed model (Fig. 3). Although the slope of the decline in postoperative pain was not significantly different between two groups, it showed a trend of difference (p = 0.096).

DISCUSSION

Hyaluronic acid is a non-sulfated glycosaminoglycan and is the predominant part of the extracellular matrix of the skin[11]. Hyaluronidase is a soluble enzyme that degrades hyaluronic acid by hydrolyzation12) and was recognized as promoting the diffusion and dispersion of fluids and wound healing[8]. Based on these properties, hyaluronidase has been revealed to enhance the diffusion of the drug so that the efficacy of local anesthetics would be increased with the combination[13,14]. Additionally, hyaluronidase might accelerate wound healing process[8,15]. In Korea, hyaluronidase of bovine is commercially available and is permitted to be used in subcutaneous infusion, local anesthesia, extravasation, and hematoma.

The use of hyaluronidase in edematous conditions would be reasonable based on the property, but as we know, there was only

Table 2. Univariate analysis for periorbital edema

Variable	Postoperative Day 1		Postoperative Day 3		Postoperative Day 7	
	OR (95% CI)	p value	OR(95% CI)	p value	OR (95% CI)	p value
Age	0.958(0.910–1.009)	0.103	1.016(0.967–1.068)	0.530	0.959(0.908–1.014)	0.145
Female sex	1.377(0.522–3.630)	0.518	1.701(0.647–4.473)	0.282	0.700(0.249–1.971)	0.500
Laterality – Left	0.543(0.189–1.555)	0.255	0.936(0.340–2.577)	0.898	0.870(0.287–2.643)	0.806
Depth of scalp	0.927(0.799–1.077)	0.321	1.057(0.914–1.222)	0.457	1.152(0.977–1.358)	0.093
Depth to superficial fascia	0.955(0.800–1.141)	0.613	1.062(0.891–1.267)	0.501	1.182(0.967–1.446)	0.103
Depth to deep fascia	0.923(0.752–1.133)	0.444	1.123(0.916–1.376)	0.264	1.329(1.045–1.689)	0.020*
I/O (100 ml)	0.900(0.824–0.982)	0.018*	0.959(0.886–1.038)	0.297	1.006(0.924–1.095)	0.891
Time of retraction	0.998(0.992–1.004)	0.487	1.001(0.995–1.007)	0.759	0.999(0.992–1.005)	0.746
Preoperative level of albumin	0.996(0.254–3.904)	0.995	2.607(0.655–10.376)	0.174	4.257(0.866–20.931)	0.075
Postoperative level of albumin	0.454(0.131–1.570)	0.212	0.854(0.256–2.848)	0.798	5.107(1.217–21.435)	0.026*
Use of drainage catheter	0.436(0.151–1.253)	0.123	3.188(1.133–8.967)	0.028*	1.823(0.621–5.354)	0.274
Use of hyaluronidase	0.318(0.120–0.844)	0.021*	0.196(0.070–0.549)	0.002*	0.256(0.087–0.753)	0.013*

I/O: Difference between input and output during the operation.
*Statistically significant, p-value < 0.05

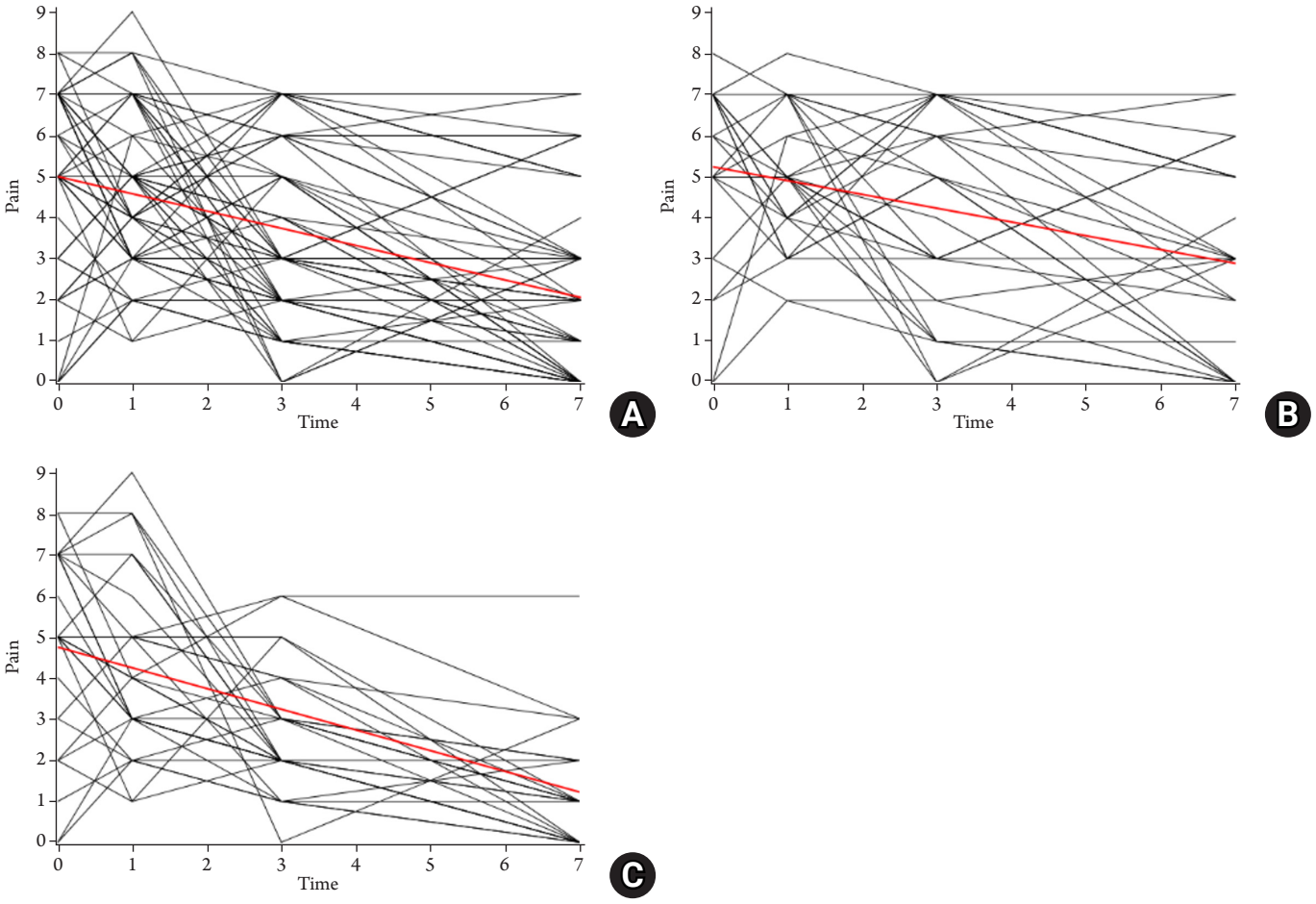

Fig. 3. Spaghetti Plot of Postoperative Pain and Postoperative Day. (A) Total population, (B) HYAL(-) group, (C) HYAL(+) group

one study of hyaluronidase injection for the treatment of eyelid edema[5]. Prior to the evaluation of periorbital edema, we made a grading system of periorbital edema based on the vertical palpebral aperture of the contralateral eye. It might be similar to the Modified Surgeon Periorbital Rating of Edema and Ecchymosis (SPREE) questionnaire, but the SPREE did not classify the edema quantitatively and also focused on the ecchymosis[16].

Although the surgery for unruptured intracranial aneurysms has been developed less invasively, the periorbital edema occurred as ever[6]. There have been efforts to reduce periorbital edema, including steroid injection and cryotherapy[10,17]. In the current study, we used hyaluronidase to reduce the periorbital edema after surgery for unruptured intracranial aneurysms. Hyaluronidase reduced the periorbital edema effectively and constantly without any related complications during the postoperative period.

