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 neurological 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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I am very happy to congratulate you on making the Journal of Neurointensive Care (JNIC), the official journal of the Korean Neurointensive Care Society.

The creation of the journal was a long-awaited wish of the Korean Neurointensive Care Society. In the meantime, many excellent papers have been published in the society for more than 8 years, but I was very disappointed because there was no space to link to the journal.

In this journal we hope to present more active and advanced treatment and research methods by addressing various problems encountered in the treatment of central nervous system.

The life of a journal is for the participation of its members and for securing readers. It is based on active involvement of members and contribution of articles in order to place the position as representative of the society which focuses on the central nervous system in the world.

I believe that you will be able to submit various papers and opinions to the journal as if they are loving the Korean Neurointensive Care Society and to raise them as a global journal.

I appreciate to the editors of the Publication Committee for preparing the journal, and to the Korean Neurosurgical Society and Foundation for support to make the JNIC.

Yong Ko, M.D., Ph.D.
President, Korean Neurointensive Care Society
We Have a Historical Inaugural Issue of JNIC ahead

We are very pleased to announce that the official English journal of the Korean Neurointensive Care Society, Journal of Neurointensive Care (JNIC), have launched in October 2018. Since the Korean Neurointensive Care Society was founded as a division of the Korean Neurosurgical Society, we have deeply felt the need for official journals. In the meantime, the former presidents and the executives have been making efforts for the publication of the journal. Finally, in December of 2017, we started to prepare the launching of the English Journal by the resolutions of the executives including the present president, professor Yong Ko. We have repeatedly held meetings with editorial committee members and related persons and finally published an inaugural issue with the dedication of all authors, editors, and reviewers for the first issue.

The JNIC is the official English journal of the Korean Neurointensive Care Society and will be published twice a year. The JNIC publishes important papers covering the whole field of neurosurgical intensive care unit, including studies in neuroscience, neurology, neurocritical care and basic researches. Studies on rare cases and technical notes of special instruments or equipment that might be useful to the field of neurosurgical intensive care are also acceptable. Drawing upon the expertise of an interdisciplinary team of physicians from neurosurgery, neurology, anesthesiology, critical care, and nursing backgrounds, JNIC covers all aspects neurosurgical intensivists need to be aware of in order to provide optimal patient care.

In the future, the editorial committee of JNIC will do its best for the continuous development and become an international journal without being satisfied with the domestic journal. On the basis of JNIC, we will make an effort for the Korean Neurointensive Care Society to become a member of the Korean Medical Association. To do this, We would like to ask all members of Korean Neurosurgical Society and readers to be enthusiastic supporters and contributors to the JNIC.

Lastly, we would like to express special appreciation to professor Yong Ko, the present president of the Korean Neurointensive Care Society, professor Jun Seok W. Hur, an editorial staff, and the other editorial committee members for the publication of this journal.

Dong-Hyuk Park, M.D., Ph.D., Sang Gu Lee, M.D., Ph.D.
Editors-in-chief
Almost all neurosurgeons have concerned with postoperative uneventful recovery of their patients. However, although rare but endlessly, unexpected postoperative adverse events have occurred. Neurosurgeons, then are embarrassed and they search the causes and/or pathogenesis of such problems. Also rare, a few neurosurgeons may have been forced to litigate because of such unexpected and thus uninformed postoperative events.

As many postoperative complications, postoperative adverse events from cerebrospinal fluid (CSF) hypovolemia may have led to tough circumstances. Although the exact pathomechanisms have not been fully cleared, a CSF hypovolemia can be spontaneous or postoperative, clinically. And both the cranial and spinal surgeries can cause CSF hypovolemia. It usually have taken benign courses, and some cases may have exhibited serious outcomes. We, neurosurgeons, then have considered the possibility of CSF hypovolemia in differential diagnosis for unanticipated postoperative neurologic deterioration.

Since only the early recognition and prompt treatment may reverse those situations, the author try to settle and summarize comprehensively the postoperative adverse events due to CSF hypovolemia through the review of recently published or frequently cited reports on the postoperative CSF hypovolemia.

**Keywords:** Postoperative complications; Intracranial hypotension; Brain sag; Pseudohypoxic brain swelling; Remote site intracranial hemorrhage; Cerebrospinal fluid
The aim of this brief review of literatures is to attempt to settle and analyze postoperative CSF hypovolemia comprehensively. As a postoperative complication, both the cranial and spinal surgeries, CSF hypovolemas might have been expressed in three different clinical types of phenomena; 1) brain sag, 2) pseudohypoxic brain swelling (PHBS), 3) remote site hemorrhage. Basically, these three clinical phenomena do not have any new theoretical concept. The author’s proposed classification and pathomechanism for these phenomena is shown in Fig. 1.

**Fig. 1.** A proposed pathomechanism of three clinical phenomena due to postoperative cerebrospinal fluid hypovolemia.

Above three types of clinical entities may have, essentially identical pathophysiologic mechanisms such as venous stretching, angulation, occlusion, or disturbed intracranial venous return to heart then venous hypertension, and may arise from the intra-or post-operative excessive loss of CSF via diverse routes including subarachnoid cisternal spaces, lamina terminalis, extraventricular drain, lumbar drain or puncture, subgaleal or epidural negative vacuum drain, or traumatic fractures of the skull base. And they also may have similar symptoms and signs whether benign or malignant form although their radiologic characteristics are quite distinct one another. In the management for these three clinical phenomena, the general principles are fundamentally same. That is, flat or Trendelenberg positioning of the patient and prevention of further CSF loss. Of course, detailed methods of treatment for each type of this clinical condition by the postoperative CSF hypovolemia can be exceedingly different.

The brain sagging, also called ‘sinking brain syndrome’ is typically mild, and an upright positional headache is the most common presenting symptom. Other complaints such as nausea, vomiting, vertigo and visual disturbance may be subtle. Mild symptomatic brain sagging tends to recover spontaneously without any intervention except a few cases that may need the patients flat position for some time with or without epidural blood patches. Some brain saggings, especially immediate postoperative, may develop serious symptoms and signs such as coma with abnormal pupillary reflexes. Diagnostic criteria for severe brain sagging by Komotar et al. are as followings; 1) clinical signs of transtentorial herniation, 2) head computed tomography (CT) scans revealing effacement of the basal cisterns with an oblong brainstem, 3) improvement of symptoms and/or signs upon placing the patient in the Trendelenberg position. In those circumstances, early detection and identification of brain sagging then Trendelenberg positioning, with primary cause management to prevent further CSF loss is mandatory. This management policy is extremely significant to arrest progression to irreversible neurologic deficits or death and to promote whole recovery.

PHBS, relatively newly coined and defined term, may be also caused by excessive CSF loss, especially through the subgaleal or epidural negative pressure suction drain. And intraoperative CSF drainage may contribute to this complication. Variable degree of severity for PHBS can occur, although majority of PHBS cases are found to be grave neurologic deficits including not awakening from anesthesia, unreactive mydriasis, generalized seizure in uneventful elective neurosurgery. This prevalence of critical severity especially, before the report by Van Roost et al., may be insufficient understanding of this phenomenon. Mild to moderate degree of PHBS may occur presenting abnormal mental status, signs of abnormal brainstem function, and etc. Typical imaging characteristics are diffuse brain swelling particularly involving bilateral basal ganglia and thalami on head CT or magnetic resonance images (MRI). Angiographic findings are commonly non-specific and may demonstrate only a slow circulation time by microcirculatory disturbance from diffuse brain swelling. Principles of management are almost conclusive i.e., prevention of further CSF loss, Trendelenberg positioning, reduction of increased intracranial pressure. The prognosis of PHBS is variable, and usually depends on the time of correct diagnosis and treatment,
then may be fatal or may show complete recovery.\(^5\)

Remote site hemorrhage is the most repeatedly reported postoperative complication among three clinical phenomena due to postoperative CSF hypovolemia as mentioned earlier.\(^{2,4,8,12,21}\). By definition, remote site hemorrhage is bleeding at a location or locations distant from the site of original surgery.\(^{20}\) Although the first report was after supratentorial craniotomy it can occur after supra- or infra-tentorial surgery especially in sitting position,\(^3\) burr hole trephination,\(^9\) or spinal surgery,\(^{20}\) i.e., neurosurgery of almost all kinds. Its prevalence is rather wide-ranging, from 0.2 to 4.9% after different kinds of neurosurgery.\(^{2,4,8,12,21}\) Many hypotheses have been advocated and published for decades though the exact pathophysiologic cause has not been fully revealed yet. Radiologic findings are often non-specific except remote site intracranial hemorrhage in epidural, intracerebral, or cerebellar, which may appear solitary or multiple on head CT and/or MRI. Once such a adverse event develop it can become fatal. Surely, perfect restoration from neurologic deterioration after conservative management or asymptomatic cases are also possible.\(^{2,4,8,12,16,17,21}\)

More recently, remote site hemorrhages have been published after successful endovascular treatment of cerebral aneurysms.\(^4\)

The suggested mechanisms of this complication have been far from the CSF hypovolemia, and are beyond the scope of the author’s discussion.

In summary, it is very crucial for neurosurgeons to remember that 1) most CSF hypovolemias after neurosurgery are probably unnoticed, and thus much underrated. 2) we, neurosurgeons always consider the possibility of above three clinical phenomena for differential diagnosis in case of neurologic deterioration after uneventful neurosurgical procedure. 3) prevention, although limited, of excessive loss of CSF perioperatively may be the best way to treat complications from postoperative CSF hypovolemia. Clear verification of the root pathomechanisms for these unanticipated and tough complications would create further investigations.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**

New Parameters for Evaluating Cerebral Autoregulation and Pressure-Volume Compensatory Reserve in Neurocritical Patients

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The goals of neurocritical care are to resolve primary causes, minimize secondary insults and maximize patient recovery. Concepts such as intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebral blood flow have been long applied in neurocritical care; however, patient care involving these concepts alone is not satisfactory. Recently, new developments have allowed integrative physiological and biochemical data to be acquired and analyzed using multimodality monitoring with invasive devices. In addition, newly developed parameters have contributed to improvement in clinical outcomes in neurocritical patients. Beyond the indiscriminate application of threshold values for ICP and CPP in all patients, precision care can be provided by finding the optimal values of parameters and adjusting treatment for each patient in a particular time period. Here, we introduce representative parameters including the pressure reactivity index (PRx) for evaluating the status of cerebral autoregulation and optimal CPP (CPP_{opt}) and the correlation between the amplitude of ICP and the mean ICP (RAP) for assessing the pressure-volume compensatory reserve. Additionally, we present a bedside software and monitoring system that we recently developed for analyzing these parameters.

Keywords: Neurocritical care; PRx; CPP_{opt}; RAP

INTRODUCTION

Practice and knowledge in the field of neurocritical care have rapidly progressed. Physicians have managed neurocritical patients for a long time based on methods with a low level of evidence and their experience. However, neurointensivists currently care for patients by integrating methods with a higher level of evidence, new devices and parameters and by determining optimal values of physiological and biochemical parameters in each individual patient. We tried to introduce significant parameters for the pressure reactivity index (PRx) and the correlation between the pulse amplitude of intracranial pressure (ICP) and the mean ICP (RAP) with a new bedside monitoring system that they developed recently.
HISTORICAL PERSPECTIVE

Neurocritical care seems to have begun from the time point when the concept of ICP was formed. The existence of ICP was first recognized by Alexander Monro approximately 200 years ago. The Monro-Kellie hypothesis or doctrine suggests that the brain, cerebrospinal fluid (CSF) and blood maintain the balance of ICP within a nonexpandable skull. When a space-occupying lesion develops, CSF and venous blood decrease, and ICP is controlled within the normal range of pressure. However, when the volume of a new lesion is beyond the compensatory capacity, ICP abruptly increases followed by a decrease in cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) and ultimately brain herniation. Harvey Cushing developed the modern field of neurocritical care. He reported a research paper on the association among ICP, systemic arterial pressure and respiration in 1901. Saline-induced increases in ICP corresponds to increases in systemic arterial blood pressure and respiratory depression. Based on the previous research, the ‘Cushing reflex’ was defined. In the 1960s, Nil Lundberg began directly measuring ICP by inserting a ventricular catheter and reported normal and pathologic waveforms of ICP. Thereafter, ICP measurement was applied in the clinical setting for treating neurocritical patients. ICP control is most important goal of neurocritical care, especially in patients with traumatic brain injury. There are many guidelines for the care of neurocritical patients, among which the guidelines from the Brain Trauma Foundation are the most well described in detail. The Brain Trauma Foundation published the first edition of “Guidelines for the management of severe traumatic brain injury” in 1995, and successive editions have been updated in 1999, 2007 and 2016. Among them, a detailed description of each topic was reported in the 3rd version of the guidelines in 2007. The 3rd version dealt with blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for ICP monitoring, ICP monitoring technology, ICP thresholds, CPP thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics and sedatives, nutrition, antiseizure prophylaxis, hyperventilation and steroids. In the chapters about ICP and CPP thresholds, treatment with a low level of evidence is recommended to maintain ICP below 20 mmHg and CPP between 50 and 70 mmHg. These thresholds were not updated even in the 4th edition of the guidelines published in 2016. In addition, those are recommended in patients with intracerebral hemorrhage and acute ischemic stroke as they are. The fixed thresholds for ICP and CPP are currently applied like a central dogma in the genetics. However, physicians have felt that these thresholds are inappropriate in some patients and insufficient in improving clinical outcomes. Recently, in 2012, a randomized controlled trial was conducted in South America that compared the survival rates of patients with traumatic brain injury between an ICP monitoring group (maintaining ICP below 20 mmHg) and another group of patients who were monitored with imaging and clinical examinations. The study failed to show the superiority of ICP monitoring compared with the other group. Some questions still exist including the followings: (1) Are ICP and CPP sufficient for saving the brain? (2) Are the thresholds for ICP and CPP truly absolute for all patients? (3) Are ICP values that are measured truly exact measurements?

From these questions regarding the usefulness of ICP and CPP values, new physiological and biochemical parameters have been developed. In addition to ICP, CPP and CBF, data regarding brain oxygenation, glucose metabolism, neuronal electrical activity, brain water content, etc., are simultaneously collected and used for evaluating brain conditions and modulating appropriate treatment in each patient in a technique called ‘multimodality monitoring’. Multimodality monitoring is applied in limited medical institutions all over the world; however, this technique is expected to become popular in Korea in the near future.

