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The effect of induced hypertension in aneurysmal subarachnoid hemorrhage: A narrative review

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Keywords
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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 2-5% of all strokes, and 10%-15% of aSAH patients will not survive until hospital admission. Induced hypertension (IH) is an emerging therapeutic option being used for the treatment of vasospasm in aSAH. For patients with cerebral vasospasm (CVS) consequent to SAH, IH is implemented to increase systolic blood pressure (SBP) in order to optimize cerebral blood flow (CBF) and prevent delayed cerebral ischemia (DCI). Prophylactic use of IH has been associated with the development of vasospasm and cerebral ischemia in SAH patients. Various trials have defined several different parameters to help clinicians decide when to initiate IH in a SAH patient. However, there is insufficient evidence to recommend therapeutic IH in aSAH due to the possible serious complications like myocardial ischemia, development of posterior reversible encephalopathy syndrome (PRES), pulmonary edema, and even rupture of another unsecured aneurysm. This narrative review showed the favorable impact of IH therapy on aSAH patients; however, it is crucial to conduct further clinical and molecular experiments to shed more light on the effects of IH in aSAH.

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 2%-5% of all strokes, and 10%-15% of aSAH patients will not survive until hospital admission. Up to 50% of those who do survive may develop long-term neurological deficits leading to decreased quality of life (QOL) and an increased socioeconomic burden.[1-4] There are numerous cases in the literature demonstrating that the development of cerebral vasospasm (CVS) and the consequent delayed cerebral ischemia (DCI) have a significant impact on the morbidity and mortality of aSAH patients.[1] Given the overall poor understanding of the underlying mechanisms contributing to injury expansion following aSAH, the number of effective pharmaceutical treatment options is limited.[1,5]

Induced hypertension (IH) is an emerging therapeutic option being used for the treatment of vasospasm in aSAH. In patients with CVS leading to SAH, IH is implemented in order to increase SBP in order to optimize cerebral blood flow (CBF) and prevent DCI. IH is suggested to have favorable effects on most neurological symptoms and DCI related to aSAH through controlling vasospasm, stimulating hypervolemia, and maintaining adequate cerebral perfusion; however, further investigations are required to confirm this mechanism.[6-11]

Despite the positive neurologic outcomes, there is insufficient evidence to recommend therapeutic IH in aSAH, due to the possible serious complications such as myocardial ischemia, development of posterior reversible encephalopathy syndrome (PRES), pulmonary edema, and rupture of another unsecured aneurysm.[6,8,10,12-14]

Bearing the above nuances in mind, this narrative review aims to review the current evidence on IH therapy in aSAH critically and comprehensively in order to shed more light on our understanding of the effects of IH in aSAH.

Definition of IH

IH is an established therapy that involves active intervention to increase the blood pressure (BP) of patients with CVS following SAH in order to optimize CBF and prevent DCI.[11] This may be done after the aneurysm has been treated with either open surgery or endovascular therapy.[15] There are also numerous examples in the literature supporting the use of IH even in unsecured aneurysms, wherein no clipping or coiling has been done. These studies suggest that IH does not significantly increase the risk of rupture of additional unsecured aneurysms. Given the heightened risk for cerebral ischemia in severe CVS, IH should not be foregone solely because a patient has other unsecured aneurysms.[16] This intervention involves the administration of vasoactive agents, such as catecholamines (norepinephrine, dobutamine, and dopamine), phenylephrine, along with the standard calcium channel antagonists (nimodipine).[15,17]

Current clinical knowledge of aSAH

The definition of aSAH is bleeding in the subarachnoid space following a spontaneous rupture of an aneurysm, and it is associated with significant morbidities and fatality.[18,19] This devastating disease accounts for up to 2%-5% of all stroke cases with a considerable mortality rate of 40%-60%.[1-4,20,21] Recent investigations have indicated decreasing mortality rate, which may be due to technical advances in medicine, along with a better knowledge of the disease, its treatment, and complications.[22,23] Its incidence varies markedly by geographic region, age, and gender, but the overall incidence of aSAH is 7.9 per 100000 person-years.[24] Moreover, aSAH most commonly occurs around 50 years of age and its incidence rate increases with age, particularly in women.[23,25] The higher incidence in women compared to men can be owing to a difference in sex hormones as well as a longer average lifespan in women.[25-27] There are also global geographic variations in the incidence of aSAH.[28] Finland and Japan have the highest incidence, while South and Central America, as well as China, have the lowest incidences.[23,28] There are several treatment options for aSAH. Generally, the primary step in medical treatment of aSAH is the regulation of BP by using drugs such as losartan and captopril to lower BP.[5,29]

