Early brain injury and subarachnoid hemorrhage: Where are we at present?

Tumul Chowdhury, Hari Hara Dash[1], Ronald B. Cappellani, Jayesh Daya

Departments of Anesthesiology and Perioperative Medicine, Health Sciences Center, University of Manitoba, Winnipeg, Canada, [1]Fortis Hospital, Gurgaon, India

Address for correspondence:
Dr. Tumul Chowdhury, Department of Anesthesia and Perioperative Medicine, HSC, University of Manitoba, Winnipeg, Canada.
E-mail: tumulthunder@gmail.com

ABSTRACT

The current era has adopted many new innovations in nearly every aspect of management of subarachnoid hemorrhage (SAH); however, the neurological outcome has still not changed significantly. These major therapeutic advances mainly addressed the two most important sequels of the SAH-vasospasm and re-bleed. Thus, there is a possibility of some different pathophysiological mechanism that would be responsible for causing poor outcome in these patients. In this article, we have tried to compile the current role of this different yet potentially treatable pathophysiological mechanism in post-SAH patients. The main pathophysiological mechanism for the development of early brain injury (EBI) is the apoptotic pathways. The macro-mechanism includes increased intracranial pressure, disruption of the blood-brain barrier, and finally global ischemia. Most of the treatment strategies are still in the experimental phase. Although the role of EBI following SAH is now well established, the treatment modalities for human patients are yet to be testified.

Key words: *Apoptosis, early brain injury, ischemia, subarachnoid hemorrhage*

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is one of the most dreaded forms of neurological disease that not only causes significant morbidity and mortality but also results in poor socioeconomic outcome.[1] Although the current era has adopted many new innovations in nearly every aspect of management of this disease, the neurological outcome has still not changed significantly.[2] However, these major therapeutic advances mainly addressed the two most important sequel of SAH-vasospasm and re-bleed. Thus, there is a possibility of some different pathophysiological mechanism that would be responsible for causing poor outcome in these patients.

In this article, we have tried to compile the current role of this different yet potentially treatable pathophysiological mechanism in post-SAH patients.

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EARLY BRAIN INJURY FOLLOWING SPONTANEOUS SUBARACHNOID HEMORRHAGE

The pathophysiological mechanism responsible for any type of brain insult during the first 72 h following SAH is termed as EBI.[3] Vasospasm usually starts after 72 h post-SAH; however, the pathophysiological mechanism of EBI would certainly play some role in either causing vasospasm or at least sharing the common pathways to produce overall bad neurological outcome at the initial period of SAH.[4] Recently, a study showed increase in neuroinflammatory response (global Tumor necrosis factor TNF-α) following SAH at 2-3 days, but there was no angiographic vasospasm. However, this inflammatory response was associated with poor outcome at 3 months.[5] The clinical consequences of both the mechanisms are usually similar, including altered consciousness or the sudden onset of new neurological deficit in patients with ruptured aneurysm. The need to elucidate the etiopathogenesis of EBI is currently a matter of great interest and mainly postulated in animal experiments. The current area of interest for EBI is emerging rapidly as many of the pathophysiological process are potentially treatable.

ETIOPATHOGENESIS OF EARLY BRAIN INJURY

Macro-mechanism

SAH is a complex pathophysiological process, wherein the initial physiological response is increase in intracranial

pressure (ICP). Though thought to be a protective mechanism, this rise in ICP usually decreases the cerebral perfusion pressure and further causes cerebral ischemia. The presence of blood and its degraded products in the ventricles produce obstructive hydrocephalus, which again causes increase in ICP. This results in the development of global ischemia, which stimulates many ischemic pathways, usually produces oxidative damage to neural tissue, and finally leads to neuronal death. The ischemic mediators disrupt the blood brain barrier and produce cytotoxic neuronal edema. This sets off the vicious cycle, producing more ischemia and so on.[6,7]

MOLECULAR MECHANISM

Apoptosis is the most common proposed mechanism for the development of EBI.[8] It is a programmed cell death that is usually devoid of cell inflammatory mediators. In the ischemic cell, mitochondrial dysfunction is the precursor of final neuronal injury. On the other hand, necrotic pathways may occur and usually difficult to differentiate; however, this process is usually followed by inflammatory mediators and often depicts irreversible cell injury. The reversible nature of apoptotic pathways has shown some promising treatment options. In general, post SAH, the ischemic insult of brain stimulates a wide array of complex pathways that finally stimulate the apoptotic mechanism and finally the production of EBI. The proposed different mechanisms to produce EBI include oxidative injury, nitric oxide dysregulation, generation of matrix metalloproteinase 9 (MMP-9), modulation of nuclear factor erythroid 2-related factor 2 and antioxidant-response element (Nrf2-ARE) pathway, activation of c-Jun N-terminal kinase pathway, interleukin-1beta activation, and other factors such as vascular endothelial growth factor and mitogen-activation protein kinase.[9-14] The role of iron overload that is produced after degradation of hemoglobin following SAH has also been shown to cause EBI.[15] On the other hand, some processes such as autophagy play a protective role in EBI by removing misfolded proteins and scavenging other dysfunctional proteins as well as organelle.[16] Understanding these molecular mechanisms will lead to promising treatment options in SAH patients and possibly would open new doors for future treatment strategies.

MANAGEMENT

The management of EBI is mainly experimental; however, the treatment options are multidisciplinary and involve all the aspects of SAH management.