CEREBRAL AUTOREGULATION AND ITS MEASUREMENT

The existence of cerebral autoregulation was established by Danish physicians in the 1970s. Cerebral autoregulation works between a mean arterial blood pressure (MAP) of 50 and 150 mmHg, and CBF is steadily maintained within the range of 45-50 mL/100 g/min by automatic regulation of vessel diameters. Thereafter, in 1997, a Cambridge group of physicians reported a new parameter that was able to indirectly measure the functional status of cerebral autoregulation, namely, the “pressure reactivity index (PRx)”. The PRx is the correlation coefficient between MAP and ICP. When cerebral autoregulation is impaired, increases in ICP lead to subsequent increases in MAP and cerebral blood volume in order to maintain CBF, and a vicious cycle without any regulations can form. In this situation, MAP and ICP are positively proportional, and the PRx increases. When cerebral autoregulation is preserved, increases in ICP are buffered by vasoconstriction and outflow of CSF and venous blood, resulting in limited increases in MAP. Thus, the slope between MAP and ICP becomes smoother, and the PRx decreases (Fig. 1). In real clinical situations, a group with lower PRx values showed more favorable outcomes than a group with higher values. Although there are some differences in standard PRx values among reports, PRx values higher than 0.2 - 0.3 are generally considered to indicate impaired cerebral autoregulation.
PRx, CPP_{opt} and RAP

In contrast, PRx values lower than 0.2 - 0.3 are thought to indicate preserved autoregulation. The same group subsequently proposed the concept of optimal CPP (CPP_{opt}) in 2002\(^\textsuperscript{11}\). When the PRx is at the lowest value, cerebral autoregulation is considered to be at its best, and CPP at this PRx value is also the best. Actually, when CPP is controlled as close to CPP_{opt} as possible, clinical outcomes are better. Thus, the most appropriate CPP is not within the absolute range of CPP = 50 – 70 mmHg, as recommended in some guidelines, and the best CPP can be different under different conditions in each patient (Fig. 2). Some institutions have developed bedside software and monitoring systems for acquiring real time PRx and CPP_{opt} measurements. Among them, the ICM+ software\(^\textsuperscript{6}\) (Cambridge, UK) and monitoring system from the Cambridge group is the most popular. Recently, we also developed a prototype of a Korean version of a software monitoring system for evaluating the pressure-volume compensatory reserve in 2004\(^{12}\). After gathering ICP data for a fixed time interval and distributing the ICP waveforms according to the frequency, waveforms are divided into 3 components: slow waves less than

**PRESSURE-VOLUME COMPENSATORY RESERVE AND RAP**

The Cambridge group also demonstrated a new parameter for evaluating the pressure-volume compensatory reserve in 2004\(^{12}\). After gathering ICP data for a fixed time interval and distributing the ICP waveforms according to the frequency, waveforms are divided into 3 components: slow waves less than

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**Fig. 1.** Concept and definition of the pressure reactivity index (PRx). A: In patients with impaired cerebral autoregulation, a vicious cycle occurs (upper), and the correlation coefficient (PRx) between MAP and ICP is positively increased (lower). B: In patients with preserved cerebral autoregulation, a positive cycle is formed by cerebral autoregulation (upper), and the PRx decreases and sometimes becomes negative (lower) (This is modified from reference 10). CBV, cerebral blood volume; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure.

**Fig. 2.** Concept of CPP_{opt}. When the PRx is the lowest, cerebral autoregulatory function is considered to be the best, and CPP at the lowest PRx is defined as CPP_{opt} (This is modified from reference 11). CPP, cerebral perfusion pressure; CPP_{opt}, optimal CPP; PRx, pressure reactivity index.
0.1 Hz, respiratory waves between 0.2 and 0.3 Hz, and pulse waves higher than 1 Hz generated by heart rate. Among them, the first pulse wave with the highest amplitude is detected at approximately 1 Hz, and the pulse amplitude of ICP (AMP) is defined as the amplitude of the first pulse wave.

Then, the correlation coefficient between AMP and mean ICP is defined as RAP. When the value of RAP is closer to 0, the pressure-volume compensatory reserve is considered to be good; when the value of RAP becomes closer to 1, the pressure-volume compensatory reserve is considered to be poor; and when the value of RAP becomes negative, brain function is thought to have shut down (Fig. 3). As intracranial volume increases and ICP begins to increase beyond the reserve capacity, AMP subsequently increases, and RAP ultimately increases; however, when ICP is constantly maintained with the aid of the compensatory reserve, AMP decreases and the value of RAP becomes closer to 0. RAP and the PRx are thought to be useful parameters for evaluating brain condition and modulating the types and intensity of treatment. As mentioned above, a bedside monitoring system developed by our group can display both of these features (Fig. 4).

CONCLUSION

The era is declining in which neurocritical patients are managed based on methods with a low level of evidence and the uniform criteria of conventional parameters. Recently, neurocritical care is performed based on personalized data and new parameters obtained from multimodality monitoring. Representative parameters include the PRx, CPPopt, and RAP. As newly developed devices and data are applied to manage these patients, their final outcomes are expected to improve, and we can save more patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Fig. 3. Concept of RAP. A: ICP waveforms in a timeline. B: After unfolding the ICP waves within a fixed time interval, some wave peaks are grouped in different frequency sections. The amplitude of the first pulse wave at approximately 1 Hz is defined as AMP. C and D: RAP is the correlation coefficient between AMP and the mean ICP. As the pressure-volume compensatory reserve decreases, AMP increases, and the value of RAP consequently becomes closer to 1. When the brain is completely damaged, AMP abruptly decreases, and the value of RAP can become negative (This is modified from reference 12). ICP, intracranial pressure; AMP, amplitude of ICP; RAP, correlation coefficient between AMP and mean ICP.
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Neurological Intensive Care for Acute Spinal Cord Injury Patients

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INTRODUCTION

In the 21st century, remarkable advances in medicine have led to the development of treatments for many diseases. However, in the case of spinal cord injury (SCI), no clear solution has been found to restore neural damage even after pouring astronomical research costs into the development of new therapeutic drugs. However, it is encouraging that many empirical knowledge about acute critical care has accumulated. We will review the problems that may appear in patients immediately after injury of the spinal cord and summarize the latest knowledge for the treatment of patients in the neurological intensive care unit.

CLINICAL MANIFESTATIONS

1. Motor and sensory deficit associated to injury level

Spinal cord injury levels due to vertebral fractures may differ from spinal cord injury levels in actual clinical symptoms. For example, fracture and spinal cord compression at T5 level could induce neurologic symptom below T10. Therefore, accurate manifestation of neurologic disorders should be held. Depending on the level of nerve damage, the sensory and motor nerve damage ranges are determined. Furthermore, there are also other important points to consider due to injured level as respiratory function failure, reduced sympathetic nervous function, immunodeficiency and etc.

2. Respiratory dysfunction

Phrenic motor neurons are located at C3-5. Therefore, damage above the C5 may affect diaphragm function, resulting in hypercapnia, hypoxemia, and poor secretion clearance\(^1\). Injuries above T11 destroy innervation to the intercostal muscles leading to reduced chest wall motion, and injuries above L1 may interfere the innervation to the abdominal muscle\(^1\). These neurological deficits can cause serious respiratory problems as dyspnea, apnea, and pneumonia.
3. Neurogenic shock

Injury above T6 may affect sympathetic nerve and induce hypotension and bradycardia due to vasodilatation. For cervical lesion injury, 20% of patients show neurogenic shock and almost all patients show bradycardia. If there is no evidence of severe blood loss after trauma, neurogenic shock should be considered.

NEUROGENIC INTENSIVE CARE

1. Methylprednisolone

Three large randomized clinical trials named National Acute Spinal Cord Injury Studies (NASCIS) were performed. First trial published at 1984 concluded there is on significant difference between high dose methylprednisolone group (1,000-mg bolus and daily thereafter for ten days) and standard dose methylprednisolone group (100-mg bolus and daily thereafter for ten days). However, second trial adapted different infusion amount and type of methylprednisolone for the treatment group (a bolus of 30 mg per kilogram of body weight, followed by infusion at 5.4 mg per kilogram per hour for 23 hours) compared with naloxone administrated and placebo groups. This study concluded methylprednisolone have positive effect for the neurology recovery at 6 months period after injury. The third NASCIS reported that patients recieving methylprednisolone within 3 hours of injury should be maintained on the treatment regimen for 24 hours and 48 hours when initiated 3 to 8 hours after injury. After this studies, high dose methylprednisolone has emerged as golden standard therapy for SCI. However, numerous comments against those have been poured out. Many scientist and physicians pointed out the statistical bias. Numerous retrospective and prospective studies refute the second and third NASCIS conclusion. They claimed there was no neurologic difference between high methylprednisolone group and placebo group, however, complications as gastrointestinal bleedings, wound infection, sudden death, pulmonary embolism seemed to be higher incidence for high dose methylprednisolone group. The two arguments are still conflicting and have been subject to contradictions that have been reversed according to the guidelines. Therefore, the authors recommends to use it according to the judgment of the clinician.

2. Hemodynamics

Maintenance of adequate blood supply to spinal cord is essential. Systemic hypotension should be avoided. Mean arterial pressure (MAP) between 85–90mmHg is recommended and systolic blood pressure under 90mmHg should be avoided for the first 7 days post injury. Oxygen saturation should be maintained over 90%. To prevent hypotension, lower extremity compression stockings, abdominal binding, volume augmentation (hydration, salt tablets or fludrocortisone), peripheral vasoconstriction (midodrine, ephedrine or droxidopa) should be considered.

3. Respiration

Depending on the level and degree of SCI, spontaneous breathing may not be smooth due to paralysis of the diaphragm, chest wall, and abdomen muscle. Therefore, if the patient's respiration pattern is paradoxical or if the saturation is continuously lowered to 90% or less, intubation and mechanical ventilation should be considered. Even if the breathing seems not so bad at early period, the oral secretions cannot be spit out well, so the airway obstruction often occurs. Theophylline could be helpful for respiratory function improvement. There are studies that muscle spasticity could affect respiration function, and in this case, baclofen could be helpful.

4. Pressure sores

With sensory loss and immobilization due to motor deficit, pressure sores develop rapidly. Sore starts with focal infection and if not controlled well, immunodeficiency and systemic infection could occur and life threatening condition could be caused. Prevention is the most important treatment. Frequent position change, using anti-sore mattress are helpful. Once a sore develops, daily dressing, surgical debridement, vacuum suction could be considered.

5. Pain control

Active control of pain is essential from the beginning of SCI treatment. If the pain is not controlled, the prognosis of the patient is adversely affected. Additionally to nociceptive pain, neuropathic pain as allodynia and hyperalgesia occur almost 40% of SCI patients. NSAIDs, anticonvulsants, antidepressants, and opioids should be considered.

CONCLUSION

SCI patients suffer various medical conditions from the early period of injury. Meticulous clinical manifestations and appropriate intensive treatments are mandatory.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.
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Surgical Treatment in Neurocritical Care for Acute Spinal Cord Injuries

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Traumatic spinal cord injury (SCI) is common devastating injury which results in enormous socioeconomic burden. Multimodal approach to the patient is essential in neurocritical care for SCI patients. Among various treatment modalities, surgical decompression and stabilization plays an important role. This article highlights the issues regarding surgical management of neurocritical and neurointensive care for SCI. Although there are still some debate regarding the optimal timing for surgery in SCI patients, it is clear by previous literature that surgery has a specific benefit for neurocritical care in SCI patients and early surgery benefits specific SCI patients. The goals of surgery in SCI are correcting and reducing the broken biomechanical alignment and stabilizing it by instrumentation while decompressing the neural structures. By understanding the role of surgery in SCI neurocritical care, we believe we can better access and treat these patients.

Keywords: Spinal cord injury; Neurointensive care; Neurocritical care; Spine

INTRODUCTION

Acute traumatic spinal cord injury (SCI) is a devastating condition which follows after high energy traumatic insult to the spinal cord, and the prevalence worldwide is more than 750 per million with annual increase5. As this type of injury usually leads to irreversible neurologic deficits, it finally results in huge social costs as well as great personal loss. The functional impairment following SCI and the socioeconomic burden is already well documented19. Although numerous previous studies have been introduced regarding the treatment for spinal cord injury and many new treatment modalities have been taken to the field, majority of hospitalized SCI patients still finally remain with residual neurologic deficits. Considering this impact of SCI on each patients personally, and also the social impact, proper approach to the individual patients and adequate selection of treatment modalities are of great interest.

When high energy insult occurs on the spinal cord, it gets damaged by two steps, which are primary and secondary injuries. It is a widely accepted concept that these two injury pathomecanisms lead to neurologic deficits25,10. Primary injury happens due to the initial impact on the spinal cord, and sudden spinal cord compression, and contusion while the secondary injury is rather a resultant cascade following the primary injury. The primary injury itself is irreversible, but there are some opportunity for neural salvation by minimizing the secondary
SCI and this is the point that most treatment modalities target. In a spinal surgeons perspective focused on neurocritical care, surgical intervention is also one of the therapeutic attempts targeting this point. In this article, the focus is on the role of surgical intervention in neurocritical care for SCI patients with a brief review on the pathophysiology of SCI.

PATHOPHYSIOLOGY OF SCI

As briefly mentioned in the introduction, SCI following high energy trauma to the spinal cord is a result of initial primary injury accompanied with a subsequent secondary injury. Thorough understanding of this pathomechanism is a key step to understanding SCI itself, and it also provides a basis for SCI management not only medical but also surgical treatments. Primary injury of the spinal cord occurs as a result of direct traumatic insult to the spine. It is commonly accompanied with breakage of the normal structural integrity of the spinal column, which results in compressive impact to the spinal cord. By this impact, direct trauma and description occurs to the neural tissues. At the same time, neuronal axons get damaged as well as blood vessels and cell structures of the spinal cord. By this primary insult the cascade of SCI is started leading to secondary injuries.

The secondary injury of spinal cord which is triggered by the primary injury, is a cascade of pathologic changes and it evolves over days or weeks. Shortly after the microvascular breakage by primary injury, a focal development of intramedullary hemorrhage occurs and edematous change follows. Hemorrhage and edema of the spinal cord does not only injure the neural axons of spinal cord, but also leads to impairment of proper blood perfusion within the cord. Impaired circulation then results in formation of microthrombus and vasospasm of microvasculature, which leads to more impaired circulation, finally a vicious cycle. Another phenomenon of secondary injury after SCI includes necrotic change of the injured cord. By exacerbated ischemia of the spinal cord, breakage of cellular membranes and dysregulation of ions occur, and the cord gets necrotic within a short time.

Considering the pathophysiology of SCI, there is no possible treatment for the initial impact of primary injury. However, the pathomechanism of secondary injury following SCI should be considered as the target for treatment. In order to maximize the effect of treatment, breaking into the early steps of secondary injury should be done, both medically and surgically.

SURGICAL TREATMENT IN NEUROCRITICAL CARE FOR SCI

It is important to optimize treatment and care for SCI patients, in order to minimize the risk of any possible loss of neurologic function. The therapeutic approach to SCI is rather a complex of multimodal neurocritical care and treatments. Neurocritical care for SCI includes various treatment steps including early pre-hospital immobilization, acute phase medical treatment, administration of neuroprotective agents, and of course surgical decompression and stabilization. In this article, the focus is on the role of surgical treatment in SCI neurocritical care.

Early surgical intervention has a significant role in controlling the secondary injury by getting rid of the compressive force made by SCI. If left untreated, ongoing dynamic damage of spinal cord cannot be stopped, and this secondary injury leads to progressive worsening neurologic deficits. Although surgical decompression and stabilization is a widely accepted therapeutic tool for SCI, there is still some points in debate regarding the timing of surgery or selecting right indications for surgery. In this section, we would like to discuss on these issues.

Rationale for surgical treatment

Surgical treatment for SCI cannot be defined in a uniform way. Each part of the spine ; cervical, thoracic, lumbar and sacral spines have each documented treatment principals, and they usually depend on both clinical and radiological classifications. In general, when considering the role of surgery in SCI, two gross points should be taken in to discussion. If the neural structure is mechanically compromised after trauma and SCI has occurred, proper decompression of the neural tissue is required. Another point is that if the primary insult has resulted in any displacement or instability of the spinal alignment, it should be reduced and then stabilized by proper instrumentations with or without instrumentation. Proper surgery can restore the mechanical stability and optimize clinical outcomes by giving the neural elements a chance to recover. So, the need of decompression and stabilization with proper fusion is a key factor and should be always taken into account when making decisions whether to operate the patient or not in SCI neurocritical care.