Furthermore, investigations have exhibited that calcium channel blocker, namely nimodipine, can improve unfavorable morbidities.[5,30] Surgical treatment is performed to secure the ruptured aneurysm and prevent rebleeding. Open surgical techniques are clipping and excisional bypass. Many endovascular therapies are utilized including coiling, flow diversion, and implantation of intrasaccular devices.[31,32] The decision regarding the best treatment option depends on the characteristics of the patient, the aneurysm, and surgeon preference.[13]

The primary aims of IH after aSAH

In the setting of SAH, the term 'vasospasm' implies a complex condition that involves much more than the simple constriction of intracranial

vessels. Studies of pathological specimens have displayed smooth muscle and myofibroblast proliferation, cellular necrosis and remodelling, intimal hyperplasia, collagen deposition and fibrosis, intraluminal platelet aggregation with microthrombus formation, arterial thrombosis, and distal embolization.[11] Along with the intravascular volume depletion and disrupted cerebral autoregulation commonly seen after aSAH, vasospasm contributes to decreasing CBF, often resulting in delayed ischemic injury. Vasospasm is one of the most common, treatable causes of morbidity and mortality following aSAH.[11] The incidence of aSAH has been reported between 10 and 15 people per 100000 in the United States. Furthermore, patients suffering from aSAH describe its headache as the "worst headache of their life," which may be accompanied by other symptoms such as nausea or vomiting, a brief loss of consciousness, seizures, or meningismus. Non-contrast brain computed tomography (NCCT) scan plays a key role in the diagnosis of aSAH patients; however, both CT angiography (CTA) and magnetic resonance angiography (MRA) could be helpful and sensitive in the identification of aSAH.[1]

DCI prevention, detection, and reversal are among the top priorities of clinicians caring for SAH patients. Based on available evidence, nimodipine administration and maintenance of euvolemia are the best treatments for the prevention of DCI.[33] A change in a previously intact patient's neurologic exam can alert a physician to possible DCI. In critically ill patients, the detection of DCI often requires advanced multimodality monitoring. Early diagnosis and treatment are the keys to managing symptomatic DCI. IH and volume optimization are the cornerstones of first-line therapy. Rescue therapy for refractory CVS relies primarily on endovascular intervention and circulatory optimization. A shift from the paradigm emphasizing large-vessel narrowing to the recognition that vasospasm represents a complex, multifaceted pathophysiological process involving microcirculation, and disrupted auto-regulation should allow for new insights into this condition and new therapeutic targets in the future.[33,34]

Mechanisms of action in IH therapy

Clazosentan is the endothelin receptor antagonist that has been investigated the most in SAH. Endothelin receptor antagonists prevent endothelin 1, a vasoconstrictive peptide that influences vascular smooth muscle contraction by attaching to its receptor. Endothelin overproduction is associated with the development of vasospasm in aSAH.[35]

Depending on the surrounding milieu of cells at a given location, and the specific kinds of cells drawn to the vasospasm site, activation of inflammation at different times after rupture can be associated with either protective or deleterious responses. The impact of inflammation on the pathogenesis of CVS has been well documented. Even in the absence of blood breakdown products from SAH, intracisternal injection of pro-inflammatory materials/compounds has been shown to cause CVS.[36] Certain cerebrospinal fluid (CSF) biomarkers of inflammation could potentially be utilized to help physicians choose the right pharmaceuticals in the treatment of SAH-associated CVS.[5]

The timing, amount, and site of cytokine release following aSAH have been studied in an attempt to better describe the types of inflammation that occur during and following SAH. For example, interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) have been shown to be released into the serum and CSF.[37]