Otherwise, on postoperative day 3, the use of a drainage catheter was correlated with increase in periorbital edema. Generally, the drainage catheter would be removed on postoperative day 1 or 2. The periorbital edema might be worsened just after the removal of drainage catheter because of fluid collection. And on postoperative day 7, the depth between bone and deep fascia of temporalis muscle was significantly correlated with the periorbital edema. The periorbital edema timely decreased, so that the thickness of temporalis muscle itself might reflect the degree of the periorbital edema on postoperative day 7.

The main limitation of the study is the retrospective design and selection bias derived from the low inclusion rate (60 of 280 patients), because only patients with postoperative photographs were included to the study. Second, the grading system does not quantitatively reflect the degree of periorbital edema. To minimize subjective judgement of periorbital edema, we made a grading system of periorbital edema based on the vertical palpebral aperture of the contralateral eye.

CONCLUSION

In the current study, the use of hyaluronidase might be helpful to reduce the periorbital edema effectively after surgery for unruptured intracranial aneurysms during the postoperative period without any related complications. Furthermore, a randomized study of a larger population to identify the effect of hyaluronidase on the reduction of periorbital edema might be required.

NOTES

Ethics statement

The authors had received approval from the Institutional Review Board. Informed Consent was waived, based on the retrospective design of the current study.

Author contributions

Conceptualization, Data curation, Formal analysis: JJK. Methodology: CHJ. Writing – original draft: SY. Writing – review & editing: CHJ, JJK

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

None.

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Bilateral Abducens Nerve Palsy and Nystagmus Resolved Upon Intravenous Dextrose Administration in Hypoglycemic Young Female: A Case Report and Review of the Literature

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Hypoglycemia can cause a variety of neurological symptoms ranging from mild confusion to seizures and coma. The brain depends heavily on glucose as its main energetic resource, and a decrease in glucose levels can lead to impaired cerebral function. A 38-year-old female presented to the Emergency department with a history of headache, dizziness and asymmetric reactive pupils in addition to bilateral medial strabismus, nystagmus and photophobia. A non-contrast brain Computed Tomography scan was performed showed no significant radiological findings. Laboratory tests were within normal ranges except for a clinically significant hypoglycemia (level II). Intravenous dextrose was administered and strabismus gradually resolved, and headache subsided gradually within an hour. Hypoglycemic state should be investigated first in any patient with sudden neurological deficit.

Keywords: Hypoglycemia; Abducens nerve diseases; Case report; Ramadan fasting

INTRODUCTION

Neurological symptoms of hypoglycemia can be classified into two categories: adrenergic and neuroglycopenic. Adrenergic symptoms include: sweating, tremors, palpitations, and anxiety, while neuroglycopenic symptoms include: confusion, dizziness, headache, visual disturbances, and altered consciousness[1)].

Hypoglycemia is classified according to the American association of diabetes into three categories:

The glucose alert value for level 1, which is less than or equal to 70 mg/dL, denotes a glucose concentration low enough to necessitate the administration of fast-acting carbohydrate and adjustment of glucose-lowering therapy. Although this level indicates the need for intervention, it is not considered a severe or clinically significant hypoglycemic episode.

Clinically significant hypoglycemia at level 2 is defined as a glucose level lower than 54 mg/dL (3.0 mmol/L), which is indicative of a serious and clinically important hypoglycemic event that requires immediate attention.

Severe hypoglycemia at level 3 is not defined by a specific glucose threshold; instead, it is distinguished by hypoglycemia that causes severe cognitive impairment and necessitates external assistance for recovery[2)]. Mild hypoglycemia may only cause mild confusion or headache, while severe or prolonged hypoglycemia can

lead to seizures or coma[3]. The severity and duration of hypoglycemia can also impact the type and extent of neurological symptoms.

Patient information

A 38-year-old 80 kg, 155 cm long young female previously healthy who was fasting the first day of Ramadan was admitted to the Emergency department with a history of severe headache, which she described as the worst in her life, accompanied by dizziness and reactive asymmetric pupils. clinical examination was within normal except for bilateral abducens palsy, horizontal nystagmus and photophobia. The informed consent was taken from the patient.

Diagnostic assessment

A non-contrast brain Computed Tomography (CT) scan was performed to rule out subarachnoid hemorrhage. The CT showed no radiological significant findings. Magnetic Resonance imaging was not available in our primary health care facility and the clinical status of the patient was unstable so that she couldn't be transferred to a tertiary health care center where an MRI is available. Full laboratory tests were within normal ranges except for a clinically significant hypoglycemia and mild hyponatremia. Glucose level was checked multiple times to avoid measurement errors. However, she was hypoglycemic (Glucose = 52 mg/dl; level II hypoglycemia according to 2017 American Diabetes Association classification of hypoglycemia).

Laboratory findings: (White Blood Cells = 6200 /mm^3, Neutrophils/Lymphocytes: 55/45, Platelets = 330 × 10^3 /mm^3, Hemoglobin = 11.3 g/dl, sodium = 130 mEq/L, potassium = 4 mEq/L, Creatinine = 0.6 mg/dL, Glucose = 52 mg/dL)

Therapeutic intervention

Intravenous dextrose was administered and strabismus gradually resolved, and headache subsided within an hour.

Follow up and outcomes

A metabolic profile was ordered which was within normal ranges except mild decrease in sodium and hypoglycemia. A follow-up appointment with an endocrinologist was scheduled to evaluate the patient's condition and ensure there are no other underlying health issues. A dietary plan was established to maintain the patient's blood glucose levels within the normal range and reduce the risk of future hypoglycemic episodes.

DISCUSSION

Hypoglycemia can affect the oculomotor system in several ways. One of the most significant effects is impairing the fixation on a target ability. Studies have shown that during episodes of hypoglycemia, individuals are more likely to experience micro-saccades, which are small involuntary movements of the eyes that can disrupt fixation and lead to blurred vision[4]. Additionally, hypoglycemia can impair the ability to perform smooth pursuits, which are slow, tracking movements of the eyes that are necessary for following moving objects[4].

In this case hypoglycemia occurred because of prolonged fasting (more than 15 hours deprived of water and food) which might depleted the glycogen storage and caused this clinically significant hypoglycemia

The mechanisms underlying these effects are not fully understood, but it is thought that hypoglycemia may interfere with the metabolism of glucose in the oculomotor system, leading to a decrease in Adenosine Triphosphate (ATP) production and subsequent impairment of neural activity[5]. Additionally, hypoglycemia may affect neurotransmitter levels in the brain, including dopamine and acetylcholine, which are important for proper oculomotor function[6].

On April 6, 2023 we searched PubMed for similar cases using the terms Hypoglycemia and abducens palsy. A case reported by Anhaus et al. where a 56-year-old woman experienced increasingly severe hypoglycemic attacks with glucose levels dropping as low as 20 mg/dl and had insulinoma. She developed a right abducens nerve paresis lasted for six weeks[7].

Another case study in which an 85-year-old woman presented to the hospital with coma and roving eye movements. Laboratory investigations revealed low serum glucose levels. Brain MRI imaging showed extensive bilateral frontoparietal lesions on FLAIR and DWI. Although her blood glucose was corrected, she did not regain consciousness and her roving eye movements stopped the next day[8].

In conclusion, hypoglycemia can have significant effects on the oculomotor system, leading to impairment of fixation and smooth pursuit. Further research is needed to fully understand the underlying mechanisms and develop effective treatments for this condition.

NOTES

Ethics statement

The informed consent was taken from the patient.

Author contributions

Conceptualization: MHA. Data curation: MHA (M-Hozaifa Alothman), MHA (Muhammad Hussam Alothman). Formal analysis: MHA. Investigation: MHA. Methodology: MHA (M-Hozaifa Alothman), MHA (Muhammad Hussam Alothman). Resources: MHA. Software: MHA (M-Hozaifa Alothman), MHA (Muhammad Hussam Alothman). Supervision: MHA. Validation: MHA (M-Hozaifa Alothman), MHA (Muhammad Hussam Alothman). Visualization: All authors. Writing – original draft: All authors. Writing – review & editing: All authors.