As mentioned in the prior section, the primary insult and injury itself is irreversible, and the initiation of secondary insult is inevitable. However, we can minimize the damage of the spinal cord my properly managing the secondary insult, and this is why mitigating secondary cord injury is the main target of neurocritical care in SCI. Both restoration of spinal stability and decompression of neural tissues can break through the vicious
cycle of SCI by minimizing secondary injury.\textsuperscript{5,15}

**Classification of Spinal Injuries and Surgical indications for SCI**

Several points should be thoroughly taken into discussion when considering a SCI patient as a candidate for surgery. Bony fracture morphology, integrity of the posterior ligamentous complex, the trauma mechanism and of course the neurologic status of the patient should all be considered.\textsuperscript{5,15} Prior to discussing about the surgical indications, the spinal injuries need to be well classified, both in order to well access the patients and also to decide proper treatment modalities according to the classifications. In this aspect, various classification systems have been introduced to support the physicians practice. Recently the Thoracolumbar Injury Classification and Severity Score (TLICS)\textsuperscript{14} and the Subaxial Injury Classification (SLIC)\textsuperscript{13} system are widely used as a classification tool for the thoracolumbar spine and cervical spine, respectively. (Tables 1 and 2) TLICS and SLIC have been developed as an alternative classification, as the formerly used systems were limited to classifying the injuries. TLICS and SLIC have advantage compared to those former classifications, not only regarding the simplicity and easy applicability but also by giving the physician a clue for surgical decisions.

Although there is an widely agreed consensus that surgical decompression and stabilization has a significant beneficial role for SCI patients,\textsuperscript{5,15} there is still debate regarding the documented indications for surgical intervention. In terms of “indications” for surgical treatment, there are only few, but significant indications. 1) Clinically and radiologically confirmed spinal cord compressive lesions with or without fractures, 2) SCI patient presenting with progressive neurologic deterioration and 3) significant instability proven by imaging studies.\textsuperscript{5,15}

### Optimal timing for surgical treatment

The optimal timing of surgery that may maximize the clinical prognosis of SCI patients are still controversial. For those whom come into the indications for surgical decompression, there are recent strong evidences that early decompression within 24 hours show better improvement than later surgeries. In a recent meta-analysis by Liu et al., the early decompression group presented significantly better neurologic outcome, earlier discharge and even a lower complication rate compared to later surgery group.\textsuperscript{8} In 2012 Fehlings et al. reported a study called the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS), which was a large multicenter prospective cohort study on the timing of surgery after SCI.\textsuperscript{5} 313 patients were involved and the clinical outcome were compared among groups; surgery within 24 hours after trauma and later than 24 hours after trauma. At 6 months post-operatively, early decompression group revealed 2.8-fold larger odds of 2 or more grades improvement in (ASIA) impairment scores. After the introduction of STASCIS study, early decompression surgery have become an feasible standard for making decisions regarding surgical timing, and many other studies have reported compatible results with this study.\textsuperscript{3,6-8,11} Not only proven by

**Table 1. Thoracolumbar Injury Classification and Severity (TLICS) score system**

<table>
<thead>
<tr>
<th>Contents</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury morphology</td>
<td></td>
</tr>
<tr>
<td>Compression</td>
<td>1</td>
</tr>
<tr>
<td>Burst</td>
<td>2</td>
</tr>
<tr>
<td>Translation/rotation</td>
<td>3</td>
</tr>
<tr>
<td>Distraction</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic status</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Nerve root injury</td>
<td>2</td>
</tr>
<tr>
<td>Complete cord injury</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete cord injury</td>
<td>3</td>
</tr>
<tr>
<td>Posterior ligamentous complex integrity</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Suspected/Intermediate injury</td>
<td>2</td>
</tr>
<tr>
<td>Definite injury</td>
<td>3</td>
</tr>
</tbody>
</table>

Non-surgical management for total score ≤ 3, surgeons decision for total score = 4 and surgical intervention for total score ≥ 5

**Table 2. The subaxial cervical spine injury classification system (SLIC)**

<table>
<thead>
<tr>
<th>Contents</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury morphology</td>
<td></td>
</tr>
<tr>
<td>No abnormality</td>
<td>0</td>
</tr>
<tr>
<td>Compression/Burst</td>
<td>2</td>
</tr>
<tr>
<td>Distraction</td>
<td>3</td>
</tr>
<tr>
<td>Rotation/translation</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic status</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Nerve root injury</td>
<td>2</td>
</tr>
<tr>
<td>Complete cord injury</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete cord injury</td>
<td>3</td>
</tr>
<tr>
<td>Continuous cord compression</td>
<td>1</td>
</tr>
<tr>
<td>Discoligamentous complex integrity</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Suspected/Intermediate injury</td>
<td>1</td>
</tr>
<tr>
<td>Definite injury</td>
<td>2</td>
</tr>
</tbody>
</table>

Non-surgical management for total score ≤ 3, surgeons decision for total score = 4 and surgical intervention for total score ≥ 5

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www.e-jnic.org
these evidence based clinical studies, it is already a widely agreed consensus by spinal surgeons. In 2010, Fehlings et al conducted a survey study asking for the preferred surgical timing to more than 900 active spinal surgeons\(^4\). More than 80% answered that they would operate a ASIA B or C patient within 24 hours, indicating that this timing is widely agreed by spinal surgeons. Therefore, medically stable patients without any other significant risk factors should be considered to be candidates for early surgery.

Recently, there are even some groups that insist that ultra-early surgery; decompression within 6 to 8 hours after SCI, should be done for even better surgical outcomes. However, more clinical evidence is needed to support this results.

On the other hand, this favorable outcomes of early decompression after SCI are rather limited to those whom present ASIA B or C. ASIA D neurologic complete deficits failed to show any difference of improvement even after early surgery\(^7\). Another group of patients whom seem that they less likely benefit from early surgical decompression are those with central cord syndromes. Central cord syndrome patients whom had early decompression did not show significant clinical difference according to the timing of surgery\(^11\).

**SUMMARY**

SCI usually results in devastating clinical outcomes, and proper neurocritical care is essential while managing these patients. Although there are still some debate regarding the optimal timing for surgery in SCI patients, it is clear by previous literature that surgery has a specific benefit for neurocritical care in SCI patients. The goals of surgery in SCI are correcting and reducing the broken biomechanical alignment and stabilizing it by instrumentation while decompressing the neural structures. Furthermore, by stabilization and decompression, minimizing the possible progressive secondary injuries to the spinal cord are the key role of surgery.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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Deep Vein Thrombosis and Pulmonary Embolism following Hemorrhagic Stroke

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Venous thromboembolism (VTE) after stroke is an infrequent but potentially fatal medical complication. The incidence of VTE was shown to be higher in hemorrhagic stroke than in ischemic stroke by several studies; however, no strategy for VTE screening and prophylaxis has been established. Lower extremity ultrasonography (US) is the diagnostic method of choice, but routine application for stroke patients is still debated. For prevention, graduated compression stockings (GCS) have little effect on VTE, and thigh-high GCS should be selected. Early use of intermittent pneumatic compression (IPC) has strong evidence for preventing VTE and is recommended in several clinical guidelines for managing intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Prophylactic heparin products are still debated for preventing VTE despite the risk of rebleeding or hematoma enlargement. To date, administering low-dose, low-molecular-weight heparin (LMWH) seems the best method to prevent VTE with less risk of hemorrhagic complications. However, the optimal product, dose, and timing are unclear.

Keywords: Venous thromboembolism; Deep Vein Thrombosis; Pulmonary Embolism; Stroke; Intracerebral hemorrhage

BACKGROUND

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are potentially fatal medical complications following intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). The incidence of PE after stroke (including both ischemic and hemorrhagic) is less than 1%; however, PE causes more than 50% of early deaths after stroke. As in ischemic stroke, patients with hemorrhagic stroke are prone to DVT due to immobility, possible hemiplegia, and older age.

Methods to prevent and properly manage VTE after ischemic stroke are relatively well established; however, strategies for hemorrhage stroke are not.

REVIEW

Incidence and risk factors

The incidence of VTE after stroke varies from 10-75% depending on the diagnostic criteria, tools, and study design. Many studies have reported a higher incidence of DVT or PE after ICH and SAH than after cerebral infarction or transient ischemic attack. In 2003, Gregory et al. retrospectively reported the incidence of DVT after hemorrhagic (n=1,926) and thromboembolic (n=15,599) stroke as 1.9% and 0.5%, respectively. In 2014, Stecker et al. reported a VTE incidence of 1.93% (1.37% of DVT and 0.68% of PE) in 1,605,000 ICH patients in 2005. In 2014, Stecker et al.
reported that the VTE incidence was 1.3% (33 of 2613 stroke patients, DVT=25, PE=3, both=5) and was higher in SAH and ICH than in ischemic patients. Higher National Institutes of Health Stroke Scale (NIHSS) score and heart failure were statistically significant risk factors in their study.

Meanwhile, the incidence of DVT is much higher in studies that used lower extremity ultrasonography (US). Lacut et al. reported a DVT incidence of 15.9% up to 10 days after ICH development. Yablonski et al. reported 16% DVT up to 120 days. In a Japanese series, Ogata et al. reported that 21 of 52 ICH patients developed DVT. Kawase et al. performed venous duplex US to detect DVT in 81 ICH patients, and 4, 9, and 17 (21%) patients were diagnosed at 1, 7, and 14 days, respectively. Female sex was the only independent predictor of DVT.

Although risk factors for stroke-related DVT are still debated, advanced age, high NIHSS score, hemiparesis, immobility, female sex, atrial fibrillation, intravenous or intra-arterial tissue plasminogen activator (tPA), and length of hospital stay have been identified. Male sex is considered to be highly associated with DVT in the general population.

**Diagnosis**

The location and extent of DVT should be identified, because DVT in infra-popliteal calf veins (below-knee or distal DVT) can spontaneously resolve and seldom results in PE. However, continuous monitoring is crucial because 1 in 6 distal DVTs progresses to proximal DVT, which carries a greater risk of PE. Clinical symptoms of DVT appear as local pain or tenderness and local leg edema in approximately 2/3 of DVT patients; however, these symptoms can be hidden in unalert hemorrhagic stroke patients. A clinical DVT prediction score (Wells score) can be useful but is still limited. Thus, it should be combined with D-dimer, (i.e., increased serum C-reactive protein [CRP] with normal fibrinogen with a fever of unknown origin can be useful but is still limited. Thus, it should be combined with D-dimer, (i.e., increased serum C-reactive protein [CRP] with normal fibrinogen with a fever of unknown origin) for evaluation.

The most important diagnostic tool is venous duplex US, which is accurate, safe, simple, and portable. Directly watching flow physiology with real-time Doppler imaging (duplex, continuous-wave and color-flow Doppler imaging) provides another advantage. To detect DVT, US has high sensitivity (93.2-95.0%) and specificity (93.1-94.4%) 19. The limitation of US is that it is only suitable to detect proximal DVT, not distal DVT or DVT above the inguinal canal. In those cases, MR and CT venography of the lower extremity and pelvis with contrast provide high sensitivity and specificity.

**Prophylaxis & treatment**

**Graduated compression stockings (GCS) / intermittent pneumatic compression (IPC)**

The CLOTS (Clots in Legs or Stockings After Stroke) trials included three randomized trials assessing the preventive effect of graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) in DVT in stroke patients. In CLOTS 1, 2518 stroke patients (including 232 ICH patients) were enrolled to investigate the preventive effect of thigh-high GCS and did not show reduced DVT, PE, or death. In CLOTS 2, the effectiveness of below-knee GCS and thigh-high GCS were compared in 1406 stroke patients. The incidence of DVT was higher in the below-knee GCS group (8.8% versus 6.3%; absolute difference, 2.5% points; 95% confidence interval, [CI] 0.7 to 4.4). Finally, CLOTS 3 enrolled 2876 stroke patients (including 376 ICH patients) and found that applying IPC as soon as possible reduced the incidence of DVT. The preventive effect was more prominent in ICH patients (6.7% versus 17.0%; odds ratio [OR], 0.36; 95% CI 0.17–0.75). In the 2015 American Heart Association (AHA) / American Stroke Association (ASA) Guidelines for the Management of Spontaneous ICH, GCS is considered not beneficial (Class III, level of evidence [LOE] A), but IPC should be used just after admission (Class I, LOE A). AHA/ASA Guidelines for the Management of Aneurysmal SAH do not describe the use IPC or GCS, but European Stroke Organization (ESO) Guidelines for the Management of Intracranial Aneurysms and SAH in 2012 and Korean Clinical Practice Guidelines for Aneurysmal SAH in 2018 recommended applying IPC, GCS, or both to prevent DVT.

**Unfractionated heparin (UFH) / low-molecular-weight heparin (LMWH)**

In ischemic stroke, prophylactic use of heparin or heparinoids has been broadly recommended. Kamphuisen et al. performed a meta-analysis of 16 randomized controlled trials dealing with heparin use to prevent VTE after acute ischemic stroke. They defined low-dose, unfractionated heparin (UFH) as ≤ 15,000 IU/day and low-dose, low-molecular-weight heparin (LMWH) as ≤ 6000 IU/day or weight-adjusted dose ≤ 86 IU/kg/day. High-dose UFH reduced PE but increased ICH or extracranial hemorrhage (ECH), and low-dose UFH reduced thrombosis but not PE and increased the risk of ICH or ECH. Meanwhile, high-dose LMWH decreased both DVT and PE but increased the risk of ICH or ECH, and low-dose LMWH decreased the risk of both DVT (OR=0.34, 95%; CI=0.19—0.59) and PE (OR=0.36, 95%; CI=0.15—0.87) without increased risk of ICH (OR=1.39, 95% CI=0.53—3.67) or ECH (OR=1.44, 95% CI=0.13—16). ESO guidelines for VTE in immobile patients with acute ischemic stroke recommend prophylactic anticoagulation with UFH.
Prophylactic use of heparin or heparinoids to prevent DVT after hemorrhagic stroke has not received consensus agreement due to the increased risk of hemorrhage or rebleeding. In 1991, Boeer et al. administered low-dose UFH (5000 IU per 8 hours) 2 and 10 days after ICH in 68 patients and reported significantly reduced PE without increasing ICH. They suggested that heparin can re-open occluded vessels in cerebral infarctions but seldom expands hematomas surrounding cerebral tissue due to elevated pressure. They ultimately recommend its use. Despite several limitations of the study design, several small prospective studies were performed thereafter. Kiphuth et al. reported no fatal PE and a moderate increase in hematoma (20-30%) after using LMWH (Enoxafarin 4000IU, dalteparin 2500 IU) within 36 hours for 97 ICH patients. Orken et al. showed that administering LMWH did not increase ICH but failed to decrease VTE compared to GCS only. In 2011, Paciaroni et al. reported a meta-analysis of four controlled (randomized or non-randomized) studies of heparin use to prevent DVT in ICH patients and found that heparin (UFH or LMWH) significantly reduced PE (1.7% vs. 2.9%; RR, 0.37; 95% CI, 0.17–0.80; p = 0.01) but not DVT (4.2% vs 3.3% [RR, 0.77]; 95%CI, 0.44–1.34; p = 0.36). However, hemorrhage did not increase significantly (8.0% vs. 4.0%; RR, 1.42; 95% CI, 0.57–3.53; p = 0.45) and mortality decreased non-significantly (16.1% vs. 20.9%; RR, 0.76; 95% CI, 0.57–1.03; p = 0.07). They concluded that heparin use should be considered with caution for high-risk patients. Khan et al. performed a systematic review of DVT in acute stroke and concluded that UFH administration should be considered for high-risk patients even in ICH and SAH. However, their conclusion does not seem to be clear. AHA/ASA Guidelines for the Management of Aneurysmal SAH and Korean Clinical Practice Guidelines for Aneurysmal SAH also indicate a lack of sufficient evidence for heparin use in SAH patients. However, the AHA/ASA Guidelines for the Management of Spontaneous ICH recommend low-dose LMWH or UFH for immobile ICH patients 1-4 days from onset until after bleeding stops (Class IIb, LOE B). To date, real-world recommendations for low-dose LMWH use are unclear, including optimal timing, dose, and products.

**CONCLUSIONS**

Because DVT following hemorrhagic stroke is an uncommon but fatal complication, early detection is crucial. Lower extremity US is the most recommended diagnostic tool, but clinical signs are preferred for immobile patients. IPC should be applied just after admission to the intensive care unit to prevent DVT. Although, the evidence is still limited, heparin could be used for high-risk patients; low-dose LMWH seems to be the most preferred form.