Matrix metalloproteinases (MMPs), a class of proteases with numerous subtypes, have been the subject of additional inflammation-specific SAH research. MMP-9 is the one that has been studied the most.[38] MMP-9 levels have been found to be elevated in brain tissue, blood, and CSF in patients during SAH clinical trials. MMP-9 levels were found to be elevated in the vessel wall as well as in serum and CSF.[39] In a preclinical model, heme released from red blood cells during SAH was demonstrated to produce a large inflammatory response in part through signaling via toll-like receptor 4 (TLR4). Once activated, TLR4 proceeds to interact with downstream effectors in order to trigger a bimodal inflammatory response mediated by nuclear factor kappa beta (NF-κβ). Compared to wild-type mice, TLR4 knockout animals show a substantial reduction in CVS after SAH.[40] TLR4 agonists, interestingly, modify the degree of CVS in TLR4 knockout animals to mirror wild-type mice. Furthermore, in an aneurysmal SAH model, attenuating the TLR4 and NFκβ-dependent inflammatory responses lowered the expression of downstream pro-inflammatory markers and offered a neuroprotective impact (Figure 1).[41]

Genetic factors

Genetic factors play a sizeable role in the development of aneurysms.

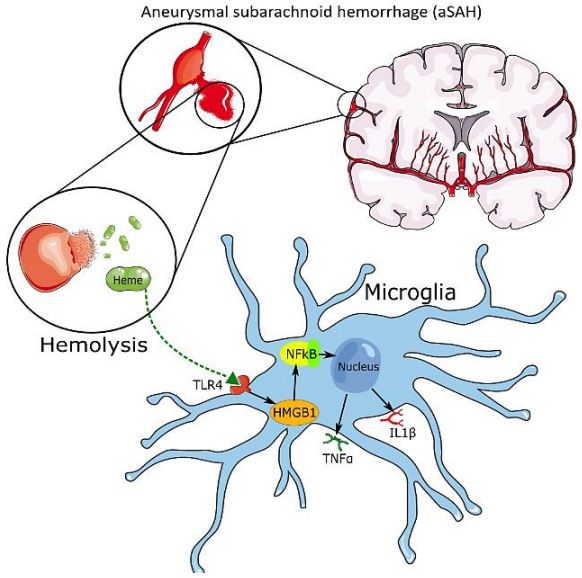

Figure 1. The role of cytokines in induced hypertension (IH) mechanism in aneurysmal subarachnoid hemorrhage (aSAH)

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Patients who are predisposed to overexpression of epoxyeicosatrienoic acid are at a higher risk of vascular dysfunction and aneurysmal rupture. SAH has also been associated with mutations in the VCAN gene. Neuroinflammation wreaks havoc on arteries that are already damaged. After a rupture, alterations in the CDKN2A gene's 9p21 region enhance neuroinflammation.[42,43]

It has been reported that certain IL-6 polymorphisms may affect SAH outcomes by increasing cerebral inflammation. Patients with the haptoglobin phenotype Hp2-2 are at higher risk of CVS after SAH, which, as previously mentioned, may be mediated by the neuroinflammatory properties of heme.[44] Additionally, certain variants of the A1166C gene, which modulates angiotensin II type 1 receptors, have been linked to worse outcomes after aSAH in the studied patients; however, these genetic associations in the broader clinical population are poorly understood.

Preclinical genetic investigations, on the other hand, have shed some light on the function of cerebral inflammation in the course of SAH and CVS.[45] In a mouse SAH model, high-mobility group box 1 increases neuroinflammation by triggering NF-κβ translocation and translation. The resulting increase in the release of NF-κβ damages the vasculature in and around the SAH location. In certain mice strains, the P2X7R/cryopyrin inflammasome axis is genetically activated, which results in an increase in IL-1 following an aSAH. Additionally, Abcc8 and Trpm4 were reported to upregulate the transcription of the sulfonylurea receptor 1-transient receptor potential melastatin 4 (Sur1-TRPM4) channels in rodents and humans after SAH.[46-48]

Candidate selection for IH

Various trials have defined parameters to help clinicians decide when to initiate IH in a SAH patient. In this review, as seen in table 1, we will focus on the collective inclusion and exclusion criteria of two prominent clinical trials: Hypertension Induction in the Management of AneurysmaL subArachnoid hemorrhage with secondary Ischaemia (HIMALAIA) and Effects of IH on Cerebral Perfusion in DCI after aSAH: A Randomized Clinical Trial.[49,50]

Methods of implementing IH protocols

Multiple case reports and series are present in the literature regarding the treatment of SAH and its complications using various drug regimens and protocols with diverse mechanisms of action.[11,51-53] A broad overview of the various protocols is presented in table 1.