Conflict of interest

There is no conflict of interest to disclose.

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Resolution of Stroke-Related Hemichorea-Hemiballismus with Haloperidol

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Hemichorea-hemiballismus (HC-HB) is a hyperkinetic disorder characterized by violent, unilateral jerking movements which usually improve to choreoathetosis with time. Etiology of HC-HB has been demonstrated in case reports and series, with acute stroke being one of the known etiologies. Among the rare post-stroke hyperkinetic syndromes, HC-HB is the most common. However, there is limited data on management and long term follow up of this debilitating condition when related to acute stroke. Here we describe a 79-year-old gentleman with acute caudate stroke, with resulting HC-HB, whose symptoms were managed with haloperidol while hospitalized. Resolution of HC-HB and subsequent discontinuation of haloperidol yielded an optimal patient outcome. Long term follow-up for this patient has demonstrated lack of symptom recurrence at 1 year. This case further supports the use of neuroleptics such as haloperidol as first line for management of HC-HB.

Keywords: Stroke; Hyperkinesias; Dyskinesia; Haloperidol

INTRODUCTION

Acute hemichorea-hemiballismus (HC-HB) is a consequence of approximately < 1% of all stroke[1,2]. Hemiballismus is a flinging, high amplitude and commonly violent movement of proximal limbs. Hemichorea is characterized by continuous, involuntary irregular movements, usually of slower cadence and lower amplitude.

Disruption of dopamine regulation may be the mechanism by which stroke originating within the basal ganglia can elicit HC-HB[3]. Management of these acute symptoms, therefore, have typically included dopamine antagonism, with variable success.

Here we detail a case of an elderly gentleman with an ischemic stroke, presenting as fluctuating aphasia and dysarthria that resolved and was followed development of persistent HC-HB within 24hrs of last known well. Management with haloperidol for his striking symptoms demonstrated significant improvement, allowing for discontinuation of the agent, without symptom recurrence by 1 year post stroke.

CASE

A 79-year-old gentleman with vascular risk factors of hypertension, hyperlipidemia, pre-diabetes, obesity, psoriasis and prior nicotine use was brought in by his wife to a primary stroke center after awakening with aphasia and mild dysarthria. He presented five hours from his last known well (LKW). Local stroke protocol was initiated, and noncontrast head computed tomography (CT) scan

noted left sided hyperdense MCA (middle cerebral artery) sign, consistent with acute thrombus. This was confirmed as a nonocclusive left M2 MCA thrombus by CT angiography of head and neck (Fig. 1A). Clinically, his National Institutes of Health Stroke Scale (NIHSS) was 0 and he had complete resolution of dysarthria thus intravenous (IV) thrombolysis (rtPA) or endovascular stroke treatment (EVT) were not indicated. He was given dual antiplatelet therapy (DAPT) and admitted to the hospital under observation.

While in the ED, his expressive aphasia briefly recurred, again spontaneously resolving 15 minutes later. Due to this stuttering course, he was transferred to a comprehensive stroke center.

During transfer to our comprehensive stroke center, he was noted to develop severe "right sided chorea-type movements" involving the arm, leg, and – to a lessor degree – face. Formal NIHSS remained 0, and he was still not considered to be a candidate for EVT. A trial of Ativan was successful in achieving an adequate MRI quality image, revealing infarctions to the caudate head, insular cortex, and corona radiata (Fig. 1B). Magnetic resonance angiography showed interval resolution of the thrombus involving the superior division of the left M2 MCA, but persistent occlusion of the inferior division. That evening, nursing noted worsening hyperkinetic movements such that he was unable to sleep due to violent right sided movements of his arm and leg and concern for resultant bruising of the right arm.

On hospital day (HD) 1, right sided movements persisted, developing more choreiform character and was noted to include his face. His wife also noted hyperverbosity, which was atypical for him. Decision was made to attempt to palliate symptoms with oral haloperidol 1 milligram twice daily. After one dose the patient experienced a decrease in the severity of symptoms, without negative sedating side effects and decision was made to increase dose to 2mg BID starting that evening. By that night movements were persistent however improving in the leg and face and he was able to sleep.

HD 2 was notable for significant improvement in all right sided movement by his third dose of haloperidol. By HD 3, his movements were minimal and his speech prosody returned to normal. Continued improvement in symptoms lead to haloperidol discontinuation by HD 4.

Stroke etiology was determined to be cardioembolic as workup as continuous telemetry revealed paroxysmal atrial fibrillation. Further telemetry monitoring demonstrated tachybradycardia syndrome and dual chamber pacemaker was placed by cardiology. DAPT was discontinued and direct oral anticoagulation (DOAC) was initiated the day after surgical procedure, on HD 4. After initial recommendations to discharge to a skilled nursing facility, his motor symptoms improved such that he was discharged home on HD 8. By time of discharge, no HC-HB movements were noted. By 1 year of follow up the patient has not had recurrence of symptoms.

DISCUSSION

Acute HC-HB is a rare consequence of stroke, with management generally accepted to involve dopamine antagonism, with variable results[2,4]. Here, we discuss a patient presentation of stroke with stuttering onset, likely of cardioembolic origin, with involvement of the caudate, insular cortex, and corona radiata. Develop-

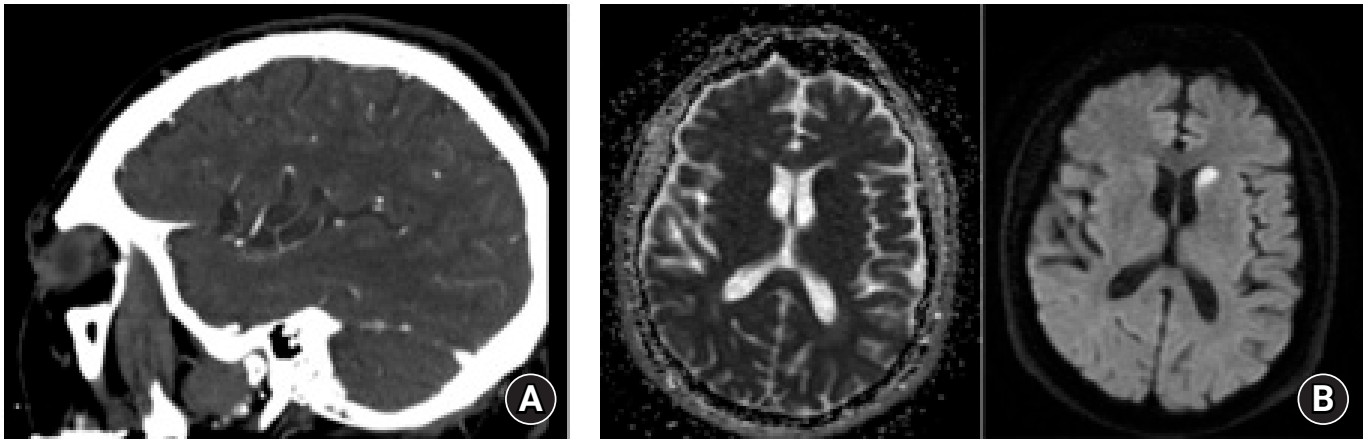

Fig. 1. (A) Computed tomography imaging from primary stroke center, demonstrating M2 lesion. (B) MRI images (left: apparent diffusion coefficient and right: diffusion weighted image) at comprehensive stroke center, after onset of hemichorea-hemiballismus symptoms.
MRI: Magnetic resonance imaging.

ment of HC-HB was noted within the first 24 hours and was successfully palliated with a trial of haloperidol.

While HC-HB is an overall rare symptom of stroke, amongst the post-stroke hyperkinetic symptoms, it is the most common. Risk factors for development of this phenomenon include location of stroke, as well as older age and possibly female gender[5,6].