**Abbreviation**

ICH     Intracerebral hemorrhage
SAH     Subarachnoid hemorrhage
PE     Pulmonary embolism
DVT     Deep vein thrombosis
VTE     Venous thromboembolism
CT     Computed tomography
MRI     Magnetic resonance imaging
US     Ultrasonography
UFH     Unfractionated heparin
LMWH     Low-molecular-weight heparin
GCS     Graduated compression stockings
IPC     Intermittent pneumatic compression

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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The Prognostic Value of Optic Nerve Sheath Diameter in Patients with Poor-Grade Subarachnoid Hemorrhages

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Objective
We evaluated if the optic nerve sheath diameter (ONSD) on brain computed tomography (CT) could be used to predict neurological outcomes of patients with poor-grade subarachnoid hemorrhage (SAH).

Methods
This was a retrospective and observational study of adult patients with poor-grade SAH admitted January 2012 through June 2017. Initial brain CT was performed within 12 hours from onset of SAH. Follow-up brain CT was performed within 48 hours from onset of SAH and after aneurysmal treatment. The primary outcome was neurological status upon six months later assessed with Glasgow Outcome Scale (GOS, 1 to 5).

Results
Among 59 patients with poor-grade SAH, survival to discharge was identified in 47 (79.7%) patients. Of these 47 survivors, 39 (66.1%) had good neurological outcomes (GOS of 3, 4 or 5). In this study, initial ONSDs and follow-up ONSDs in the poor neurological outcome group were significantly greater than those in the good neurological outcome group (all p<0.03). The intracranial pressure (ICP) was monitored in only 13 (22.0%) patients at that time of follow-CT scanning. Using simple correlation analysis, there was a linear correlation between ONSD and ICP (ρ=0.683, p=0.010). In ROC curve analysis for prediction of poor neurological outcome, ONSDs and ONSD indices had considerable predictive values (C-statistics: 0.683 to 0.804) and similar predictive performances for poor neurological outcome.

Conclusion
The ONSDs and ONSD indices measured on CT scanning may be beneficial for predicting neurological outcomes in patients with poor-grade SAH.

Keywords: Optic nerve sheath diameter; Brain computed tomography; Subarachnoid hemorrhage
INTRODUCTION

Subarachnoid hemorrhage (SAH) is a complex neurovascular syndrome and a devastating condition with high mortality and morbidity rates for those that survive the initial hemorrhage. In SAH patients, the level of consciousness on admission is the most critical early predictor of clinical outcome. Patients with poor-grade SAH (World Federation of Neurosurgeons [WFNS] grade 4 and 5) could have high mortality and poor neurological outcome. However, there are recent reports on patients with poor-grade SAH treated early and aggressively with coil embolization and neurointensive care could achieve a good neurological outcome. Therefore, to accurately evaluate the prognosis of these patients, new predictors other than the initial level of consciousness are needed.

Poor neurological outcome is usually secondary to early brain injury or delayed cerebral ischemia in SAH patients. Uncontrolled intracranial hypertension results in decreased cerebral perfusion and transient global cerebral ischemia. Therefore, early monitoring of intracranial hypertension may be beneficial in predicting neurological outcomes of the patients with poor-grade SAH.

Measurement of optic nerve sheath diameter (ONSD) has been proposed as an alternative method for detection of intracranial hypertension. However, if ONSD may be beneficial to systemically estimate neurological outcomes of patients with poor-grade SAH has not been reported. Therefore, the objective of this study is to investigate if the ONSD with some modifications could be used to predict neurological outcomes of patients with poor-grade SAH.

MATERIALS AND METHODS

Study population

This was a retrospective, single-center, and observational study of adult patients with poor-grade SAH admitted to the neurosurgical intensive care unit at Samsung Medical Center January 2012 through June 2017. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2018-07-154). The requirement for informed consent was waived due to its retrospective nature. Clinical and laboratory data were collected by a trained study coordinator using a standardized case report form. We included patients with SAH admitted to the neurosurgical intensive care unit during the study period. Those that were obtunded or unconscious (a score of ≤12 on the Glasgow Coma Scale) on admission to the hospital and those given brain computed tomography (CT) scan within 12 hours from onset of SAH were selected. Those given follow-up brain CT scan were performed after treatment of ruptured aneurysm. Of these patients, we excluded patients under age 18, those with malignancy whose expected life span was less than one year, those with insufficient medical records, those with a history of head trauma, neurosurgery, cardiac arrest, or chronic neurological abnormality on admission, and those that transferred from other hospitals after more than one day of onset of SAH. In addition, we excluded patients with anomaly of orbits, orbital mass lesions, and ocular or retro-orbital injury. A total of 59 patients with poor-grade SAH were analyzed in this study (Fig. 1).

Definitions and outcomes

In this study, poor-grade SAH was defined as World Federation of Neurosurgical Societies (WFNS) grade 4 and 5. The primary outcome was neurological status upon six months later assessed with Glasgow Outcome Scale (GOS, 1 to 5). GOSs of 3, 4, and 5 were classified as good neurological outcomes. GOSs of 1 and 2 were considered poor neurological outcomes. We thoroughly reviewed medical records. Patients were graded on the GOS by two independent neurologists. Initial brain CT angiography was performed within 12 hours from onset of SAH. Follow-up brain CT was performed within 12-48 hours from onset of SAH and after aneurysmal treatment. If aneurysmal treatment was not possible, a follow-up brain CT scan was performed within 48 hours. For all CT studies, 64-channel scanners (Light Speed VCT; GE Healthcare, Milwaukee, Wisconsin, USA) with a 5-mm slice width were used. Brain CT images were reviewed by two independent neurologists. Investigators blinded to clinical information opened these CT scans for each patient using commercial image-viewing software (Centricity RA1000 PACS Viewer; GE Healthcare, Milwaukee, Wisconsin, USA). Optic nerve sheath diameter (ONSD) and eyeball transverse diameter (ETD) were measured using the same initial CT scan and subsequent scan. ONSD was measured at a distance of 3 mm behind the eyeball, immediately below the sclera in a perpendicular vector in reference to the linear axis of the nerve. The images were changed to the ‘chest/abdomen’ window (window width 300 & window level 10) and were magnified threefold on the particular image slice that demonstrated the largest diameter of the optic nerve sheath. ONSD was measured from one side of the optic nerve sheath to the other as a section through the center of the optic nerve. The transverse diameter of the eyeball was chosen because the ONSD is usually measured in the transverse plain. ETD was defined as the maximal transverse diameter of the eyeball measured from one side of the retina to the other (in-to-in, Fig. 2B). The ONSD/ETD index was defined as multiplied...
median ETD (22.5 mm) by average value of bilateral ONSDs over average value of bilateral ETDs (22.5 × ONSD average / ETD average). The intracranial pressure (ICP) at that time of follow-up CT scanning was defined as immediately measured ICP after the CT scanning.

**Statistical analyses**

All data are presented as medians and interquartile ranges (IQRs) for continuous variables and numbers (percentages) for categorical variables. Data were compared using Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Simple linear regression was used to plot the relationship between simultaneously measured ONSD and ICP. Spearman's rank correlation coefficient (ρ) was calculated to evaluate correlation between ONSD and ICP. Predictive performances of ONSDs and ONSD indices were assessed using area under the curve (AUC) of the receiver operating characteristic (ROC) curves for sensitivity vs. 1-specificity. AUCs were compared using the nonparametric approach published by DeLong et al. for two correlated AUCs. Optimal cut-off value of each ONSD and its modification for predicting poor neurological outcome was obtained by ROC curve and Youden index. All tests were two-sided and p values < 0.05 were statistically significant. Data were analyzed using IBM SPSS statistics version 20 (IBM, Armonk, NY, USA).
RESULTS

Baseline characteristics and clinical outcomes
The median age of patients was 64 (IQR: 53-73 years). Of 59 patients, 18 (30.5%) were males. Hypertension (45.8%) and smoking (18.6%) were most common comorbidities among poor-grade SAH patients. Thirty-five (59.3%) patients were Hunt and Hess grade 5 and 32 (54.2%) patients were WFNS grade 5. Forty-two (71.2%) patients had ruptured aneurysms of anterior circulation. Around middle cerebral artery (27.1%) and anterior communicating artery (20.3%) were most common location of ruptured aneurysm. However, aneurysm or ruptured aneurysm was not detected in four patients (6.8%). Treatment of ruptured aneurysm was performed within 72 hours in most patients (83.1%). Endovascular coiling of the ruptured aneurysm was performed in 36 (61.0%) patients. Surgical clipping was performed in 12 (20.3%) patients. Delayed cerebral ischemia accompanied in 16 (27.1%) patients. Baseline characteristics of SAH patients are presented in Table 1. Survival to discharge was identified in 47 (79.7%) patients. Of these 47 survivors, 39 (66.1%) had good neurological outcomes (GOS of 3, 4 or 5, Fig. 1).

Optic nerve sheath diameters and their modifications
In this study, initial ONSDs and follow-up ONSDs in the poor neurological outcome group were significantly greater than those in the good neurological outcome group (Table 2). However, initial ETD and follow-up ETD were not significant differences between the good neurological outcome group and poor neurological outcome group (p=0.227 and p=0.108, respectively). The ICP was monitored in only 13 (22.0%) patients at that time of follow-CT scanning. Using simple correlation analysis, there was linear correlation between ONSD and ICP (p=0.683, p=0.010) (Fig. 3). In ROC curve analysis for prediction of poor neurological outcome (Fig. 4), the C-statistic of initial ONSD_max was 0.729 (95% CI: 0.583 to 0.875). A cut-off > 6.33 mm had a sensitivity of 80.0% (95% CI: 56.3% to 94.3%) and a specificity of 69.2% (95% CI: 52.4% to 83.0%). The C-statistic of follow-up ONSD_average was 0.760 (95% CI: 0.633 to 0.887). A cut-off > 6.26 mm had a sensitivity of 70.0% (95% CI: 45.7% to 88.1%) and a specificity of 74.4% (95% CI: 57.9% to 87.0%). The C-statistic of follow-up ONSD/ETD was 0.804 (95% CI: 0.684 to 0.926). A cut-off > 6.46 had a sensitivity of 65.0% (95% CI: 40.8% to 84.6%) and a specificity of 87.2% (95% CI: 72.6% to 98.7%). However, there were similar predictive performances of ONSDs and ONSD indices for poor neurological outcome; the predictive performance of follow-up ONSD/ETD for poor neurological outcome was not significantly different compared to that of initial ONSD_max or follow-up ONSD_average (p=0.199 and p=0.156, respectively).

DISCUSSION
In this study, we evaluated if the ONSDs and their modifications could be used to predict neurological outcomes of patients
**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Good neurological outcome</th>
<th>Poor neurological outcome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) — median (IQR)</td>
<td>58.0 (49.0 – 68.0)</td>
<td>72.0 (61.5 – 76.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gender, male — no. of patients (%)</td>
<td>11 (28.2)</td>
<td>7 (35.0)</td>
<td>0.812</td>
</tr>
<tr>
<td>BMI (kg/m²) — median (IQR)</td>
<td>23.4 (21.1 – 26.5)</td>
<td>22.0 (20.2 – 24.0)</td>
<td>0.206</td>
</tr>
<tr>
<td>Hypertension — no. of patients (%)</td>
<td>20 (51.3)</td>
<td>7 (35.0)</td>
<td>0.362</td>
</tr>
<tr>
<td>Current smoker — no. of patients (%)</td>
<td>8 (20.5)</td>
<td>3 (15.0)</td>
<td>0.872</td>
</tr>
<tr>
<td>Diabetes mellitus — no. of patients (%)</td>
<td>3 (7.7)</td>
<td>4 (20.0)</td>
<td>0.338</td>
</tr>
<tr>
<td>Previous stroke — no. of patients (%)</td>
<td>3 (7.7)</td>
<td>0 (0.0)</td>
<td>0.518</td>
</tr>
<tr>
<td>Hunt &amp; Hess Classification — no. of patients (%)</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>4</td>
<td>22 (56.4)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17 (43.6)</td>
<td>18 (90.0)</td>
<td></td>
</tr>
<tr>
<td>WFNS grade — no. of patients (%)</td>
<td></td>
<td></td>
<td>0.044</td>
</tr>
<tr>
<td>4</td>
<td>22 (56.4)</td>
<td>5 (25.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17 (43.6)</td>
<td>15 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Fisher classification — median (IQR)</td>
<td>4.0 (3.0 – 4.0)</td>
<td>4.0 (4.0 – 4.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>Modified Fisher classification — median (IQR)</td>
<td>3.0 (3.0 – 4.0)</td>
<td>4.0 (3.5 – 4.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Glasgow Coma Scale — median (IQR)</td>
<td>7.0 (4.0 – 8.0)</td>
<td>4.0 (3.0 – 6.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>Pupil reactivity — no. of patients (%)</td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Both intact pupil reflex</td>
<td>27 (69.2)</td>
<td>6 (30.0)</td>
<td></td>
</tr>
<tr>
<td>One unreactive pupil</td>
<td>3 (7.7)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Both unreactive pupil</td>
<td>9 (23.1)</td>
<td>12 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location — no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>8 (20.5)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral artery &amp; distal</td>
<td>5 (12.8)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery &amp; distal</td>
<td>14 (35.9)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>1 (2.6)</td>
<td>6 (30.0)</td>
<td>0.016</td>
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<tr>
<td>Posterior communicating artery</td>
<td>6 (15.4)</td>
<td>3 (15.0)</td>
<td></td>
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<tr>
<td>Posterior circulation</td>
<td>4 (10.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>No aneurysm</td>
<td>1 (2.6)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus — no. of patients (%)</td>
<td>23 (59.0)</td>
<td>16 (80.0)</td>
<td>0.185</td>
</tr>
<tr>
<td>Intraventricular hemorrhage — no. of patients (%)</td>
<td>18 (46.2)</td>
<td>15 (75.0)</td>
<td>0.066</td>
</tr>
<tr>
<td>EVD — no. of patients (%)</td>
<td>32 (82.1)</td>
<td>8 (40.0)</td>
<td>0.003</td>
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<tr>
<td>Vasospasm — no. of patients (%)</td>
<td>20 (51.3)</td>
<td>4 (20.2)</td>
<td>0.021</td>
</tr>
<tr>
<td>Delayed cerebral ischemia — no. of patients (%)</td>
<td>13 (33.3)</td>
<td>3 (15.0)</td>
<td>0.134</td>
</tr>
<tr>
<td>Early treatment within 72hr — no. of patients (%)</td>
<td>39 (100.0)</td>
<td>10 (50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aneurysm management — no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coiling</td>
<td>27 (69.2)</td>
<td>9 (45.0)</td>
<td>0.127</td>
</tr>
<tr>
<td>Clip operation</td>
<td>10 (25.6)</td>
<td>2 (10.0)</td>
<td>0.284</td>
</tr>
<tr>
<td>Endotracheal intubation during over 24hr</td>
<td>23 (59.0)</td>
<td>20 (100.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Decompressive craniectomy — no. of patients (%)</td>
<td>5 (12.8)</td>
<td>3 (15.0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Barbiturate coma therapy — no. of patients (%)</td>
<td>2 (5.1)</td>
<td>3 (15.0)</td>
<td>0.427</td>
</tr>
</tbody>
</table>

IQR : interquartile range, BMI : body mass index, WFNS : World Federation of Neurosurgeons, EVD : external ventricular drainage

with poor-grade SAH. Major findings of this study were as follows: 1) the patients with poor-grade SAH had considerable survival rate (79.7%) and favorable neurological prognosis (66.1%); 2) Simultaneous measurement of ONSD on CT and ICP were moderately correlated; 3) In initial CT and follow-up CT, ONSDs and ONSD indices of the poor neurological outcome group were significantly greater than those of the good neurological outcome group and these markers could be used to
predict neurological outcomes of patients with poor-grade SAH. Although it is difficult to predict the outcome following SAH, level of consciousness on admission would be associated with prognosis of SAH patients. One widely accepted predictor is the WFNS grade based on the level of consciousness as assessed by the Glasgow coma scale. Especially, patients with poor WFNS grade SAH historically have had high mortality and poor neurological outcomes. However, in recent years, a considerable number of patients with poor-grade SAH treated aggressively with early coil embolization and supportive neurointensive care could achieve a favorable neurological outcome and survival. Therefore, to accurately evaluate the prognosis of patients with poor-grade SAH, other predictors other than the initial level of consciousness are needed.