Acute management

Management of SAH starts from early resuscitation steps, such as airway control, adequate breathing to maintain normoventilation, avoiding hypoxemia, maintaining adequate perfusion, and identifying other disabilities. Maintenance of cerebral oxygenation and perfusion is the utmost goal. The supportive care should aim to prevent secondary brain injury and involve seizure control, avoid hypoglycemia or hyperglycemia, maintain normothermia, and minimize the increase in ICP.[17] The role of external ventricular drain to relieve increase in ICP should be discussed with the surgeon and this sometimes remains the only lifesaving maneuver, especially in poor-grade patients.

Most of the patients with SAH are hypovolemic. Maintenance of normovolemia with isotonic fluids is recommended.[18] Avoidance of glucose-containing solutions and correction of underlying electrolytes abnormalities are important in preventing secondary brain injury. The use of hypervolemia to prevent vasospasm is now not a part of standard care because it can aggravate cerebral edema and hence ischemia and produce other systemic complications including pulmonary edema and congestive heart failure.[19]

Poor-grade patients often require intubation and elective ventilation. Normocarbia should be maintained. Hypocarbia can cause cerebral vasoconstriction and may worsen the ischemia. However, transient hyperventilation should be used only in the situation of ICP raised ICP due to re-bleed, hydrocephalus, or massive infarct. Early tracheostomy will be beneficial in patients with massive ischemia/infarct, in which prolonged ventilation would be anticipated.

Definitive treatment

Options include either clipping or coiling of the ruptured aneurysm. Previous studies have shown that outcome (free of disability) at 1 year is significantly better with endovascular coiling and the survival benefit continues for at least 7 years.[20,21] Although a small risk, there were more episodes of re-bleed in the coiling group. The current evidence also favors coiling if aneurysm is suitable for both coiling and clipping.[22]

The prevention of SAH sequel in the form of either EBI or vasospasm would depend on definite management if done at an early phase. The prophylactic use of calcium channel antagonist-nimodipine is the standard care to prevent and treat vasospasm.

SPECIFIC MANAGEMENT OF EARLY BRAIN INJURY

Blocker of apoptotic pathway

Apoptotic pathways play a crucial role in developing EBI following SAH. This apoptotic pathway involves

many enzymes including Cytochrome-C, Caspase, and P53. There are many agents that specifically block these different enzymes at different levels and have been shown to attenuate EBI. The noteworthy point is that these enzymatic processes are essential for normal regulation also, so the blockage of these may produce many untoward effects.

Statins (Hydroxymethylglutaryl coenzyme A reductase inhibitors) such as atrovastin has been shown to inhibit Caspase-dependent proapoptotic pathway and found to be neuroprotective.[23] The role of cyclosporine A in the stabilization of mitochondrial membrane by inhibiting mitochondrial permeability transition pore (mPTP) opening was also found to be one of the antiapoptotic mechanisms to attenuate SAH-induced EBI.[24]

Recent studies have demonstrated the possible role of volatile anesthetic in the prevention of EBI. In this study, use of isoflurane in post-SAH animals delayed the EBI produced by SAH. Isoflurane is found to be an inhibitor of apoptotic pathway through sphingosine-related activation and this study further concludes that the use of isoflurane in early surgery or intervention might be beneficial.[25] In another study, use of isoflurane was also associated with decrease in BBI disruption, which has an important role for causing EBI following SAH.[26]

Other agents

The other agents found to attenuate or prevent EBI are mainly the inhibitors of other pathways. These agents include desferoxamine (iron overload), minocycline (MMP-9 inhibitor), hydrogen-rich saline (decreases oxidative stress), osteopontin (deactivation of nuclear factor-κB activity and MMP-9 inhibitor), sodium orthovanadate (tyrosine phosphatase inhibitor), melatonin, and recombinant human erythropoietin (activation Nrf2-ARE pathway).[27-33]

HYPOTHERMIA

Hypothermia attenuates the mediators of ischemic cascade and confers neuroprotection. The ischemia-induced apoptotic pathways could be blocked by hypothermia; however, the exact therapeutic window is still a matter of investigation. The current literature, however, does not support the use of mild therapeutic hypothermia, especially in good-grade aneurysm patients.[34] On the other hand, it has shown some promising results in experimental poor-grade aneurysms. There is also a conflict about the timing to institute hypothermia to maximize its beneficial role.[35,36] Large, randomized studies are further required to elucidate the role of hypothermia in EBI, especially in poor-grade patients.

HYPERBARIC OXYGEN THERAPY

Post SAH, there is increased lipid per oxidation and upregulation of Nicotinamide Adenine Dinucleotide Phosphate NADPH oxidase (NOX), a major enzymatic source of superoxide anion in the brain. Hyperbaric oxygen has found to blunt these oxidative responses. This therapy has also shown to reverse early ischemia and prolong neuroprotective effects.[37,38]

INTERPRETATION OF EXPERIMENTAL RESULTS

The major researches for therapies to attenuate or to prevent EBI in post-SAH patients are only carried out in animal models. The interpretation of these data to human are not always direct, because some cerebro-physiological differences exist among different species. Thus, it would be interesting to observe the results in human patients in the near future.

In conclusion, the role of EBI following SAH is now well established and its pathogenesis mainly involves the ischemic-apoptotic pathways; however, the management strategies are still in the experimental phase and are yet to be performed on patients. The future therapies would also be more focused toward the role of gene and stem cell therapies in such cases.

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