For the purpose of this review, the focal point will be a detailed elucidation regarding only the IH portion of those protocols. We have chosen to focus on IH because IH combined with volume management is currently the established first-line therapy for DCI in patients who have suffered a SAH.[33]

It is important to note that IH should likely only be instituted once vasospasm has been detected by clinical, sonographic, or imaging criteria. In some instances, the prophylactic use of IH has been associated with the development of vasospasm and cerebral ischemia in SAH patients[52] (Figure 2).

Emerging issues and risks associated with IH

IH is often utilized in the treatment of DCI, and the efficacy of IH relies on its ability to improve cerebral perfusion and restore blood flow during periods of vasospasm. An emerging potential complication that has only recently begun receiving attention is PRES.[54] The most widely discussed hypothesis explaining the cause of PRES is that severe hypertension may interrupt normal cerebral autoregulation. Once cerebral autoregulation fails, uncontrolled intracranial hypertension could lead to cerebral vessel damage, resulting in vasogenic edema.[55] PRES usually evolves over a matter of hours, with the most common presenting symptoms being seizures, disturbed vision, headache, and altered mental state.

Table 1. Inclusion and exclusion criteria for induced hypertension (IH) candidate selection

Inclusion and exclusion criteria for IH candidate selection
Inclusion criteria
Age above 18 years
SAH with an aneurysmatic bleeding pattern
DCI based on a decrease of at least one point on the GCS sum-score, and/or the development of new focal neurological deficits according to the NIHSS, diagnosed by a neurologist, neurosurgeon, or intensivist, unless the deterioration does not reflect DCI as evaluated by the treating physician
Exclusion criteria
Coexisting severe head injury
Perimesencephalic hemorrhage
A history of ventricular cardiac rhythm disorder or heart failure necessitating medical treatment
Moribund
Pregnancy
No informed consent
Any contraindication for IH
Another cause for neurological deterioration, e.g.:
• (Increasing) Hydrocephalus
• Recurrent bleeding
• Clinical signs of epilepsy
• Severe infectious disease with associated decrease in level of consciousness
• Hypoglycemia
• Hyponatremia
• Metabolic encephalopathy due to renal or hepatic failure
An untreated symptomatic aneurysm
A spontaneous MAP of above 120 mmHg before the induction procedure

SAH: Subarachnoid hemorrhage; DCI: Delayed cerebral ischemia; GCS: Glasgow coma scale; NIHSS: National Institutes of Health Stroke Scale; IH: Induced hypertension; MAP: Mean arterial pressure

The severity of these clinical symptoms varies widely.[56] The low number of reported cases of PRES in the earlier years of IH therapy could perhaps be attributed to the under-recognition of this complication, as neurological deterioration could instead be attributed to persistent or worsening DCI. Presuming that a patient's deterioration is due to vasospasm in the setting of PRES could result in even more aggressive IH and further worsening of the PRES.[57]

Table 2. Various aspects of subarachnoid hemorrhage management; where does induced hypertension (IH) fit in?

1. First line therapy	**2. Rescue therapy: Tier one**			**3. Rescue therapy: Tier two**
Pharmacological therapy and volume optimization	**Cardiac output augmentation and hemoglobin optimization**	**Endovascular therapy**	**Intra-arterial pharmacological therapy**	**Novel therapies**
Vasospasm and DCI Prevention: Nimodipine* IH (Target CPP of 80–120 mmHg and Target MAP of 90–130 mmHg) Norepinephrine* Phenylephrine* Dopamine* Arginine* Vasopressin Volume Optimization (Isotonic Crystalloids targeting Euvolemia) Fasudil $MgSO_4$ and Endothelin receptor antagonists Statin therapy	Dobutamine* (CI > 4.0 L/min/m^2) Hemoglobin Optimization (Hb > 80 g/L)	Percutaneous Transluminal Balloon Angioplasty	Papaverine, Amrinone, Milrinone*, Verapamil, Nimodipine*, Nicardipine, Fasudil Hydrochloride, Colforsin daropate hydrochloride	NeuroFlo Catheter BrainsGate Intra-aortic balloon pump Counter pulsation Intrathecal therapies Therapeutic hypothermia