In patients with poor-grade SAH, poor neurological outcome is usually secondary to early brain injury or delayed cerebral ischemia. Secondary cerebral injury can occur, that is the additive cerebral injury characterized by an imbalance in post-resuscitation cerebral oxygen delivery and use, ultimately culminating in neuronal death. In addition, cerebral autoregulation may be disturbed to different extents and disturbed autoregulation in SAH is associated with delayed cerebral ischemia, vasospasm and unfavorable outcome. Especially, uncontrolled intracranial hypertension results in decreased cerebral blood flow and transient global cerebral ischemia and associated with early brain injury and poor neurological outcome. Therefore, early monitoring of intracranial hypertension may be beneficial in predicting neurological outcomes of the patients with poor-grade SAH.

Measurement of ONSD has been proposed as an alternative method for the detection of increased intracranial pressure. The optic nerve is surrounded by cerebrospinal fluid because it is a part of the central nervous system. Therefore, increased intracranial pressure will be transmitted through the subarachnoid space surrounding the optic nerve, within the nerve sheath, especially the retrobulbar segment, unless circulation of cerebrospinal fluid is not blocked. ONSD on initial brain CT may be correlated with neurologic outcomes after traumatic brain injury. Simultaneous measurement of ONSD on initial CT and intracranial pressure were correlated, and ONSD was indicative of intracranial hypertension in patients with severe traumatic brain injury. In this study, ONSD measured on CT scanning may be also a good predictive marker associated with intracranial pressure and prognosis in patient with poor-grade SAH.

This study has several limitations. First, it was a retrospective review of medical records. Therefore, the GOS was also retrospectively determined based on medical records. Second, the non-randomized nature of the registry data may have resulted in selection bias. Although brain CT scans were performed within 48 hours after SAH, a major limitation of this study may be that the CT scans were performed at different time settings. Third, invasive ICP monitoring was performed in a limited number of patients after aneurysmal treatment. Finally, our study was conducted at one institution and involved a lesser number of subjects. Although there were no significant differences between ONSDs and their modifications in this study, there may be different outcomes in larger cohorts. Therefore, future studies with larger cohorts are needed to validate these findings.

CONCLUSION

The ONSDs and ONSD indices measured on CT scanning may be used to predict neurological outcomes of patients with poor-grade SAH.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.
INFORMED CONSENT

Informed consent was obtained from all individual participants included in this study.

REFERENCES

Clinical Advantage of Propofol Compared with Barbiturate for the Coma Therapy in the Patients with Severe Traumatic Brain Injury

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Objective
Barbiturates have been demonstrated to reduce intracranial pressure (ICP), but adverse effects, which include hypotension and a long recovery time, make clinical applications difficult. Propofol is also known to have same effect. In the present study, we undertook coma therapy using propofol or barbiturate and compared clinical value in the practical point.

Methods
From June 2014 to April 2017, 38 patients with severe traumatic brain injury underwent thiopental or propofol coma therapy for the 3 days following neurosurgery. Seventeen patients were treated with thiopental (group A) and 21 patients with propofol (group B).

Results
Mean doses were 6.1 mg/kg/hr of thiopental and 4.4 mg/kg/hr of propofol. In group A, mean bispectral indexes were 29.4 on day 1, 27.4 on day 2, and 26.0 on day 3, and in group B, 31.4 on day 1, 29.9 on day 2, and 27.8 on day 3. Mean ICP was 16.8 cm on day 1, 24.4 cm on day 2 and 15.1 cm on day 3 in group A, and 18.3 cm on day 1, 25.4 cm on day 2 and 18.0 cm on day 3 in group B. To maintain systemic normotension, dopamine was infused continuously at mean doses of 10.2 μg/kg/min in group A and 4.4 μg/kg/min in group B. Mean times to stationary state were 32.9 hours in group A and 6.6 hours in group B.

Conclusion
The present study suggest that propofol coma therapy has less systemic hypotension and shorter time to stationary state than thiopental therapy for achieving the same depth of anesthesia and ICP-reducing effect.

Keywords: Propofol; Barbiturate; Coma therapy; Bispectral index; Traumatic brain injury
INTRODUCTION

The potential neuroprotective effects of barbiturates and propofol have been long recognized. These drugs induce a dose-dependent reduction in the cerebral metabolic rate of oxygen (CMRO₂) until silence on electroencephalography (EEG), after which additional doses have no beneficial effects. Furthermore, they can reduce cerebral blood flow (CBF) in the non-ischemic brain by increasing vascular resistance and reduce intracranial pressure (ICP). Numerical theories have been proposed to explain the ability of barbiturates and propofol to prevent or treat cerebral ischemia. The most quoted major neuroprotective mechanism involves the dose-dependent diminution of CMRO₂ (up to 50 percent) in human and animals until EEG silence. Other potential mechanisms of neuroprotection include: stabilization of lysosomal membranes, the attenuation of intracellular calcium concentrations, anti-oxidative and anti-excitotoxic processes.

The general brief is that maximal neuroprotection is achieved at doses producing silent EEG. However, higher doses can cause many complications in clinical practice. Moreover, smaller doses may be as efficacious as those required to obtain burst suppression. This is important when considering the deleterious side effects of barbiturates, because of: 1) cardiopulmonary dose-dependent depressant effects and the prolonged ventilation required in patients receiving burst-suppression doses, 2) the increased risk of infection attributable to barbiturates and the need for invasive monitoring, and 3) a depression of mental status that obscures neurological evaluations.

However, propofol has a shorter recovery time and induces less systemic hypotension than barbiturate. Therefore, coma therapy using propofol might be more convenient and less complicated than therapies based on barbiturate. In an attempt to compare the clinical application of two drugs, such as depth of anesthesia, changes of ICP, methods to maintain systemic normotension, recovery time from coma therapy and their complications, we performed retrospective study of coma therapy after craniotomy or craniectomy for severe traumatic brain injury (TBI) using propofol or thiopental as general anesthetic agents in two patient groups.

MATERIAL AND METHODS

From June 2014 to April 2017, 38 patients underwent coma therapy after brain surgery for the severe TBI at our institute. Of these, 17 patients (group A) underwent coma therapy with thiopental (Pentotal Sodium®) after brain surgery for the first 18 months (from June 2014 to November 2015), whereas, 21 patients (group B) underwent coma therapy with propofol (Fresofol 2%) during the next 17 months (from December 2015 to April 2017).

Based on preoperative consciousness of patients and intraoperative findings, the following conditions were considered before deciding to perform neuroprotective coma therapy: 1) in severe TBI patients with Glasgow Coma Scale (GCS) score < 9; 2) in the case of that severe brain swelling and midline shifting may lead to cerebral herniation; 3) in the case of that discoloration of brain and weak or absent brain pulsation of the operative findings.

Monitoring of burst-suppression patterns by EEG

After brain surgery, all the patients were transfer to a neurosurgical intensive care unit under a deep hypnotic state. The induction of coma therapy and anesthetic agent titration targeted the appearance of EEG burst-suppression patterns. EEG signals were obtained using gold cup electrodes applied to the scalp with cream, and were located according to the international 10-20 systems. Skin impedance was maintained at < 5 KΩ. The following leads were recorded: left and right frontal-mastoid (F₂-A₂, F₀-Z₀, channels 1 and 2), left and right frontal-C₂ (F₀₁-C₀₂, F₀₂-C₀₂, channels 3 and 4), plus a ground electrode placed at the center of the forehead. EEGs were recorded using a portable Aspect A-1000 EEG monitor (Aspect Medical System, Inc., Natick, MA, USA).

Setting of bispectral index (BISTM)

After achieving a burst-suppression pattern on the portable EEG, we replaced electrodes for the BISTM (BisSensor; Aspect Medical Systems, Inc., Newton, MA, USA) on the forehead, as specified by the manufacturer, and measured signals using an Aspect A-2000 EEG monitor (software version 3.3; Aspect Medical System, Inc., Newton, MA, USA). For polysomnography, we placed a midline frontoparietal electrode for EEG, an electrode at canthus and above unilateral eye for electro-oculography and a submental electrode for electromyography. BIS scores on the monitor were recorded at 2-hours interval using a monitor and data were collected. And then we compared the scores between two groups.

Anesthetic procedures

In group A, thiopental was administered in increments of 50-100 mg intravenously at 1- to 5-minutes intervals, and in group B, propofol was administered in increments of 10-20 mg intravenous push at 5- to 10-minutes intervals in an attempt to achieve an EEG burst-suppression pattern. BIS scores were
then recorded. Anesthetic doses were incrementally and slowly adjusted upward to achieve the desired endpoint, i.e., an EEG burst-suppression pattern, and BIS scores were then recorded.

After the induction of general anesthesia and loss of consciousness (no response to verbal commands, loss of eyelid reflex, and loss of self respiration), respiration was conducted using a mechanical ventilator with 30–40% oxygen via an endotracheal tube. No other neuromuscular blockers were used. After determining target BIS scores below 40 with silence on EEG, to maintain general anesthesia, patients in group A received thiopental and those in group B propofol at doses of between the previously determined target BIS score +5 and –5.

Other monitoring during therapy

Patient’s anesthetic states were clinically monitored using the modified Observer Assessment of Alertness and Sedation (MOAAS) scale, i.e., when a patient responded readily to his/her name spoken in normal tone a score of 5 was allocated; when a patient responded lethargically a score of 4 was allocated; when a patient responded only after calling in a loud voice or repeatedly a score of 3 was allocated; when a patient responded only after mild prodding or shaking a score of 2 was allocated; when a patient did not respond to mild prodding or shaking a score of 1 was allocated; and a score of 0 was allocated when a patient did not respond to a noxious stimulus.

ICP was monitored by use of epidural fiberoptic catheter and sensor that was placed in the space between dura and craniectomized muscle or scalp. Digitalized numbers on the ICP monitor were recorded every 2 hours. Vital signs were checked and recorded every hour. When systolic blood pressure fell below 100 mmHg, a catecholamine (e.g., dopamine) was used to raise and maintain systolic blood pressure to at least 100 mmHg; doses administered were recorded.

Recovery time from coma therapy to stationary state

After the discontinuance of anesthetics, patient consciousness was checked every two hours using the MOAAS and GCS scores. Recovery time was calculated from the time of stopping anesthesia to the point when these scales indicated a neurologically stationary state, which was checked at least 12 times with 2-hours interval. When the patient recovers slowly after a day, the identical results in the 6 times sequential repeated tests was determined as stationary state. When a patient’s vital signs, neurological signs, and respiration became stable, mechanical ventilation was stopped. No thiopental or propofol antagonists were administered. And then, the recovery time was compared between two groups.

Statistical analysis

The t-test, the Chi-square test and Fisher’s exact test were used to compare the two groups in terms of baseline characteristics and each parameter for assessment. Results were considered significant when p-values were less than 0.05. Statistical analyses were performed using SPSS version 20.0 (SPSS Institute, Inc, Chicago, IL)

RESULTS

Characteristics of the patient populations

Table 1 summarizes patient characteristics and initial diagnoses. There were 16 male and 22 female patients of mean age of 54.5 years (range: 33-68) when coma therapy was performed. In group A, there were 10 men and 7 women of mean age 55.5 years (range: 37-68), and in group B, there were 9 men and 12 women of mean age 53.7 years (range: 33-68). Initial diagnoses were as follows; 16 acute subdural hemorrhages (7 in group A and 9 in group B), 10 traumatic intracerebral hemorrhage (4 in group A and 6 in group B), 5 diffuse cerebral hemorrhagic contusion (3 in group A and 2 in group B), 3 epidural hemorrhages (2 in group A and 1 in group B), 3 diffuse cerebral edema with diffuse axonal injury (1 in group A and 2 in group B), and 1 other disease. All the patients underwent craniotomy or craniectomy. The mean overall preoperative GCS score was 6.6 (6.4 in group A and 6.8 in group B) and ranged from 4 to 8. No significant difference was observed between

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 38)</th>
<th>Group A (N = 17)</th>
<th>Group B (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (42.1%)</td>
<td>10 (58.8%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (57.9%)</td>
<td>7 (41.2%)</td>
<td>15 (57.1%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
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<td>55.5</td>
<td>53.7</td>
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<tr>
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<td>(37 - 68)</td>
<td>(33 - 68)</td>
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<td><strong>Diagnosis</strong></td>
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<td>7 (41.2%)</td>
<td>9 (42.9%)</td>
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<tr>
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<td>10 (26.3%)</td>
<td>4 (23.5%)</td>
<td>6 (28.6%)</td>
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<tr>
<td>Hemorrhagic contusion</td>
<td>5 (13.2%)</td>
<td>3 (17.6%)</td>
<td>2 (9.5%)</td>
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<tr>
<td>Epidural hematoma</td>
<td>3 (7.9%)</td>
<td>2 (11.8%)</td>
<td>1 (4.8%)</td>
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<tr>
<td>Diffuse cerebral edema</td>
<td>3 (7.9%)</td>
<td>1 (5.9%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (2.6%)</td>
<td>0 (0.0%)</td>
<td>1 (4.8%)</td>
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<td><strong>Initial GCS score</strong></td>
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<tr>
<td>Mean</td>
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<td>6.4</td>
<td>6.8</td>
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<tr>
<td>Range</td>
<td>(4 - 8)</td>
<td>(4 - 8)</td>
<td>(4 - 8)</td>
</tr>
</tbody>
</table>

*GCS : Glasgow Coma Scale
two groups in terms of demographic parameters, diseases, or preoperative GCS scores.

**BIS scores**

After achieving a burst-suppression pattern on EEG, BIS scores were recorded every 2 hours for 3 days during coma therapy, and average values were calculated (Table 2). For all patients, mean BIS scores were: 29.4 on the first day, 27.4 on the second day, and 26.0 on the last day. In group A, mean BIS scores were 26.9 on the first day, 24.3 on the second day, and 23.7 on the last day. In group B, mean BIS scores were 31.4 on the first day, 29.9 on the second day, and 27.8 on the last day. The two groups had no differences in terms of BIS scores.

**MOAAS scores**

Hypnotic depth was checked by physicians, and MOAAS scores were recorded every 2 hours during coma therapy (Table 2). For all patients, mean MOAAS scores were 0.66 on the first day, 0.61 on the second day and 0.39 on the last day. In group A, mean MOAAS scores were 0.24 on the first day, 0.17 on the second day and 0.00 on the last day. In group B, mean MOAAS scores were 1.00 on the first day, 0.95 on the second day, and 0.71 on the last day. In terms of MOAAS scores, no significant differences were found between the two groups and all the patients were well controlled under deep anesthesia.

**Results of ICP monitoring**

In the first day of coma therapy, mean ICP for all the patients was 17.5 cmH\textsubscript{2}O and 16.8 cmH\textsubscript{2}O in group A and 18.3 cmH\textsubscript{2}O in group B, respectively. In the second day, mean ICP for all the patients was increased to 24.9 cmH\textsubscript{2}O and 24.4 cmH\textsubscript{2}O in group A and 25.4 cmH\textsubscript{2}O in group B. In the last day, mean ICP for all the patients was decreased again to 16.6 cmH\textsubscript{2}O and 15.1 cmH\textsubscript{2}O in group A and 18.0 cmH\textsubscript{2}O in group B, respectively. No statistical difference was found between two groups in the ICP (Table 2).