Other conditions such as hyperglycemia (coined diabetic striatopathy)[7,8], less commonly vascular malformations, CNS toxoplasmosis in AIDS patients[4], tuberculoma[9], and amphetamine use[10] (although usually bilateral motor symptoms) have been published as alternative etiologies for this phenomenon.

Neuroanatomical classic teaching detail that insults to the contralateral subthalamic nucleus (STN) result in hemiballismus. More recently, a review of 29 patients with stroke which produced HC-HB were collated onto a reference brain map, identifying a broader network that may underlie this clinical phenomenon. Culprit lesions included: STN, caudate, putamen, other subcortical white matter, and cortex with each case demonstrating connectivity to the posterolateral putamen[3].

It is postulated that the underlying pathophysiology of HC-HB involves dysfunction in the Direct and Indirect Extrapyramidal pathway. This pathway functions to modulate the activity of cortical motor neurons thus facilitating voluntary movements and suppressing any unwanted involuntary movements. Striatal lesions result in increased excitation of motor cortex due to loss of thalamic inhibition resulting in unopposed motor activity and unwanted movements such as HC-HB.

Symptom onset has been documented as variable, with most occurring within 24 hours, however also commonly within one week of stroke onset[6]. It is typical, if present, for ballistic movements to occur at onset of symptoms, with a transition to choreiform movements, and sometimes dystonia. All aspects of the symptomatology, evolution, and timing (within 12 hours from initial symptom) were fitting in our patient. We hypothesize the initial presentation with aphasia and dysarthria to be more reflective of hypoperfusion in the superior M2 territory, with resolution of those symptoms upon spontaneous recanalization of the same vessel. The persistent occlusion of the inferior division and lenticulostriate arteries resulting in caudate head DWI restriction was felt responsible for HC-HB in our patient.

Neuroleptics have been used for dopamine antagonism effect, as well as topiramate and benzodiazepines[4]. Tetrabenazine has also been used in a dopamine-depleting manner to reportedly good effect. Dopamine receptor blockers, including first-and second-generation antipsychotics, have been generally considered the most effective agents to reduce the severity of choreiform movements, regardless of the cause. Benzodiazepines may also have a mild anti-chorea effect by potentiating the inhibitory effects of GABA, although the use of such agents is poorly documented. In our case, lorazepam produced useful for mild, temporary symptom improvement in preparation for MRI.

Literature on symptom resolution is variable, with cited recovery in anywhere from 10%–67% of cases[5,6]. There is a notable number of cases with unknown long term outcomes[6]. It has been suggested that those with a cortical lesion have improved rates of recovery vs. subcortical lesions, with sparse literature to support this.

In our patient, dopamine antagonism with haloperidol yielded remarkable improvement in symptoms, such that the agent itself was able to be discontinued after 4 days of use. Outpatient follow up demonstrated lack symptom recurrence since the initial stroke. This trial of haloperidol, with a meaningful follow up period of 1 year may suggest that, when effective, patients may be able to discontinue their treatment in the post-stroke setting.

CONCLUSION

This case highlights haloperidol as a viable management strategy in a striking presentation of stroke-related HC-HB, with long term follow up demonstrating sustained resolution of symptoms. While the symptom improvement is most notable, other aspects to this patient's presentation, which include caudate head involvement, time of onset, evolution of the motor syndrome, and long-term outcome, add to the literature characterizing this rare, stroke-related phenomenon.

NOTES

Ethics statement

Informed consent was obtained from the patient herein for publication of his clinical information.

Author contributions

Conceptualization: MA, Supervision: BS. Writing – original draft, Writing – review & editing: All authors.

Conflict of interest

There is no conflict of interest to disclose.

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Individualized Periprocedural and Intraprocedural Management for Coil Embolization of Unruptured Cerebral Aneurysm in a Patient with Severe Thrombocytopenia due to Liver Cirrhosis

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A female patient in her early 60's with advanced liver cirrhosis and thrombocytopenia having a platelet count under 30,000/μL, visited an outpatient clinic. Computed tomography angiography revealed an unruptured aneurysm on the left middle cerebral artery bifurcation with 6.0 mm of maximal diameter. Endovascular coiling was planned, considering the patient's medical condition. Eight pints of platelet concentrate were transfused 6 hours before the procedure, and a platelet count of 57,000/μL was achieved 3 hours before the procedure. No antiplatelet premedication and intraprocedural heparin was administered. A bail-out use of intra- or postoperative Tirofiban (Aggrastat®) was prepared for inadvertent thromboembolic events. The aneurysm was successfully occluded with no procedure-related event. The patient's hospital course was uneventful, and she was discharged without complications. Despite the potential hemorrhagic risk caused by hemostatic failure in patients with cirrhosis, successful endovascular coiling can be performed with highly individualized management.

Keywords: Intracranial aneurysm; Thrombocytopenia; Liver cirrhosis; Blood coagulation disorders

INTRODUCTION

Preprocedural antiplatelet therapy and intraprocedural anticoagulation are widely accepted methods to avoid thromboembolic events that may occur during or after an endovascular procedure for unruptured intracranial aneurysms[1]. However, in a particular population lacking adequate hemostasis, there may be a hesitation in adopting the conventional periprocedural antithrombotic management concerning the procedure-related hemorrhagic risk. Thrombocytopenia and hemostatic failure are common conditions in liver cirrhosis (LC) patients[2]. Although many studies have assessed procedure-related bleeding risk and periprocedural management in LC patients, there are no established guidelines for periprocedural hemostatic management in LC patients with thrombocytopenia, especially before neurointerventional procedures[2]. Herein, we report a case of successful endovascular coiling of an unruptured intracranial aneurysm (UIA) in a LC patient with severe thrombocytopenia. We also studied the appropriate

periprocedural and intraprocedural management for UIA coiling in LC patients with hemostatic defects.

CASE

A female patient in her early 60s visited the outpatient department complaining of a chronic headache. Computed tomography (CT) angiography revealed a saccular aneurysm at the bifurcation of the left middle cerebral artery with 6.0 mm of maximal diameter and 3.8mm of neck size (Fig. 1). The patient had nonalcoholic decompensated LC with a Child–Turcotte–Pugh score of 8 and was, categorized as class B. Laboratory tests revealed severe thrombocytopenia (30,000cells/μL), International normalized ratio (INR) of 1.22, activated partial thromboplastin time (aPTT) of 38.3 seconds (normal range of 28.0–45.0 seconds in our institution), and a fibrinogen level of 230 mg/dL (normal range of 190–450 in our institution). Considering the life expectancy of this patient with decompensated LC, observation of this unruptured aneurysm was also an option. However, the decision to treat the aneurysm was made due to the expectations of liver transplantation and the patient's fear of aneurysmal rupture. Endovascular coiling was planned, considering the patient's medical condition.

The traditional thresholds of platelet count > 50,000/μL and INR < 1.5 have been accepted for the safety of major surgery[3]. Based on literature on successful endovascular coiling of UIA in a patient with idiopathic thrombocytopenic purpura (ITP) with periprocedural platelet count of 53,000/μL, we decided to normalize the thrombocytopenia as much as possible, aiming for a platelet count > 50,000/μL[4]. Detailed blood transfusion procedures were performed in accordance with the Korean domestic blood transfusion guidelines. Eight pints of platelet concentrate were transfused 6 hours before the procedure, and a platelet count of 57,000/μL was achieved 3 hours before the procedure. No perioperative antiplatelet therapy was administered. Considering the shape of the aneurysm based on the CT angiography findings, simple coiling without an adjunctive device was planned. Off-label, bail-out use of Tirofiban (Aggrastat®) administration was prepared if rescue stenting was required or an inadvertent intraprocedural thromboembolic event occurred. Coiling was performed under general anesthesia, and systemic heparinization was not performed. Heparinized saline was used only for device preparation. A 6 French Envoy DA XB (Cordis, Miami Lakes, FL, USA) guiding catheter was advanced through a 7 French femoral sheath (Terumo, Tokyo, Japan). The aneurysm was selected using an SL-10 pre-shaped S microcatheter (Stryker, Fremont, CA, USA). Catheters and wires were navigated with extreme caution. Six detachable coils (Stryker, Fremont, CA, USA) were deployed, and complete aneurysm occlusion was achieved (Fig. 2). The arterial puncture site was closed using a suture-mediated device (Perclose; Abbott Vascular, CA, USA). The procedure was performed successfully without any copmlications. Diffusion magnetic resonance (MR) image acquired on the first postoperative day revealed multiple high embolic signals; however, the patient was asymptomatic (Fig. 3). The hospital course was uneventful, and the patient was discharged with a modified Rankin Scale score of 0. A 6-month follow-up MR angiography showed no evidence of recanalization, and the patient's general medical condition remained unchanged.