CI: Cardiac index; Hb: Hemoglobin; CPP: Cerebral perfusion pressure; MAP: Mean arterial pressure; IH: Induced hypertension
*Commonly used drugs

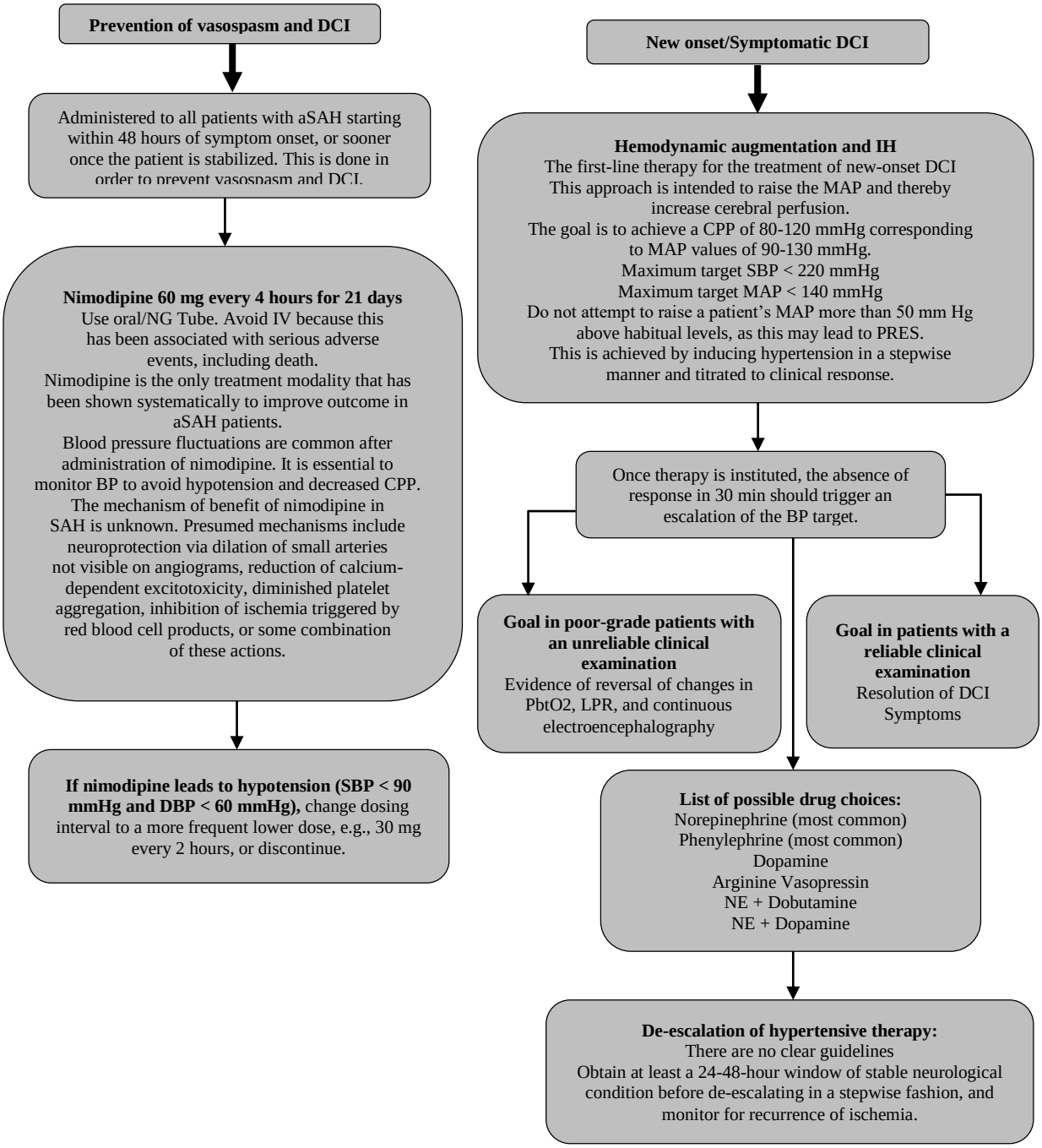

Figure 2. Induced hypertension (IH) guideline in aneurysmal subarachnoid hemorrhage (aSAH (patients
aSAH: Aneurysmal subarachnoid hemorrhage ; DCI: Delayed cerebral ischemia; MAP: Mean arterial pressure; CPP: Cerebral perfusion pressure; SBP: Systolic blood pressure; PRES: Posterior reversible encephalopathy syndrome; BP: Blood pressure; PbtO2: Continuous brain tissue oxygen monitoring; LPR: Lactate-to-Pyruvate Ratio; NE: Norepinephrine; NG: Nasogastric; IV: Intravenous; SAH: Subarachnoid hemorrhage; DBP: Diastolic blood pressure; IH: Induced hypertension

Depret and Coutrot found that raising the mean arterial pressure (MAP) by approximately 30% led to PRES patients attaining much higher MAPs that could exceed the limits of autoregulation.[54] They suggested that clinicians consider the wide-ranging effects of BP elevation including the degree of spontaneous hypertension when selecting IH goals. In this study, attempting to raise patients' MAP more than 50 mm Hg above their normal levels (or to absolute levels above 130-140 mm Hg) appeared to be associated with the development of PRES with high sensitivity and specificity.[54] Such aggressive IH may be reserved for refractory cases of DCI, and patients should be

closely examined for neurological changes suggestive of PRES. PRES appears to be a relatively common complication of more aggressive IH therapy and should be suspected in any patient with unexplained neurological deterioration. Alternative interventions may be preferred for refractory DCI when IH to these levels has already been attempted or in patients that are already spontaneously hypertensive.[54,57]

Current clinical evidence of IH therapy in aSAH

There is controversy regarding whether or not IH therapy is one of the best treatments for symptomatic cerebral ischemia in patients with aSAH.[58] Interestingly, the use of IH therapy has been steadily increasing compared with other treatment modalities for DCI in aSAH.[59-61]