**Dose of anesthetics and cardiotonics**

In group A, the mean dose of thiopental administered was 6.1 mg/kg/hr (range: 4.5-7.5 mg/kg/hr) and in group B, the mean dose of propofol administered was 4.4 mg/kg/hr (range: 3.5-6.0 mg/kg/hr).

To maintain systemic normotensive state, dopamine was administered to counter cardiac depression due to anesthetics. Except for dopamine, no other agent was administered to increase systemic pressure. The mean overall dose of dopamine administered was 7.0 μg/kg/min (range: 0.0-14.0 μg/kg/min). In group A, the mean dose of dopamine was 10.2 μg/kg/min (range: 8.0-14.0 μg/kg/min) and in group B, 4.4 μg/kg/min (range: 0.0-8.0 μg/kg/min). Significantly less dopamine was administered to maintain systemic pressure in group B than in group A (p=0.000) (Table 2).

**Recovery from anesthesia to the stationary state**

The mean overall recovery time was 18.4 hours (range: 4.0-48.0 hours) and summarized on table 2. In group A, it was 32.9 hours (range: 20.0-48.0 hours) and in group B, 6.6 hours (range: 4.0-10.0 hours). It took shorter time to recover from anesthesia for patients who were treated with propofol than those who were treated with barbiturate (p=0.000).

---

**Table 2. Clinical features during coma therapy**

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 38)</th>
<th>Group A (N = 17)</th>
<th>Group B (N = 21)</th>
<th>p-value†</th>
</tr>
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<tbody>
<tr>
<td>Mean dose of anesthetics (mg/kg/hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>6.1 (4.5 - 7.5)</td>
<td>4.4 (3.5 - 6.0)</td>
<td>0.752</td>
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</tr>
<tr>
<td>Mean bispectral Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>29.4 (21.5 - 40.1)</td>
<td>26.9 (21.5 - 33.5)</td>
<td>31.4 (25.4 - 40.1)</td>
<td>0.691</td>
</tr>
<tr>
<td>Day 2</td>
<td>27.4 (19.3 - 35.6)</td>
<td>24.3 (19.3 - 27.2)</td>
<td>29.9 (22.6 - 35.6)</td>
<td>0.721</td>
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<tr>
<td>Day 3</td>
<td>26.0 (20.7 - 37.0)</td>
<td>23.7 (20.7 - 30.2)</td>
<td>27.8 (21.0 - 37.0)</td>
<td></td>
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<tr>
<td>Mean MOAAS Score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.66 (0.0-1.0)</td>
<td>0.24 (0.0-1.0)</td>
<td>1.00 (1.0-1.0)</td>
<td>0.902</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.61 (0.0-1.0)</td>
<td>0.17 (0.0-1.0)</td>
<td>0.95 (0.0-1.0)</td>
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<tr>
<td>Day 3</td>
<td>0.39 (0.0-1.0)</td>
<td>0.00 (0.0-0.0)</td>
<td>0.71 (0.0-1.0)</td>
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<tr>
<td>Intracranial pressure (cmH\textsubscript{2}O)</td>
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<td></td>
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<tr>
<td>Day 1</td>
<td>17.5 (11.6 - 28.6)</td>
<td>16.8 (11.6 - 24.0)</td>
<td>18.3 (14.0 - 28.6)</td>
<td>0.639</td>
</tr>
<tr>
<td>Day 2</td>
<td>24.9 (13.6 - 35.4)</td>
<td>24.4 (13.6 - 33.5)</td>
<td>25.4 (17.3 - 35.4)</td>
<td>0.756</td>
</tr>
<tr>
<td>Day 3</td>
<td>16.6 (11.0 - 22.4)</td>
<td>15.1 (11.0 - 22.0)</td>
<td>18.0 (12.0 - 22.4)</td>
<td>0.108</td>
</tr>
<tr>
<td>Dose of dopamine (μg/kg/min)</td>
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<td>&lt;0.001</td>
</tr>
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<td>7.0</td>
<td>10.2</td>
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</tr>
<tr>
<td>Range</td>
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<td>(0.0 - 8.0)</td>
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<tr>
<td>Recovery time (hour)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Mean</td>
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<td>32.9</td>
<td>6.6</td>
<td></td>
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<tr>
<td>Range</td>
<td>(4.0 - 48.0)</td>
<td>(20.0 - 48.0)</td>
<td>(4.0 - 10.0)</td>
<td></td>
</tr>
</tbody>
</table>

* MOAAS : Modified Observer Assessment of Alertness and Sedation.  
† t-test.
Outcome

GCS score after stationary condition from coma therapy was not significantly different before coma therapy. The mean overall post-therapeutic GCS score was 6.8 (6.7 in group A and 7.0 in group B) and ranged from 3 to 10. Four patients (23.5%) in group A got worse than before and 4 patients (19.0%) in group B did. Seven patients (41.2%) in group A improved and 11 patients (52.4%) in group B did. However, the difference between two groups did not have statistical significance (p=0.352).

Complications of coma therapy

Table 3 presents the complications that occurred during coma therapy. No patient died during therapy. Although all patients experienced side effects to some degree, their complications were minimal and not life-threatening, i.e., systemic hypotension (systolic blood pressure < 100 mmHg) occurred in 35 patients (17 in group A and 18 in group B), electrolyte imbalances (hyponatremia, hypokalemia, or hypercalcemia) occurred in 10 patients (4 in group A and 6 in group B), leukocytosis (>10,000/μL) occurred in 7 patients (4 in group A and 3 in group B), appearance of pneumonic consolidation on chest X-ray occurred in 6 patients (3 in group A and 3 in group B), increased erythrocyte sedimentation rate (ESR) (> 20 mm/hr) or C-reactive protein (CRP) (> 5 mg/L) in 5 patients (3 in group A and 2 in group B), increased serum blood urea nitrogen (BUN) (> 25 mg/dL) or creatinine (> 1.5 mg/dL) in 4 patients (1 in group A and 3 in group B), acidosis in 4 patients (2 in group A and 2 in group B), arrhythmia by electrocardiography (ECG) in 3 patients (2 in group A and 1 in group B), increased lactate dehydrogenase H (LDH) in 2 patients (0 in group A and 2 in group B) and deep vein thrombosis in 2 patients (1 in group A and 1 in group B). No fever (> 38.0°C) was found in any patient. There was no statistical difference in complication between two groups.

Illustration of case

A 64-year-old woman visited emergent care unit with acute alteration of mentality after head trauma from fall-down. Her pupils did not respond to the light and she had decorticated movement to noxious stimulation. GCS score was 6. On the computed tomographic (CT) scan, crescent-shaped, high-density lesion on the left fronto-temporal area was found. And midline was shifted to the right side and sulci were obliterated. Under impression of acute subdural hemorrhage, she underwent decompressive craniectomy and subdural hemorrhage was removed. In the neurosurgical field, the brain was tense and swelling up severely and decreased brain pulsation and discoloration was found. Initially, the dose was titrated by use of portable EEG monitoring with confirmation of burst-suppression pattern and then was maintained with a dose of 6 mg/kg/hr. BIS score was ranged from 35 to 50 during coma therapy. Dopamine with a dose of 4 μg/kg/min was administrated to reduce intracranial pressure and lessen the brain damage. Initially, the dose was titrated by use of portable EEG monitoring with confirmation of burst-suppression pattern and then was maintained with a dose of 6 mg/kg/hr. BIS score was ranged from 35 to 50 during coma therapy. Dopamine with a dose of 4 μg/kg/min was administrated to maintain normotensive systemic pressure. During coma therapy, she experienced increase of serum LDH (315 IU/mL), leukocytosis (15,000/μL) and metabolic acidosis (serum pH 7.30). She recovered from coma therapy 6 hours to stationary state after discontinuance of propofol administration. Fortunately, she improved minimally with withdraw movement to pain and pupillary response to the light returned. But she was unable to cooperate with physician and GCS score was 8. Fig. 1 shows pre- and immediate postoperative imaging scan, EEG finding and BIS setting.

| Table 3. Complications of neuroprotective coma therapy* |
|---------------------------------|-----------------|----------------|----------------|
| Total (N = 38)                  | Group A (N = 17) | Group B (N = 21) | p-value†   |
| Hypotension (SBP<100 mmHg)      | 35 (92.1%)      | 17 (100%)       | 18 (85.7%)   | 0.752       |
| Electrolyte imbalance           | 10 (26.3%)      | 4 (23.5%)       | 6 (28.6%)    | 0.911       |
| Leukocytosis (>10,000/μL)       | 7 (18.4%)       | 4 (23.5%)       | 3 (14.3%)    | 0.535       |
| Pneumonic consolidation         | 6 (15.8%)       | 3 (17.6%)       | 3 (14.3%)    | 0.902       |
| Increase of ESR or CRP          | 5 (13.2%)       | 3 (17.6%)       | 2 (9.5%)     | 0.887       |
| Increase of BUN/Cr              | 4 (10.5%)       | 1 (5.9%)        | 3 (14.3%)    | 0.135       |
| Acidosis                        | 4 (10.5%)       | 2 (11.8%)       | 2 (9.5%)     | 0.826       |
| Arhythmia                       | 3 (7.9%)        | 2 (11.8%)       | 1 (4.8%)     | 0.604       |
| Increase of LDH                 | 2 (5.3%)        | 0 (0.0%)        | 2 (9.5%)     | 0.078       |
| Deep vein thrombosis            | 2 (5.3%)        | 1 (5.9%)        | 1 (4.8%)     | 0.921       |

* ESR : erythrocyte sedimentation rate; CRP : C-reactive protein; BUN : blood urea nitrogen; Cr : creatine; LDH : lactate dehydrogenase H.
† Fisher’s exact test.
**DISCUSSION**

In this study, we found that propofol coma therapy has a shorter recovery time from general anesthesia, induces less systemic hypotension, and requires less dopamine than thiopental coma therapy. However, no difference was observed between the propofol and thiopental groups in terms of BIS scores, MOAAS scores, changes in ICP, outcome, and side effects.

In general, propofol has similar neuroprotective effects as barbiturate, but also has several advantages. First, propofol has a shorter half time and recovery time from anesthesia than barbiturate, which can facilitate early neurological evaluation. Second, the lower systemic hypotension associated with propofol can reduce catecholamine requirements. Third, some authors have suggested that the risk of infection may be lower for propofol than barbiturate. Finally, propofol provides an energy source due to its lipid content. With coincidence, in presenting study, patients who underwent propofol coma therapy had shorter recovery time and lower systemic hypotension and less catecholamine requirement. But, in terms of infection, there was no difference between two groups. Hatch DJ suggested that propofol coma therapy for > 2 days has much higher risk of infection. In this study of 3 day-schedule coma therapy, as many as six patients gained pneumonic consolidation on chest X-ray without fever.

However, despite the practical advantages of propofol, it is not completely safe, especially when administered at high doses, because at high levels propofol accentuates lactate accumulation and edema formation in cases of cerebral ischemia with hyperglycemia. Moreover, propofol infusion syndrome is a rare but often fatal syndrome that was originally described in critically ill children undergoing long-term (>48 hours) propofol infusion at high doses (> 4 mg/kg/hr). Its features consist of severe metabolic acidosis, rhabdomyolysis, renal failure, and fatal cardiac failure. Moreover, this pathologic condition can be aggravated by the combined use of glucocorticoid and catecholamine. In combination with glucocorticoid, high dose of propofol can exert profound effects on immunity and inflammation. In combination with catecholamine, the negative inotropic effects of propofol can increase catecholamine requirement, and thus, create a vicious cycle that results in a progressive myocardial depressive effect. For these reasons, high-dose propofol for prolonged period (>48 hours) is not recommended. Therefore, determination of optimal barbiturate and propofol concentration is of considerable importance.

In this point of view, BIS scores can titrate the optimal dose of barbiturate and propofol until burst-suppression pattern appear on the EEG. In fact, BIS scores were developed to measure the effects of anesthetic agents on the brain. Over several years, a large database of high fidelity EEG recordings and clinical recordings from more than 2,000 patients that
received a wide variety of anesthetic regimens, were collected by Aspect Medical Systems, Inc. This database contains recorded EEG segments and records of associated clinically derived hypnotic states. According to this setting, BIS score of 65-85 have been recommended for sedation, score of 40-65 have been recommended for general anesthesia, and at the score of lower than 40, cortical suppression becomes discernible in EEG as a burst suppression pattern. Almost patients in this study had the BIS score of lower 40 during coma therapy. Therefore, BIS scores can be used to manage anesthetics effectively and reduce drug usage, reduce recovery time, facilitate higher quality recovery, and reduce the side effects of prolonged anesthesia.

In presenting study, we monitored ICP with epidural catheter and sensor and performed coma therapy during continuous 3 days. However, according to guideline by Martin R. et al., severe TBI patients were recommended to monitor ICP with ventricular catheter. Although true ICP shows a potential to warn against the elevation of ICP, continuous analysis of intracranial pressure adds information to simple recording of mean trend values actually. In fact, there are no strict and absolute guideline for coma therapy. In the traditional stair step treatment of intracranial hypertension, barbiturate coma therapy has the most potential capacity to reduce ICP. Therefore, many neurosurgeons consider barbiturate coma therapy for the refractory high ICP. In the point of limitation of this study, 3-days coma therapies were performed without precise scientific considerations, and further comprehensive studies are needed to confine the duration of therapy and the time of weaning coma therapy.

CONCLUSION

Barbiturate and propofol coma therapy are known to have similar important neuroprotective roles. However, in spite of the several practical advantages of propofol over barbiturate such as less systemic hypotension during coma therapy and shorter time to stationary state, it is not a completely safe anesthetic agent. The determination of the optimal dose required to maximize its neuroprotective effects and avoid fatal complications is of considerable importance. The findings of the present study suggest that BIS can be used to determine the optimal dose of propofol so as to increase its neuroprotective effects and reduce its side effects during coma therapy.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest.

ACKNOWLEDGEMENTS

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Analysis of Predisposing Factors of the Treatment of Patients with Unruptured Intracranial Aneurysms

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Objective

To investigate the factors that influence the determination of treatment of unruptured intracranial aneurysms (UIAs), we retrospectively compared various well-known risk factors that are associated with future rupture for treated and observed groups.

Methods

Between January 2006 and December 2016, a total of 279 patients treated UIAs with surgical clipping or coil embolization have been included in this study. In the same period, 100 patients did undergo transfemoral cerebral angiograms and were initially managed with observation. Aneurysmal characteristics and patients were compared between the treated and the observed group. The association between these factors and the decision of treatment was performed using a multivariate logistic regression analysis.

Results

279 patients with treated unruptured aneurysms and the observation group included 100 patients with unruptured aneurysms. A multivariate study revealed that young age (OR=0.959 / p=0.001), high aneurysms height, (OR=1.906 / p=0.002), daughter sac (OR=4.072 / p=0.001), location of aneurysms (anterior communicating artery (OR=3.729 / p=0.022) and middle cerebral artery bifurcation (OR=4.110 / p=0.009) were significantly associated with the treatment group when compared to the observation group.

Conclusion

Young age, a small aspect ratio, a large aneurysmal height, a daughter sac, and the location of aneurysm were strongly associated with the treatment of unruptured aneurysms.

Keywords: Predisposing factors; Unruptured intracranial aneurysms; Rupture risk; Observation; Treatment
INTRODUCTION

Autopsy studies have shown an occurrence of unruptured intracranial aneurysms (UIAs) incidences in approximately 5 percent of all performed autopsies. 6 of 100,000 patients will have ruptured aneurysm induced subarachnoid hemorrhage each year in the USA. UIAs are a cerebrovascular condition that are commonly diagnosed due to improved imaging techniques. While the rupture risk of UIAs leads many neurosurgeons to advise its preventive treatment, the management of patients with UIAs remains controversial. Surgeon preference and experience as well as morphologic and anatomic considerations play important roles in the debates that continue over the controversy about whether to treat UIAs. Many studies have reported that certain patient characteristics increase the risk of rupture, including old age, female gender, and Japanese or Finnish descent. Aneurysms characteristics that increase the risk of rupture are location at the posterior circulation and increasing size.