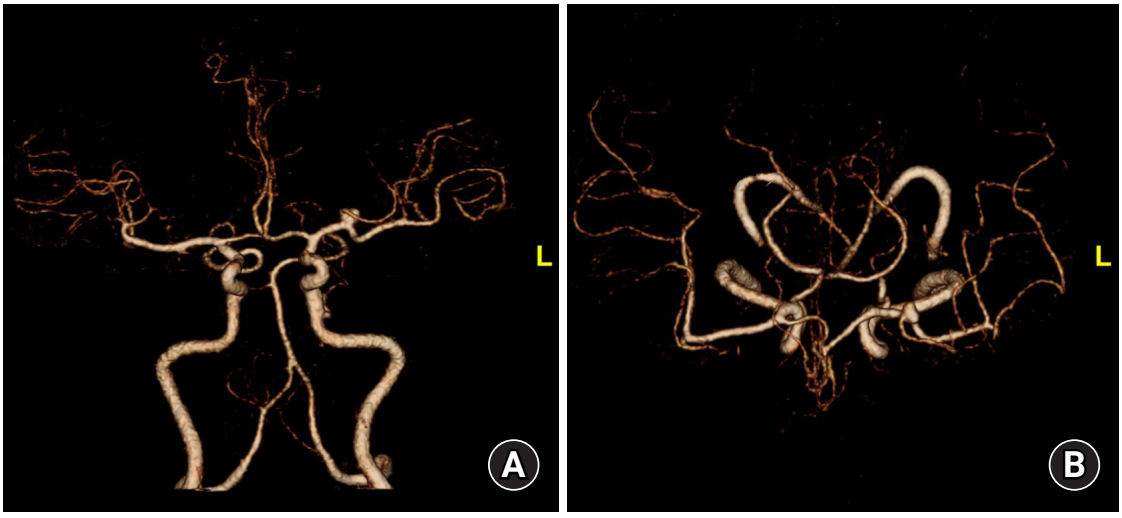

Fig. 1. (A) Anterior-posterior view and (B) dorsal view of computed tomography angiography revealed a saccular aneurysm at the bifurcation of the left middle cerebral artery.

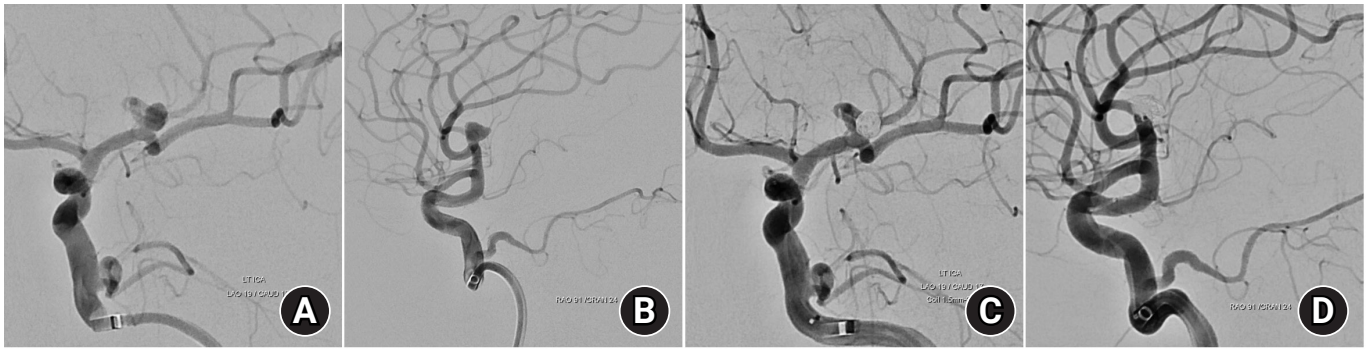

Fig. 2. (A) Working angle angiogram of anterior-posterior view and (B) Lateral view before coil packing, (C) Final angiogram of anterior-posterior view and (D) Lateral view showed complete occlusion of aneurysm.

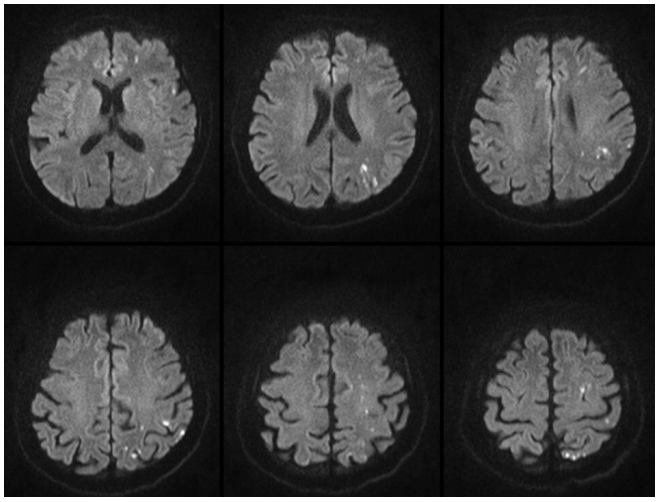

Fig. 3. Diffusion magnetic resonance image of the first postoperative day showed multiple high embolic signals, but the patient was asymptomatic.

DISCUSSION

Periprocedural management of thrombocytopenia in neurointervention

Literature on elective coil embolization of UIA in patients with thrombocytopenia is scarce[4]. Ishihara et al. reported endovascular trapping of a vertebral artery fusiform aneurysm in a patient with ITP[4]. That patient received glucocorticoid and high-dose gamma globulin to correct the platelet count from 29,000/μL to 53,000/μL, and the aneurysm was successfully occluded without complication[4].

Even in the whole field of neuroendovascular procedures, few studies have been conducted in patients with thrombocytopenia. Several studies on patients with acute ischemic stroke (AIS) and thrombocytopenia who underwent mechanical thrombectomy (MT), have reported that patients with thrombocytopenia did not suffer an increased risk of symptomatic intracerebral hemorrhage compared with those with normal platelet counts[5-7]. However, patients with severe thrombocytopenia, with platelet count < 50,000/μL, were rarely identified or unspecified in similar studies[5-7]. The expert opinion from the recently published Society of Neurointerventional Surgery guideline on MT for AIS patients is that hemorrhagic complication in patients with platelet count < 20,000/μL is concerning[8]. The guidelines also state that platelet transfusion for patients with a very low platelet count may be considerable[8]. However, a clear cut-off level for platelet count is not provided in the guideline[8].

Preprocedural hemostatic management for LC-induced coagulopathy

The consensus of the hemostatic goal for the high-risk procedure, including the arterial intervention of the central nervous system (CNS), is the same as the traditional thresholds of platelet count > 50,000/μL and INR < 1.5[3]. Consideration of platelet transfusion and correction of INR were also suggested but were only weakly recommended[3]. In LC patients who undego pathological changes in both the procoagulant and anticoagulant pathways, the hemostatic condition cannot be accurately assessed by traditional laboratory tests, such as INR, aPTT, and platelet count[2,3]. Therefore, preprocedural hemostasis guidelines recommend that physicians make judicious decisions of prophylactic preprocedural platelet transfusion in patients with cirrhosis[2,3]. This recommendation was extracted from studies on low-risk procedures, such as thoracentesis and paracentesis, the absence of CNS procedures, or unknown whether CNS or not[9-11].