Haegens et al. believe that IH therapy plays a crucial role in preventing DCI and can lead to better outcomes.[9] However, if IH therapy is routinely advisable for DCI treatment, PRES could appear as a common complication after aggressive IH therapy. In IH, due to the MAP being raised more than baseline, caution should be taken; moreover, alternative interventions should be considered which may be utilized in the treatment of DCI.[57,62]

Remarkably, despite the possibility of aSAH presenting with unsecured aneurysms, IH appears to be a safe treatment for symptomatic CVS regardless of the presence of unsecured aneurysms according to the data reviewed here. For the protocols of this study regarding IH's potential impacts on additional unruptured aneurysms, the treatment goal was to achieve a cerebral perfusion pressure (CPP) of 80 to 120 mmHg alongside the MAP values of 90-130 mmHg.[16,63]

However, Lee et al. have reviewed this paradigm that the efficacy of triple-H therapy (combination of IH, hypervolemia, and hemodilution) in the treatment of aSAH remains doubtful and eventually concluded that this type of therapy should be used judiciously.[62] It is notable to mention that the management of aSAH in the context of PRES should be replaced with methods other than triple-H therapy, due to some difficulties and complications.[64]

In addition, it is hypothesized that IH (raising MAP by 25%) and volume loading (with an isotonic crystalloid bolus of 15 ml/kg) act to reverse or prevent the progression of ischemia primarily through their ability to raise CBF, thus reversing reductions in O_2 delivery (DO_2) to watershed areas of the brain that are most at risk, despite some claims that these effects are inconsistently observed.[65,66]

Conclusion

Given the steep increase in the trend, we reviewed the current body of evidence comprehensively to elucidate the clinical aspects, mechanism of action, protocols, risks, and clinical outcomes of IH therapy in aSAH patients. To the best of our knowledge, some studies have showed the favorable impact of IH therapy on aSAH patients; however, it is crucial to conduct further clinical and molecular experiments to enlighten the IH therapy guidelines.

Conflict of Interests

The authors declare no conflict of interest in this study.

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