Thus, these factors affect the management of UIAs. In this study, we evaluated the association between these risk factors, which are involved in future rupture of UIAs and management decision.

METHODS

Patient selection and inclusion criteria

The treatment group included a total of 279 patients with UIAs and who were treated with surgical clipping or coil embolization between January 2006 and December 2016. In the same period, 100 patients who underwent transfemoral cerebral angiography (TFCA) and who were initially managed with observation were included in the observation group. Patients with UIAs who did not undergo TFCA were excluded. Patients were also excluded if they had any of 1) Prior SAH, 2) symptomatic aneurysm, and 3) fusiform aneurysm. Clinical outcomes, aneurysmal characteristics (location, size, and morphological characteristics of lesions) and clinical presentation parameters, underlying disease were evaluated for both groups.

Analysis of aneurysmal characteristics

All UIAs were classified into the following categories based on location: 1. middle cerebral artery (MCA), 2. anterior communicating artery (ACoA) including distal anterior cerebral artery, 3. cavernous ICA, 4. internal carotid artery (ICA), 5. posterior communicating artery (PCoA), 6. Basilar top, and 7. vertebrobasilar artery (VBA). ICA included the location between the cavernous portion of ICA and the internal carotid artery bifurcation and the origin of the anterior choroidal artery, excluding those located at the origin of the posterior communicating. Aneurysmal factors included height, neck and width of aneurysm, which were measured via TFCA images. The maximum diameter was defined as the longest diameter of UIA. Aspect ratio means the ratio of height to neck (Fig. 1).

Analysis of the patients factors

The following factors of the patients with aneurysms, whether treated or not, were collected and analyzed to examine their relationships with treatment indication. Included patient factors were age, sex, underlying disease: hypertension (previously known, patient being treated with antihypertensive medications, or blood pressure 140/90 mm Hg during the nonacute phase), and diabetes mellitus (DM) (fasting glucose > 7 mmol/L or patient being treated with antidiabetic medication), smoking history (current or past), alcohol history, and other diseases, such as history of ischemic stroke or cardiac disease (heart failure, arrhythmia). 18 patients of the treated group had multiple aneurysms (6.4%) and 7 patients of the observation group had multiplicity (7%). The total number of treated aneurysms was 297 and 108 aneurysms were observed.

Procedure: diagnosis and treatment methods

After patients were diagnosed with UIA through CT angiography or MR angiography, they were admitted and underwent the TFCA. Based on the results, medical staff (neurosurgeon and neuroradiologist) consulted with the patients and their caregivers to determine a treatment plan. The methods of operation mean surgical clipping and endovascular treatment included coil embolization and stent assisted coiling.
Analysis of post-operative state and follow up of observation group

In the treated group, the outcome of each patient was assessed using the Glasgow Outcome Scale (GOS) 1 month after the operation day. A Glasgow Outcome score of 5 indicates no disability, a score of 4 or 3 indicates both moderate disability, i.e., no need for assistance in everyday life, employment is possible but may require special equipment, and severe disability, i.e., severe injury with permanent need for help with daily living, a score of 1 to 2 indicates death or a persistent vegetative state. The mean follow up duration for the observation group was 33.66 month.

Statistical analysis

A statistical analysis was performed via binary logistic regression to analyze any independent association between the groups, and odds ratio (ORs) and their 95% confidence interval (CIs) were estimated. Both multivariate and univariate analysis were performed. The data are expressed as a mean ± standard deviation (SD). P values of less than 0.05 (p<0.05) were considered statistically significant. Between-cohort comparisons of the distributions of baseline characteristics were done with the Chi-squared test for categorical variables and with the Mann-Whitney test for continuous variables. Analyses were performed with SPSS ver. 23.0 (IBM corporation, Armonk, NY, USA).

RESULTS

Comparison of risk factors between the treatment and observation groups

Table 1 showed the comparison of patient and aneurysmal characteristics between the treated and observation groups.

Patient characteristics

A total of 279 patients with newly diagnosed aneurysms that underwent treatment for aneurysms were reviewed over a period of 10 years. The group included 84 men (31%) and 195 women (69%) with an average age of 58.49 years (± 10.71). The observation group consisted of 27 men (27%) and 73

Table 1. Complications of neuroprotective coma therapy

<table>
<thead>
<tr>
<th></th>
<th>Treated group (279 patients)</th>
<th>Observation group (100 patients)</th>
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<td>&gt;70 yr – no (%)</td>
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<td>30 (30%)</td>
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<td>No.of females (%)</td>
<td>195 (69%)</td>
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<td>Hypertension (%)</td>
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<td>29 (10%)</td>
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<tr>
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</tr>
<tr>
<td>Neck</td>
<td>3.60±1.51</td>
<td>3.34±1.78</td>
<td>0.153</td>
</tr>
<tr>
<td>Height</td>
<td>5.13±3.39</td>
<td>3.37±3.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Width</td>
<td>5.62±5.09</td>
<td>4.08±3.77</td>
<td>0.006</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>6.27±5.26</td>
<td>4.27±4.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspect ratio (%)</td>
<td>1.46±0.79</td>
<td>1.18±1.61</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Location of aneurysms (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>68 (24%)</td>
<td>12 (12%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>31 (11%)</td>
<td>11 (11%)</td>
<td>0.570</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>91 (32%)</td>
<td>19 (19%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cavernous ICA*</td>
<td>46 (16%)</td>
<td>34 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>26 (9%)</td>
<td>13 (13%)</td>
<td>0.338</td>
</tr>
<tr>
<td>Basilar toptop</td>
<td>7 (2%)</td>
<td>6 (6%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Vertebrobasilar artery</td>
<td>10 (3%)</td>
<td>5 (5%)</td>
<td>0.554</td>
</tr>
<tr>
<td>Daughter sac</td>
<td>56 (20%)</td>
<td>5 (5%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
* :Internal carotid artery
women (73%) with an average of 61.9 years (± 11.11). Both groups together included 77 patients who were older than 70 years (19%). Age and smoke history were statistically association in comparison between treated and observation group (p=0.007 and 0.011, respectively). 268 patients had female gender, 216 patients had hypertension and 41 patients had diabetes mellitus, however their distribution between treated group and observation group was not statistically significant (p=0.610 for sex, p=0.242 for hypertension and p=0.708 for diabetes mellitus). The number of patients who with a history of drinking alcohol showed no difference between two groups (p=0.893).

Aneurysms characteristics
160 patients underwent surgical clipping and 119 patients underwent endovascular treatment. Mean neck size which was 3.60±1.51 in treated group, was not significant higher than the 3.34±1.78 of the observation group (p=0.153). However mean height was significantly different (5.13±3.39 in treated group and 3.37±3.30 in observation group, p=0.001). The height of aneurysms was bigger than 5 mm in 94 patients. The mean width was also statistically higher in treated group (5.62±5.09) than observation group (4.08±3.77) (p=0.006). The maximum diameter (6.27±5.26 in treated group and 4.27±4.04 in observation group) and aspect ratio (1.46±0.79 in treated group and 1.18±1.61 in observation group) were also significantly difference (p=0.001 in maximum diameter and p=0.027 in aspect ratio, respectively). The most common location of aneurysms in the surgical clipping group was the MCA (49%, 79 patients), whereas that in the endovascular treatment group was the cavernous ICA (35%, 42 patients). The most common location of aneurysms in the observation group was the cavernous ICA artery (32%, 32 patients) and the MCA (19%, 19 patients). The distribution of location of UIA was significantly different in AcoA (p=0.016), MCA (p=0.01), and cavernous ICA (p=0.001). A total of 61 patients had daughter sac, of which 56 patients were in the treated group and 5 patients were in the observation group. The ratio with daughter sac was statistically significant(p=0.001).

Postoperative mortality and morbidity
266 patients (95%) achieved a good outcome (Glasgow Outcome scale 5) at 1 month follow up. The mortality rate was 1%, and the overall surgical morbidity was 5%. In total 3 of the 279 patients died after the operation within 1 month. 1 death was due to intraoperative rupture and 2 due to sepsis. Twelve patients had a GOS of 4 after 1 month, these patients showed 3rd nerve palsy diplopia and short term memorial impairment. 2 patients had a GOS 3 or 2 and showed hemiparesis and severe cognitive dysfunction.

Association between risk factors of rupture and treatment
Tables 2 and 3 demonstrates the results of logistic regression analysis of associations between rupture risk factors and treatment. Univariate analyses showed that young patient age (OR=0.970, p=0.007), smoke history (OR=2.252, p=0.013), high height of aneurysms (OR=1.340, p=0.001), large width (OR=1.142, p=0.006), large maximum diameter (OR=1.192, p=0.001), large aspect ratio (OR=1.493, p=0.024), AcoA (OR=2.209, p=0.016), MCA (OR=2.064, p=0.011), and present daughter sac (OR=3.317, p=0.001) were significantly associated with the treated group. However, cavernous ICA was associated with the observation group (OR=0.420, p=0.001). Multivariate analysis revealed that a high height of aneurysm (OR=1.906, p=0.001), a small aspect ratio (OR=0.493, p=0.006), the presence of daughter sac (OR=4.072, p=0.001), and young age (OR=0.959, p=0.001) were significantly associated with the treated group. Further associated with the treated group were AcoA and MCA (OR=3.729, p=0.022 and OR=4.110, p=0.009, respectively).

DISCUSSION
Our study found the following factors as significant between treated and observation group: age, smoke history, aneurysmal height and width, maximum diameter, aspect ratio, aneurysm located in AcoA. MCA, Cavernous ICA and daughter sac. The significant factors for the treated group were different than those for the observation group and included the following: young mean age (58.49 years vs 61.9 years), more patients with a smoke history (25% patients vs 13% patients), high height (5.13 mm vs 3.37 mm) and width (5.62 mm vs 4.08 mm), a large maximum diameter (6.27 mm vs 4.27 mm), large aspect ratio (1.46 vs 1.18), more AcoA location (24% vs 12%), MCA (32% vs 19%), less cavernous ICA (16% vs 34%) and more daughter sac (56% vs 5%).

In a multivariate analysis, young age, high height, small aspect ratio, presence of daughter sac, and UIA located in AcoA and MCA were independently associated with the treatment group. The effect of age as a risk factor of the rupture of UIA has been consistently reported in the past. Rinkel et al. and Vlak et al. described a higher incidence rate of SAH among older populations22,32. In our study, young age was significantly associated with the treated group. This is presumably due to...
the reason that treatment is recommended and implemented in younger patients because of their better general condition than those of older patients. Several researchers reported that the size and location of aneurysm were predictors of UIA rupture. The International Study of Unruptured Intracranial Aneurysms [ISUIA] in 1998 demonstrated a low rupture rate for an unruptured aneurysm smaller than 7 mm. A larger size and a posterior circulation site were predictors as independent risk factors of aneurysm rupture, and patients with a history of ruptured aneurysms were at higher risk. A Japanese cohort study reported that the following factors increased the risk of rupture: aneurysms of 7 mm or larger, aneurysms located in posterior circulation except for PcoA, and aneurysms with a daughter sac. While recent literature recommends treatment of aneurysm that are more than 4 mm in size and multilobular or aneurysms with bleb changes, our study showed that the most commonly treated location was the MCA and the maximum diameter was 6.27±5.26 mm. Further, the location of the aneurysm in the AcoA and MCA is significantly associated with the treated group in the multivariate analysis. MCA was easier to access in surgical clipping, and there were more cases of surgery.

Table 2. Univariate analysis between treated group and observation group

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>OR</th>
<th>Univariate analysis (95% CI for OR (Lower-upper))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.970</td>
<td>0.949-0.992</td>
<td>0.007</td>
</tr>
<tr>
<td>No.of females</td>
<td>0.859</td>
<td>0.515-1.430</td>
<td>0.558</td>
</tr>
<tr>
<td>Hypertension (Positive)</td>
<td>0.760</td>
<td>0.480-1.202</td>
<td>0.241</td>
</tr>
<tr>
<td>Diabetes mellitus (Positive)</td>
<td>1.176</td>
<td>0.575-2.404</td>
<td>0.658</td>
</tr>
<tr>
<td>Smoke history (Positive)</td>
<td>2.252</td>
<td>1.184-4.283</td>
<td>0.013</td>
</tr>
<tr>
<td>Alcohol user (Positive)</td>
<td>0.921</td>
<td>0.541-1.568</td>
<td>0.761</td>
</tr>
<tr>
<td>Size of aneurysms Mean ± SD – (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>1.126</td>
<td>0.956-1.325</td>
<td>0.155</td>
</tr>
<tr>
<td>Height</td>
<td>1.340</td>
<td>1.170-1.535</td>
<td>0.001</td>
</tr>
<tr>
<td>Width</td>
<td>1.142</td>
<td>1.038-1.256</td>
<td>0.006</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>1.192</td>
<td>1.077-1.319</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspect ratio (%)</td>
<td>1.493</td>
<td>1.053-2.115</td>
<td>0.024</td>
</tr>
<tr>
<td>Location of aneurysms (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>2.209</td>
<td>1.161-4.204</td>
<td>0.016</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>1.011</td>
<td>0.488-2.097</td>
<td>0.976</td>
</tr>
<tr>
<td>Middle cerebral artery bifurcation</td>
<td>2.064</td>
<td>1.180-3.608</td>
<td>0.011</td>
</tr>
<tr>
<td>Cavernous ICA*</td>
<td>0.420</td>
<td>0.248-0.710</td>
<td>0.001</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>0.688</td>
<td>0.388-1.397</td>
<td>0.301</td>
</tr>
<tr>
<td>Basilar top</td>
<td>0.403</td>
<td>0.132-1.230</td>
<td>0.110</td>
</tr>
<tr>
<td>Vertebrobasilar artery</td>
<td>0.706</td>
<td>0.235-2.119</td>
<td>0.535</td>
</tr>
<tr>
<td>Daughter sac (Positive)</td>
<td>3.317</td>
<td>2.028-5.427</td>
<td>0.001</td>
</tr>
</tbody>
</table>

OR: Odds ratio, CI: Confidence interval

* :Internal carotid artery

Table 3. Multivariate analysis between treated group and observation group

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>OR</th>
<th>Multivariate analysis (95% CI for OR (Lower-upper))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.959</td>
<td>0.934-0.984</td>
<td>0.001</td>
</tr>
<tr>
<td>Height</td>
<td>1.906</td>
<td>1.445-2.513</td>
<td>0.001</td>
</tr>
<tr>
<td>Neck</td>
<td>0.783</td>
<td>0.611-1.004</td>
<td>0.054</td>
</tr>
<tr>
<td>Aspect ratio</td>
<td>0.493</td>
<td>0.299-0.814</td>
<td>0.006</td>
</tr>
<tr>
<td>Shape(Daughter sac; Positive)</td>
<td>4.072</td>
<td>2.295-7.223</td>
<td>0.001</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>3.729</td>
<td>1.213-11.463</td>
<td>0.022</td>
</tr>
<tr>
<td>Middle cerebral artery bifurcation</td>
<td>4.110</td>
<td>1.423-11.868</td>
<td>0.009</td>
</tr>
</tbody>
</table>

OR: Odds ratio, CI: Confidence interval
Contrary to previous studies, our study implies that a low aspect ratio was related to the treatment group. Some known risk factors did not show a significantly different. While a female gender has been reported as risk factor in some studies, more incidences of ruptured aneurysm are found in women than in men, and, in our study the female gender was the dominant gender of total patients. However the gender was not associated with the treated group. Hypertension was a controversial risk factor as hypertension did not significantly increase the risk of rupture. However, in other study hypertension is a major risk factor for subarachnoid hemorrhage. In our study, hypertension did not show a significant difference between the treated and the observation group. Several researchers reported smoking history, alcohol history and previous episode of SAH as risk factors for UIA rupture. In our analysis, the smoke history was significantly related to the treated group in the univariate study but not in the multivariate study, and alcohol use was not statistically significant in both analyses. In our study, we excluded patients who underwent previous episodes of SAH and symptomatic aneurysm. Further investigations of a larger number of patients is warranted to determine any significant relationships.