Therefore, whether these results opposing platelet transfusion can be wholly adapted to neurointervention is questionable. Regardless of its volume and location, a hemorrhage within the CNS can be fatal. Reflecting this unique situation of the CNS, individualized decision-making regarding platelet transfusion for LC pa-

tients before high-risk procedures is recommended[2,3].

Prophylactic fresh frozen plasma for LC patients even before a high-risk procedure is not recommended because the risk of circulatory overload outweighs the benefit of its minimal increment in hemostasis[2,3]. The administration of thrombopoietin receptor agonists and 1-Deamino-8-d-arginine vasopressin to prevent procedure-related bleeding is discouraged due to insufficient evidence from studies on small sample size[2]. Only cryoprecipitate can be used to correct plasma fibrinogen levels > 100 mg/dL before a high-risk procedure[2].

Antithrombotic use for UIA coiling in patients with hemostatic failure

Before high-risk procedures for patients with cirrhosis, antithrombotics should be discontinued without bridging therapy unless there is an evident thrombotic risk, such as a high risk of venous thromboembolism or a presence of a mechanical heart valve, not exclusively for LC[3]. In current practice, antiplatelet therapy is typically administered when stenting is planned and is not always used before coiling without an adjunctive device[12]. Therefore, we omitted preprocedural antiplatelet agents for LC patients with severe thrombocytopenia in this study.

Generally, systemic heparinization is a preventive measure for thromboembolic events during procedures for UIAs[1]. However, heparin use for patients with cirrhosis has extremely limited indication and is contraindicated in patients with platelet count < 100,000/μL[13]. Even in situation of severe LC complication such as portal vein thrombosis, unfractionated heparin has been rarely used[2]. In our study, unfractionated heparin was used only for device preparation.

Off-label tirofiban use in patients with hemostatic defects

Even in cases of hemostatic failure, thromboembolic event caused by coil mesh or device may be a concern. Tirofiban has been widely used to manage acute thromboembolisms during coil embolization of cerebral aneurysms[14]. Tirofiban is a short-acting, potent Glycoprotein IIb/IIa receptor inhibitor capable of dissolving even a fresh thrombus[15]. In studies on continuous intravenous (IV) tirofiban infusion in a cohort of 86 patients during or after neuroendovascular procedures, no significant differences in intracranial hemorrhage were found between in-label and off-label use[15]. Its safety profile is acceptable even for off-label use beyond the contraindications, including thrombocytopenia (< 100,000/μL), aPTT > 1.3-fold, INR > 1.5, and severe liver insufficiency (Child–Pugh class C)[15]. Considering that the previous report was on IV maintenance infusion, intra-arterial tirofiban injection with a relatively lower dose and a short-acting mechanism seems acceptable for intraprocedural thrombolysis, even in patients with inadequate hemostasis. This study has limitations due to the nature of a case report. However, despite our best efforts of search, published literature on elective UIA coiling in patients with advanced LC and severe thrombocytopenia was scarce. Our study will help patients in similar situations of coagulopathy. And we raised the need for further research on intra- and periprocedural antithrombotic strategies in patients with hemostatic failure who require neurointerventional procedures.

CONCLUSIONS

A highly individualized approach is needed for hemostatic management of LC patients with severe thrombocytopenia before UIA coiling. We suggest prophylactic transfusion to achieve a platelet count > 50,000/μL and an INR < 1.5. Bail-out use of tirofiban for inadvertent intra- or postoperative thromboembolism may be considered for patients with hemostatic failure.

NOTES

Ethics statement

The study was approved by the Institutional Review Board (IRB) of Sanggye Paik Hospital Hospital (No. SGPAIK 2023-08-015). The retrospective nature of this case report waived the informed consent requirement.

Author contributions

Conceptualization: SYC. Data curation, Methodology, Writing – original draft: HJK, SYC. Formal analysis: SYC. Project administration: SYC. Visualization: SYC. Writing – review & editing: SYC.

Conflict of interest

There is no conflict of interest to disclose.

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Data availability

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Early Detection and Urgent Surgical Repair of Pharyngeal Injury after Anterior Cervical Surgery: A Case Report

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This case report addresses pharyngeal perforation, an uncommon complication after anterior cervical discectomy and fusion (ACDF). A 78-year-old male, who initially presented with quadriparesis, underwent ACDF. Post-surgery, the porridge he consumed was observed in the drain tube, leading to complications such as respiratory distress and fever. An emergency exploratory surgery was performed, and a suspected pharyngeal perforation was identified and treated with primary repair and sternocleidomastoid flap. Through thorough post-operative observation, we identified critical signs requiring immediate intervention, allowing for a successful recovery without additional complications. This report emphasizes the importance of early detection and intervention for complications following ACDF, providing valuable insights for clinical practice in neurosurgical intensive care.

Keywords: Anterior cervical surgery; Complication; Perforation; Pharynx; Spinal fusion

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) remains the prevailing standard for treating degenerative cervical myelopathy, especially when one or two-level herniated discs are present. Despite its efficacy, the anterior approach associated with ACDF can lead to certain complications. Dysphagia and hoarseness are most common[1], but more severe complications could arise. One severe, though rare, complication includes the inadvertent perforation of the cervical esophagus or hypopharynx. Such perforations are life-threatening and present a significant risk of descending mediastinitis. The severity of these complications is further highlighted by the challenges in managing infections and the uncertainty in the resulting cervical alignment deformations[2]. Hence, when considering post-operative management from a critical care medicine perspective, it is imperative to acknowledge that these complications necessitate immediate surgical intervention. This report outlines our experiences, emphasizing the significance of early detection and appropriate intervention following pharyngeal injuries after anterior spinal surgery.

CASE

A 78-year-old male presented to our institution with a six-month progressive history of quadriparesis. Preoperatively, the patient exhibited motor grade 3 strength in the right upper and lower limbs and motor grade 2 strength in the left upper and lower limbs. Preoperative cervical magnetic resonance imaging (MRI) demonstrated cord compression attributed to herniated nucleus pulposus (HNP) at the C3-4 level (Fig. 1). Consequently, ACDF was performed at this level.

