Subarachnoid Hemorrhage

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The incidence of hemorrhagic stroke in the general population accounts for approximately 20% of all the strokes, with 5% due to subarachnoid hemorrhage (SAH). The morbidity and mortality remains high for this patient population. For aneurysmal SAH, 30% of patients die and 50% of survivors have long-term cognitive deficits that preclude their return to work. The two most important determinants of outcome after SAH are initial hemorrhage severity and secondary brain injury due to early brain injury (EBI) and delayed cerebral ischemia (DCI). EBI occurs in 12% of patients, develops 1–3 days after SAH and is characterized by blood–brain barrier (BBB) disruption, neuronal cell death, neuroinflammation and cerebral edema. DCI occurs in ~30% of patients, develops 4–12 days after SAH and is characterized by large artery vasospasm, distal autoregulatory dysfunction, microvessel thrombosis and cortical spreading depression. Though many strategies to prevent EBI and DCI have been explored over the years, none have proven efficacious. New therapies are desperately needed to treat these conditions.

anesthetics anesthetic adjuvants neurovascular protection aneurysmal subarachnoid hemorrhage early brain injury delayed cerebral ischemia neurological outcomes

1. Overview

Aneurysmal rupture accounts for the majority of subarachnoid hemorrhage and is responsible for most cerebrovascular deaths with high mortality and morbidity. Initial hemorrhage severity and secondary brain injury due to early brain injury and delayed cerebral ischemia are the major determinants of outcomes after aneurysmal subarachnoid hemorrhage. Several therapies have been explored to prevent these secondary brain injury processes after aneurysmal subarachnoid hemorrhage with limited clinical success. Experimental and clinical studies have shown a neuroprotective role of certain anesthetics in cerebrovascular disorders including aneurysmal subarachnoid hemorrhage. The vast majority of aneurysmal subarachnoid hemorrhage patients require general anesthesia for surgical or endovascular repair of their aneurysm. Given the potential impact certain anesthetics have on secondary brain injury after SAH, appropriate selection of anesthetics may prove impactful on overall outcome of these patients. This narrative review focuses on the available evidence of anesthetics and their adjuvants in neurovascular protection in aneurysmal subarachnoid hemorrhage and discusses current impact on clinical care and future investigative directions.

2. Hemorrhagic Stroke

The incidence of hemorrhagic stroke in the general population accounts for approximately 20% of all the strokes, with 5% due to subarachnoid hemorrhage (SAH) [1]. The morbidity and mortality remains high for this patient population. For aneurysmal SAH, 30% of patients die [2] and 50% of survivors have long-term cognitive deficits that preclude their return to work [3]. The two most important determinants of outcome after SAH are initial hemorrhage severity and secondary brain injury due to early brain injury (EBI) and delayed cerebral ischemia (DCI). EBI occurs in 12% of patients, develops 1–3 days after SAH and is characterized by blood–brain barrier (BBB) disruption, neuronal cell death, neuroinflammation and cerebral edema [4]. DCI occurs in ~30% of patients, develops 4–12 days after SAH and is characterized by large artery vasospasm, distal autoregulatory dysfunction, microvessel thrombosis and cortical spreading depression [5]. Though many strategies to prevent EBI and DCI have been explored over the years, none have proven efficacious. New therapies are desperately needed to treat these conditions.

In recent decades, many experimental studies have shown a strong neuroprotective effect of certain anesthetics on EBI and DCI. Some of these studies have also shown an impact on mortality and neurological outcome. A more limited set of clinical studies suggest that certain anesthetics may have a protective effect in SAH patients. The vast majority of aneurysmal SAH patients will be exposed to anesthetics either in the operating room for surgical repair of the aneurysm, the interventional neuroradiology suite for endovascular treatment of the aneurysm, or in the neurointensive care unit for sedation after the initial hemorrhagic insult. Given the potential protective effects of certain anesthetic agents and their adjuvants, choice of anesthetic technique may prove critical in the management of SAH patients. The aim of the present review is to critically analyze the available evidence implicating a role of certain anesthetics and their adjuvants in neurovascular protection in aneurysmal SAH.

3. Limitations

(1) Current preclinical studies have used male animals for their SAH experiments. Importantly, however, SAH in patients occurs more frequently in females vs. males [6] and differences in SAH outcome between males and females have been noted in preclinical studies [7]. It is therefore essential that future experimental studies include female animals to address gender as a potential biologic variable. (2) The anesthetic dose used in the majority of experimental studies may not correlate with the anesthetic dose utilized in SAH patients. Different strains, species and the age group used in the experiments further complicates this issue. (3) Several of the experimental studies did not identify a causal mechanism for anesthetic/adjuvant induced neuroprotection in SAH, which is critical in the development of drug therapeutics. (4) Limited clinical studies are available to show the impact of anesthetics on secondary brain injury and long-term neurobehavioral outcomes after SAH. These studies are further limited by their (a) retrospective nature; (b) smaller cohort size to causally show an impact on patient outcomes; and (c) lack of standardized measures to examine cognitive and long-term neurobehavioral outcomes. Hence, well designed properly controlled larger randomized prospective studies are critical in evaluating the impact of anesthetics on the secondary brain injury outcomes after SAH.

4. Conclusions

A growing body of literature—both experimental and clinical—indicates certain anesthetics likely have substantial protective effects against both EBI and DCI following SAH [8]. From animal studies, we have learned that protection afforded by anesthetics is multifaceted including positive effects on inflammation, blood–brain barrier breakdown, cerebral edema, neuronal apoptosis, microvascular thrombi, autoregulatory dysfunction and large artery vasospasm. The pleiotropic nature of the protective effects of certain anesthetics (EBI and DCI; neurons and cerebral vessels) has a great potential for anesthetic-based therapies to ultimately translate into robust protection against secondary brain injury in SAH patients and improvement in overall neurological outcome. The excellent safety profile and relative ease at which anesthetic agents can be delivered to acutely ill patients only enhances the promise of this therapeutic approach. Studies to further elucidate the underlying mechanisms of anesthetic-induced neurovascular protection in SAH in the hopes of identifying novel and druggable therapeutic targets are warranted, as are clinical studies designed to identify the most appropriate anesthetics, optimize their dosing and rigorously test for therapeutic benefit in SAH patients.

5. Future Studies

Based on the breadth of experimental and clinical data implicating certain anesthetics and anesthetic adjuvants with reducing EBI and DCI and improving neurological outcome after SAH, additional studies examining the impact of these agents in SAH are warranted. In particular, studies designed to address the following would be especially impactful: (1) determining the differential benefit of various anesthetics on SAH outcome; (2) defining optimal dosing and effective therapeutic window for SAH; (3) elucidating underlying mechanisms of anesthetic-induced neurovascular protection in SAH; and (4) exploring the impact of anesthetic treatment on long-term neurobehavioral and cognitive outcomes after SAH.

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