The indication for UIA in our institution is for patients with a tolerable whole body condition, with an aneurysm height of 5 mm or more, and with the UIA located in AcoA or MCA with or without a daughter sac. Furthermore, treatment of UIA located in MCA was usually performed by surgical clipping.

Conversely, Cavernous ICA or posterior circulation aneurysms are performed mainly by endovascular treatment.

Our study has some limitations. Patient data were collected and analyzed at a single center, as a consequence, the potential for bias in treatment choice and conservative management may exist. The number of patients who were enrolled in our study was relatively small. Especially for the group of PcoA and posterior circulation, which are known to have a high risk of rupture, there was no difference between the treatment group and the observation group. It is estimated that the bias was generated from the limit that the subject was relatively small. We did not consider statistical errors or differences in the tendency of the operator.

CONCLUSION

Management of UIA has never been straight forward. Decisions on treatment of UIA should be carefully made after investigation of many risk factors for rupturing. In the present study, we conclude that a young age, a small aspect ratio, a large aneurysmal height, a daughter sac, and some locations of aneurysm (AcoA, MCA) are associated with the treatment group. Prospective studies should be performed in larger sample sizes and more concise evaluation to make better decisions for the treatment of UIA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES


Posterior Reversible Encephalopathy Syndrome in a Patient with Spinal Metastasis

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INTRODUCTION

In 1996, posterior reversible encephalopathy syndrome (PRES) was first described as reversible leukencephalopathy by Hinchey1. This syndrome is characterized by various kinds of neurologic signs and symptoms that include headache, seizure, altered mental status, lethargy, visual loss and focal neurological disability. A 63-year-old female visited with upper back pain and both leg weakness. She has been receiving chemotherapy with gemcitabine and cisplatin for lung cancer with multiple bone metastasis. According to the imaging, we diagnosed the patient as T8 pathologic fracture. Five days after surgical decompression, she suddenly complained of visual loss. Magnetic resonance imaging (MRI) of the brain showed bilateral subcortical and cortical edema in the parieto-occipital area. Her MRI finding and symptoms suggested the PRES. Five days after conservative treatment, her visual disturbance was completely recovered. We believe that accurate and early detection of PRES and adequate treatment is very important for the patient having a history of chemotherapy.

Keywords: Posterior reversible encephalopathy syndrome; Blindness; Metastasis

CASE REPORT

A 63-year-old woman was admitted to a department of neurosurgery with a history of upper back pain and both leg weakness for 2 months. About two years ago, she was diagnosed with lung cancer and multiple bone metastasis. And...
she has been receiving chemotherapy for metastatic cancer in
department of internal medicine. Six cycles of chemotherapy
with gemcitabine and cisplatin had been completed 30 days
prior to admission. Except metastatic lung cancer, she has not
been diagnosed with other disease, including hypertension.
MRI of thoracic spine revealed multiple fracture. And there were
severe central canal stenosis and cord signal change in T8 spinal
cord level due to collapse of 8th thoracic vertebral body (Fig. 1).

We scheduled surgical decompression. T8 total laminectomy
and T7, 9 subtotal laminectomy was performed and
instrumentation on T6, 7, 9, 10, 11 was done. On the
intraoperative field, a definite problem has not been found.

After the operation, back pain and motor grade have improved.
Five days later, however, she suddenly complained of visual loss.
The patient checked computed tomography(CT) scans initially,
which didn’t show definite intracranial abnormality. After several
minutes, a generalized tonic clonic seizure attack occurred. With
sodium valproate 900mg loading, diazepam 10mg was given
intravenously to control the seizure. After the seizure stopped,
we transferred the patient to the intensive care unit and then she
was scanned by MRI. T2-weighted imaging showed bilateral
high intensity signal in the parieto-occipital regions (Fig. 2).

According to the imaging, we diagnosed the patient as PRES.
We checked her blood pressure during the operation and post
operation, also. But her blood pressure was consistently within
a normal range. Two days after being diagnosed as PRES, her
vision gradually improved and there was no further seizure
attack. And five days after the event, her visual disturbance was
completely recovered.

DISCUSSION

We have reported a case of posterior reversible encephalopathy
syndrome (PRES). Hinchey et al. were first described as a
reversible posterior leukoencephalopathy syndrome in 1996,
and the name was changed to PRES in 2000 and since then
the terminology has been widely used. But PRES is not
still familiar to most of neurosurgeons due to their limited
experience.

PRES is generally associated with severe hypertension,
eclampsia, preeclampsia, immunosuppressive treatment,
electrolyte imbalance, chemotherapeutic agents and autoimmune
disease. Especially, severe hypertension is regarded as the major
risk factor in these patients. Some authors reported that about

![Fig. 1. T2-weighted magnetic resonance imaging showing the
spinal metastatic tumors compressing spinal cord at the level of
8th thoracic vertebra.](image1)

![Fig. 2. T2-weighted magnetic resonance imaging showing
bilateral high signal intensity in parieto-occipital cortical and
subcortical region(arrows).](image2)
70–80% of these patients have severe hypertension\(^9\). But similar to our case, PRES can occur even in the absence of severe hypertension. According to several studies, a few cases of PRES are associated with chemotherapeutic agent such as gemcitabine, cisplatin, 5-fluoruracil, oxaliplatin, cytarabine\(^2\). Symptoms of PRES include headache, seizure, altered mentality, visual disturbance and focal neurological signs. According to the report of Roth et al.\(^12\) the one of the most common symptoms of the patient with PRES is seizure, which occurred in 84% of the patients. Visual disturbance was also found in 60% of these patients\(^13\). Most symptoms of PRES usually occur suddenly, so accurate and early diagnosis is important. Typically, PRES can be diagnosed by brain MRI. Cerebral edema involving the parieto-occipital area is seen as increased signal of T2 imaging and fluid attenuated inversion recovery (FLAIR) imaging\(^13\).

Although pathogenesis of PRES is still controversial, but the most widely accepted hypothesis is that it is associated with vasogenic edema\(^4\). If the blood pressure is increases more than a certain level, the cerebral autoregulation can fails. Acute failure of cerebral autoregulation lead to disruption of the blood brain barrier and cerebral vasodilatation. Consequent leakage of transudation into the interstitium results in cerebral vasogenic edema.

Mechanism of chemotherapeutic agents related with PRES is also unclear. Cisplatin and gemcitabine are commonly used in many cancer patients, but it is not certain that which drug is main cause of PRES. Some authors have suggested that cisplatin induced PRES may be related to hypomagnesemia\(^5\), but that is not yet clear.

Eventually, control of leading cause is very important to this syndrome. If there was a history of high blood pressure, controlling of blood pressure is needed. If the patient is in the treatment of cancer chemotherapy, drug must be discontinued or changed to other drug. Typically, radiologic findings and clinical symptoms are reversible within 2 weeks after early and accurate treatment\(^4\). But if adequate treatment is not initiated or PRES is not diagnosed, irreversible ischemic damage may occur.

**CONCLUSION**

Although PRES is not familiar with surgeon, it is reversible with supportive therapy and control of leading cause. It is often difficult to diagnosis early and it can be progressively result in permanent neurologic damage. We believe that an accurate and prompt diagnosis of PRES is important to avoid permanent neurological disability for the patient having a history of chemotherapy.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**

Concurrent Isolated Cortical Vein Thrombosis and Pulmonary Thromboembolism as an Initial Presentation of Protein S Deficiency

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Protein S is a vitamin K-dependent anticoagulant protein. Its deficiency is a rare condition and can lead to deep vein thrombosis, pulmonary embolism or stroke. The incidence of cerebral venous thrombosis (CVT) is low, and in particular, isolated cortical vein thrombosis (ICVT) is very rare. Early diagnosis and treatment are quite important, as ICVT is potentially fatal. There are many known risk factors as pregnancy, puerperium, using oral contraceptive and etc. Here we report the case of a 59-year-old woman with isolated cortical vein thrombosis causing subarachnoid hemorrhage and intracerebral hemorrhage as clinical onset of Protein S deficiency. This case report discusses the possible mechanism and treatment of this extremely rare condition that is an association between ICVT and Protein S deficiency.

Keywords: Isolated cortical vein thrombosis; Pulmonary thromboembolism; Protein S deficiency

INTRODUCTION

Protein S is a vitamin K-dependent anticoagulant protein. Which prevents clotting by acting as a cofactor for activated protein C in the degradation of clotting factors Va and VIIa. An inherited or acquired deficiency of protein S leads to a prothrombotic state, with predisposition to thrombosis. Its deficiency is a rare condition and can lead to deep vein thrombosis, pulmonary embolism or stroke.

Cerebral venous thrombosis (CVT) is a relatively rare cause of stroke, and it has been reported to cause 0.5–1.0 % of all strokes. Isolated cortical vein thrombosis (ICVT) is the thrombosis of 1 or more cerebral cortical veins without occlusion of the major dural venous sinuses or the deep cerebral veins. ICVT accounts for less than 1% of all cerebral infarctions and has only been reported in case reports and small patient series. Here, we report an extremely rare case of an ICVT patient with type II Protein S deficiency.

CASE REPORT

A 59-year-old woman, who was admitted to the emergency department due to right-sided hemiparesis and aphasia. She was alert, and had apparent right side motor weakness, when she woke up at 9 AM. She had no medical history and family history of cerebral infarction of her mother. On admission, body temperature, heart rate, and blood pressure were 37 °C, 88 beats/min, and 130/80 mmHg, respectively. An initial computed tomography (CT) scan revealed acute intracerebral hemorrhage & subarachnoid hemorrhage in left frontal lobe.
Fig. 2. Digital subtraction angiography shows time delayed contrast wash-out isolated cortical vein. This vein coincided with intracerebral hemorrhage area.

and cortical sulcus (Fig. 1A). Considering the patient’s age and absence of a hypertension history, brain CT angiography was performed to rule out conditions such as a cerebral aneurysm, arteriovenous malformation (AVM), or sinus thrombosis, and no such conditions were noted. Brain CT angiography showed diffuse narrowing of Lt ICA and severe stenosis (about 75%) at left supraclinoid ICA.

Her ICH was treated with conservative medical therapy in order to maintain systolic BP below 130 mmHg, including immediate intravenous administration of mannitol. MRI and cerebral angiography were planned on another day to identify the definite etiology Magnetic resonance (MR) images and DSA confirmed a left frontal ICVT as the underlying disease. (Fig. 2)

At admission, the coagulation profile was assessed, and blood laboratory studies were performed to check for connective tissue diseases. No abnormal data was found, except that the protein S activity was low at 31 %. In hospital day 7th, she had a GTC type seizure. After postictal period, follow up brain CT showed no specific change (Fig. 1B). However, her condition rapidly deteriorated and she went into a coma approximately 2 hours after seizure. Her consciousness level was E1V1M2 on the Glasgow Coma Scale (GCS). At chest CT, multifocal pulmonary thromboembolisms (PTE) in both lungs, acute to chronic phase, combined pulmonary hypertension and RV enlargement (Fig. 3). The patient had no significant dyspnea or chest discomfort symptom during admission. To address IVCT and PTE, systemic heparinization was promptly applied.

Although the resolution of pulmonary embolism was confirmed after anticoagulation, she expired at hospital day 30th.

Fig. 1. Intracranial imaging. A: Initial brain CT shows acute intracerebral hemorrhage & subarachnoid hemorrhage in left frontal lobe and cortical sulcus. B: Follow-up brain CT (postictal state) shows interval resolution of subarachnoid hemorrhage in left frontal region.
DISCUSSION

ICVT is rare in developed countries, with an incidence rate ranging from 1:10,000 to 1:25,000.1 There are no specific symptoms for ICVT. Diagnosis is very difficult owing to the condition’s rarity and the obscurity of symptoms. Of help, is to note a patient’s background and history. Risk factors easily identifiable from a medical history included, pregnancy, puerperium, connective tissue disease, malignancy, contraceptive use, and infections such as, sinusitis, otitis, and mastoiditis.4 Young individuals, especially young women, are more vulnerable. The International Study on ICVT reported that 78% of all cases were aged less than 50 years, and that the incidence of ICVT was three times greater in women than men.4 When a young, pregnant, or postpartum woman presents with new onset, stroke-like symptoms, such as headaches and seizure, it is significant to examine for the ICVT risk factors. If ICVT is suspected, CT venography or MR venography should be performed. However, due to its small size, ICVT is hard to detect using these conventional modalities. A recent study proved that T2* susceptibility-weighted MR imaging sequences are very effective in detecting such lesions. Treatment for ICVT is still controversial; however, heparin has been reported as a safe and effective treatment. This is true even when ICVT is accompanied by hemorrhagic lesions. Anti-seizure medication should be given to those who present with early seizures. Anticoagulation therapy for ICVT averts aggravation of the thrombus, and allows for improvement of the occlusion lesion. This therapy is supported by European Federation of Neurological Societies guidelines. However, in cases of hemorrhagic presentation, appropriate therapy is highly controversial. It has been reported that 39–41% of ICVT patients present with ICH, hemorrhagic venous infarcts, or isolated subarachnoid hemorrhage.5 Although heparin and warfarin have been used for more than 50 years, newer oral anticoagulants (eg. dabigatran, rivaroxaban, apixaban) might offer an alternative to traditional therapies for ICVT, and pulmonary thromboembolism.

Protein S (named in reference to its isolation and characterisation in Seattle in 1979) is a vitamin K-dependent protein synthesised in the liver, vascular endothelium and megakaryocytes. It helps in cleaving activated clotting factors Va and VIIa on vascular endothelium by acting in association with protein C. PS deficiency is classified as type I (low total and free antigen, reduced activity), type II (normal total and free antigen, reduced activity), and type III (normal total antigen, reduced free antigen and activity). Our patient was diagnosed with type II PS deficiency, which is an extremely rare disease.6 Few case reports have also implicated protein S deficiency in recurrent ischemic strokes in the young. Similarly, progressive intracranial occlusive disease has been reported in association with protein S deficiency. However, current data do not support an association

Fig. 3. Chest CT angiography shows multifocal pulmonary rhromboembolisms in both lungs, acute to chronic phase. Combined pulmonary hypertension and RV enlargement.
between hereditary protein S deficiency and an increased risk of arterial thrombosis. The recommended therapy for ICVT is anticoagulation with heparin followed by oral anticoagulation, which should be continued indefinitely for patients with underlying thrombophilia.

CONCLUSION

Here, we presented an extremely rare case of an ICVT patient with type II PS deficiency. For early diagnosis, it is vital to suspect CVT, including ICVT, considering the patient’s background. In such a case, CT-DSA should be performed and the images should be thoroughly checked. A hematoma associated with ICVT caused by a cortical vein might expand without early anticoagulation therapy, as was noted in our case. Therefore, early anticoagulation therapy might be essential, even in isolated cases involving ICH.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

General Information

1. Journal of Neurointensive Care (JNIC) is the official journal of the Korean Neurointensive Care Society and published biannually (the last day of April and October). This Journal publishes important papers covering the whole field of neurosurgical intensive care unit, including studies in neuroscience, neurology, and molecular biology. Studies on rare cases and technical notes of special instruments or equipment that might be useful to the field of neurosurgical intensive care are also acceptable. Drawing upon the expertise of an interdisciplinary team of physicians from neurosurgery, neurology, anesthesiology, critical care, and nursing backgrounds, (JNIC) covers all aspects neurosurgical intensivists need to be aware of in order to provide optimal patient care.

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