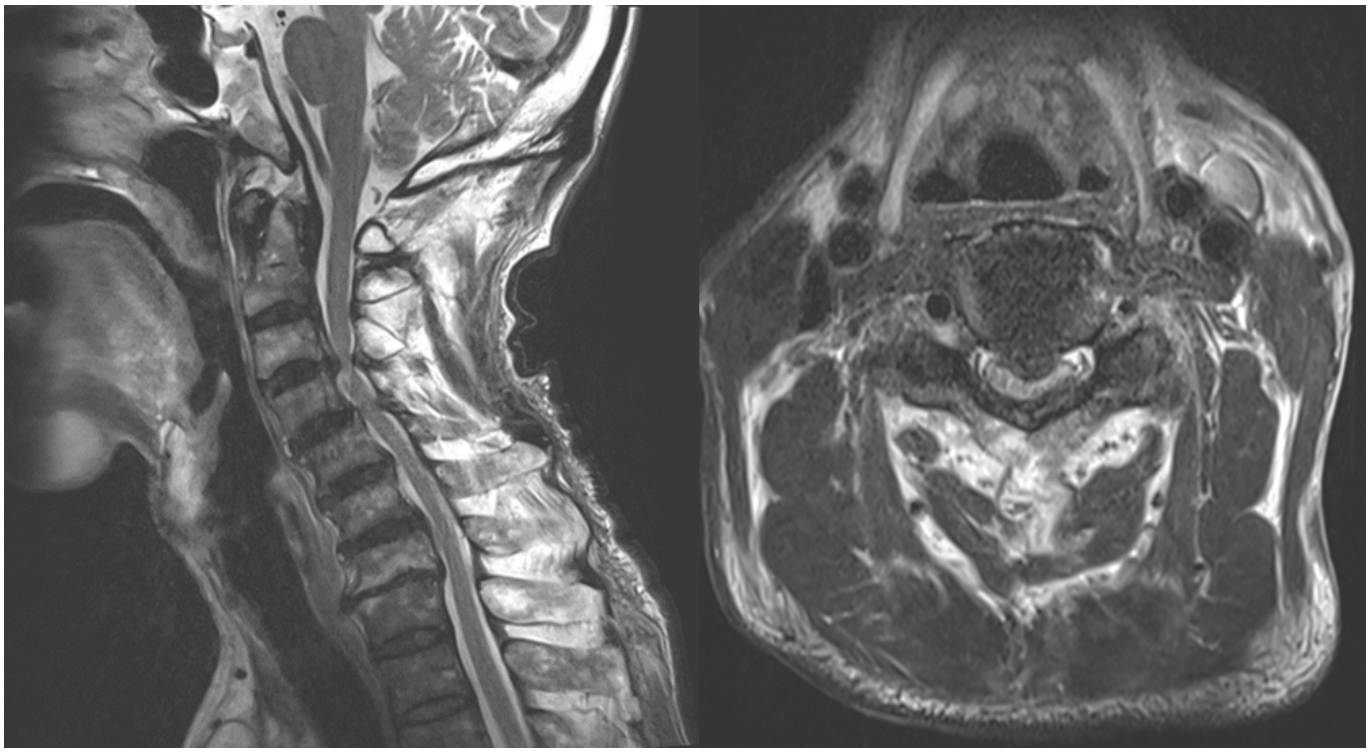

Fig. 1. The preoperative magnetic resonance imaging revealed severe stenosis with herniated nucleus pulposus at the C3-4 level, leading to cord compression and signal changes. This level was assessed as the symptomatic lesion, prompting the decision to proceed with anterior cervical discectomy and fusion surgery.

The intraoperative examination was unremarkable. Adhering to standard protocol, oral feeding commenced on the first post-operative day. However, the patient subsequently reported persistent coughing during meals and exhibited a fever of 38.1°C four hours after oral intake. Initially, this was considered a post-operative physiological fever and was closely monitored. The following day, a purulent, cloudy discharge was noted from the drainage catheter removal site (Fig. 2). This prompted the immediate administration of antibiotics (Vancomycin, Ceftriaxone) and intensified patient monitoring. Subsequent respiratory distress reduced oxygen saturation to 80%, and a chest X-ray identified pneumonia (Fig. 3), necessitating urgent intubation.

Suspicion arose that the cloudy fluid at the drain catheter removal site might have been orally ingested porridge rather than infectious pus, prompting consideration of pharyngeal wall perforation. This led to the decision to perform an emergent exploratory surgery. During the procedure, pharyngeal wall perforation was identified and repaired, with reinforcement provided using a sternocleidomastoid (SCM) muscle flap (Figs. 4 and 5). Following surgery, the patient was transferred to the neurosurgical intensive care unit (NSICU) for continued care. The intraoperative wound tissue culture yielded negative results. Subsequently, in consultation with

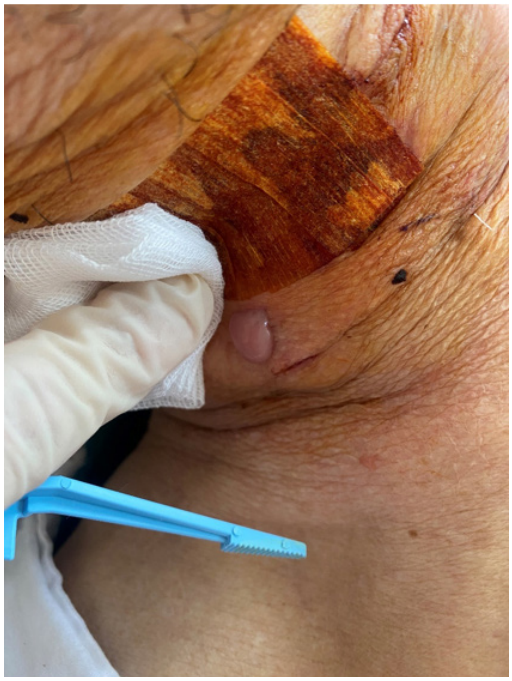

Fig. 2. The image depicts the appearance after removing the drain tube, from which purulent, cloudy fluid was observed. External drainage continued even after the removal of the Jackson-Pratt drain. Since it was the first day post-surgery, the substance was assessed not as pus but as porridge the patient had orally ingested.

the Infectious Disease team, the antibiotic regimen was adjusted to include piperacillin-tazobactam and vancomycin, which the patient continued to receive.

After the second surgery, minimal drainage was noted. The surgical site Jackson-Pratt (JP) drain was retained under negative pressure with the coordination of the Otolaryngology team. After a 12-day stay in the NSICU, the patient's pneumonia improved, enabling transfer to a general ward. Although two attempts at esophagography were made, the patient's limited cooperation rendered both efforts inconclusive. Given the minimal drainage and the clinical course, pharyngeal healing was hypothesized, prompting the initiation of oral feeding. Regrettably, this led to recurrent aspirations and a pneumonia relapse.

Consequently, L-tube feeding was instituted for approximately six weeks post-surgery, after which the patient successfully transitioned to an oral diet. Remarkably, no additional complications were encountered, such as surgical site infections or extensions to adjacent areas. Post-operative treatment was successfully concluded without further morbidity.

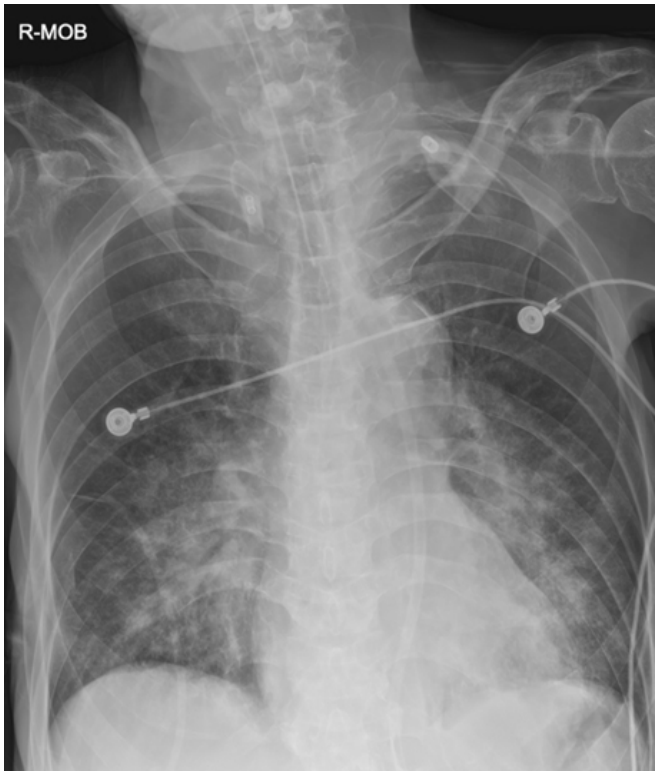

Fig. 3. Due to decreased oxygen saturation and respiratory distress, immediate intubation was performed. Subsequent chest X-ray confirmed the presence of aspiration pneumonia.

DISCUSSION

In this case, the patient's pharyngeal perforation was treated sim-

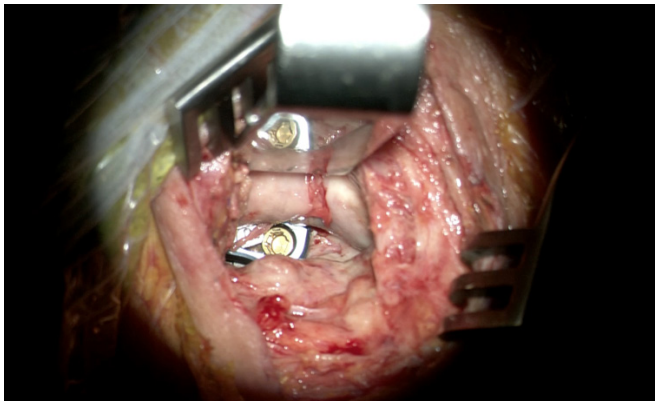

Fig. 4. A microscopic finding during the emergency exploratory surgery. A vertical perforation was identified in the pharynx. No inflammation or adhesion was observed at the margins, and the tissue appeared to be in a vital state.

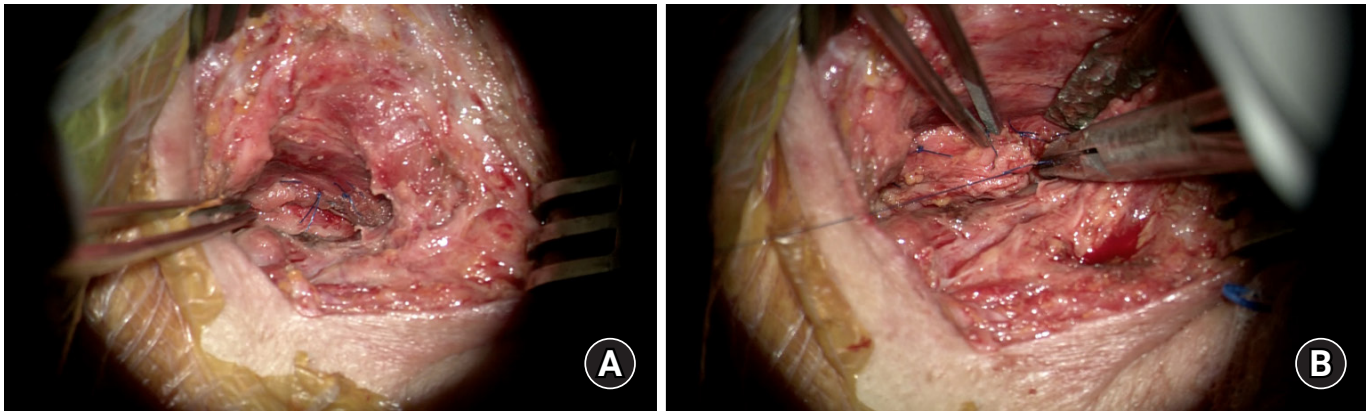

Fig. 5. (A) Intraoperative microscopic image showing the primary repair executed with Prolene 6-0 sutures. (B) Additionally, a sternocleidomastoid flap procedure was performed.

ilarly to the few other cases reported in the literature. The treatment involved early surgical repair of the pharyngoesophageal perforation, supported by a sternocleidomastoid muscle flap. The wound was then closed over a vacuum drain. The decision for immediate follow-up surgery was based on the drainage of the oral diet through the JP drain, and other signs like fever, dysphagia, cough, and following aspiration pneumonia were critical in suspecting a pharyngeal perforation.

The patient developed a fever on the first day after surgery, and we initially judged this to be a physiologic fever. This is because most early post-operative fevers are caused by surgically stimulated inflammation and resolve spontaneously. However, post-operative fever rates at the surgical site are reportedly higher after posterior cervical spine surgery than after anterior cervical spine surgery[3]. That may have been the first clue that a pharyngeal perforation had occurred.

After surgery involving an anterior approach to the cervical spine, the most common complaint is dysphagia caused by pharyngoesophageal retraction. A more serious complication is the perforation of the pharyngeal or esophageal tissue. This perforation can lead to dysphagia, local soft-tissue infection, and deeper infection, which might result in hardware failure, pseudarthrosis, osteomyelitis/discitis, sepsis, and in severe cases, infectious mediastinitis and death[4,5]. The incidence of these complications ranges from 0.02% to 1.52% and is higher when the initial spinal injury is trauma-related[2,4,6-9].

Acute injuries may occur accidentally during surgery due to incorrect placement or movement of sharp-toothed retractor blades in the esophagus. Retraction is especially dangerous when a nasogastric tube is used because the wall of the hypopharynx or esophagus might get "trapped" between the retractor and the tube. This can cause an ischemic injury and

then a secondary perforation.8 Early detection and the proper treatment of pharyngoesophageal injury after anterior spinal surgery can improve the patient's chances by preventing further complications[10].

The pharyngoesophageal junction is located posterior to the cricoid cartilage and is formed at the union between the pharynx and the esophagus. The region, Killian's triangle (approximately at the level of C5-6), is known to be most vulnerable to mechanical injury as it lacks protective muscular layers[11]. Another frequently affected area in pharyngoesophageal injury is the lateral aspect of the thyrohyoid membrane (approximately at the level of C3-4)[12]. Esophageal injuries are more likely to occur at these two specific locations[8].

When a patient has acute dysphagia after cervical spine surgery, physicians should consider the possibility of pharyngoesophageal perforation and immediately proceed with more diagnostic evaluations and treatment. The treatment depends on when the perforation is detected and how large it is. In the early stages, when the tissues are still healthy, the treatment of choice is primary suturing.2 This is made possible by checking for abnormalities in the drainage pattern during intensive post-operative care after anterior cervical spine surgery and by not overlooking the signs of dysphagia accompanied by fever.

CONCLUSION

This case highlights the critical need for prompt detection and intervention for pharyngeal perforation following ACDF, which is a rare yet severe complication. The perforation was effectively treated with rapid surgical repair using a sternocleidomastoid flap. Intensive post-operative care, paying close attention to signs such as abnormal drainage patterns at the surgical site and dysphagia accompanied by fever, is essential to prevent further complications and enhance the chances of a successful recovery.

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NOTES

Ethics statement

The patient and guardian have consented to the submission of the case report for submission to the KJCCM.

Author contributions

Conceptualization: SL, JBL, JWH, SA, YO. Data curation: JWJ. Formal analysis: SA. Methodology: JWH. Visualization: JWJ, SL. Writing – original draft: JWJ. Writing – review & editing: SL, JBL, JWH, SA, YO.

Conflict of interest

There is no conflict of interest to disclose.

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Erratum: Decompressive Laparotomy as a Treatment Option for Refractory Intracranial Hypertension in Patients With Traumatic Brain Injury: A Systematic Review

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In the article by William et al. in the April 2023 issue of Journal of Neurointensive Care (Decompressive Laparotomy as a Treatment Option for Refractory Intracranial Hypertension in Patients With Traumatic Brain Injury: A Systematic Review [pages 20-25]), the name of one of the author was incorrectly spelled. The name of the first author on first page of this article is incorrectly stated as William Florez-Perdo.

The correct author name follows:
Before
William Florez-Perdo
After
William Florez-Perdomo

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Special articles are devoted to providing updated reports by specialists in various fields or significant issues (e.g., history of the field) for the members of the society. The authors and topics of special drafts will be assigned and specially requested by the editorial board.The authors' views in special drafts will be respected as much as possible.

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Website

1. World Health Organization, The International Spinal Cord Society. International perspectives on spinal cord injury. Geneva, CH: World Health Organization, 2013(http://apps.who.int/iris/bitstream/10665/94192/1/WHO_NMH_VIP_13.03_eng.pdf?ua=1) [Accessed October 1, 2018]

Book

1. Conover WJ: Practical Nonparametric Statistics, ed 2. New York: Jon Wiley & Sons; 1971. p. 216-218.

Article in a Book

1. Ojemann RG: Surgical management of bacterial intracranial aneurysms in Schmideck HH, Sweet HH (eds): Operative Neurosurgical Techniques. Indications, Methods and Results, ed 2. Orlando: Grune& Stratton; 1988. p. 997-1001

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