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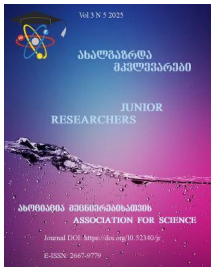

Emerging Therapeutics and Precision Critical Care in Aneurysmal Subarachnoid Hemorrhage

Parvin Mozafari [1], Prisca Heshani Kapuge [2], Sarah Towsif Shaikh [3], Taahira Arief [4]

1-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

2-Tbilisi State Medical University, Tbilisi, Georgia.

3-Tbilisi State Medical University, Tbilisi, Georgia.

4- Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.

**Corresponding author: Parvin Mozafari1, Faculty of medicine, University of Georgia, Tbilisi, Georgia, Parvinmozaffari73@gmail.com, Phone number: +995-591096156

** ORCID: Parvin Mozafari: 0009-0002-8107-2390, Prisca Heshani Kapuge : 0009-0000-6319-2474, Sarah Towsif Shaikh : 0009-0008-3575-8088, Taahira Arief : 0009-0007-6513-5036.

Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious neurological emergency that has a high rate of morbidity and mortality. The management of aSAH is still difficult despite improvements in neurocritical care, especially when it comes to avoiding and treating complications like cerebral vasospasm and delayed cerebral ischemia (DCI). This review examines new treatments and how precision critical care can help patients with aSAH achieve better results.Oral and intravenous nimodipine has been promising in the reduction of DCI and better neurological outcomes. But the fluctuating outcomes of other medications, including clazosentan, fasudil and cilostazol make it necessary to conduct more research. Examples of precision critical care approaches that could be used to offer individualized treatment according to the needs of individual patients include advanced imaging, biomarker-guided care and multimodal neuromonitoring. The approaches enable the anticipation of the risk of DCI, early identification of secondary brain injury, and optimization of the blood pressure and fluid balance. Some of the barriers to the implementation of precision critical care include patient variability, medical costs, the need to have certain infrastructure and knowledge. Some of the ways in which AI-assisted tools, better imaging techniques, assessment tools to identify genetic risks and new biomarkers will be applied in the management of aSAH are the future directions. In order to bridge the evidence to clinical practice gap and ensure that advanced therapies are available and affordable to a large group of patients, multicenter research programs and investments in

healthcare are essential and scavenging incremental improvement of survival and long-term neurological recovery for aSAH patients is possible by adopting state-of-the-art technology and precision medicine approaches.

Keywords: Aneurysmal subarachnoid hemorrhage, Emerging therapeutics, Cerebral ischemia, Nimodipine, Endovascular therapy.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a condition of emergent nature with severe mortality and morbidity. Early detection and early treatment are crucial in an attempt to prevent subsequent complications such as rebleeding, delayed cerebral ischemia (DCI), and to improve the patient's outcome overall (1,2). The selection of a treatment method for an aneurysm rupture is a trade-off between securing the aneurysm and the dangers of the procedure. Open surgical clipping and endovascular therapy, such as coiling, are two primary forms of treatment of aneurysms. Each of them has advantages and disadvantages, and the choice depends on the nature of aneurysms, patient factors, and clinical manifestation.

Close monitoring, systemic stabilization and the prevention of neurological and systemic complications should be prioritized in ICU care. In case of possible reduction of sedation, clinical neuromonitoring should be as much as possible and ventilation time and hospital stay may be reduced. However, it may be necessary in cases of increased intracranial pressure, agitation, pain, seizures, or respiratory failure (2). Nevertheless, since evidence-based guidelines are not comprehensive, several management choices are made on the basis of personal factors of the patient, organizational protocols and experience of the medical practitioners (3).

Cerebral ischemia is a major complication following aSAH and its development is driven by multiple factors, including vasospasm, microthrombi formation, and cortical spreading ischemia (4). Recent evidence does not support delayed cerebral ischemia (DCI) being entirely due to vasospasm. Treatment modalities reported to demonstrate mixed efficacy include nimodipine, clazosentan and fasudil, and preliminary evidence indicates that circulatory management and evacuation of hematoma could decrease risk of DCI, which is yet to be proved over the long term. It also seems promising but remains to be confirmed in large-scale trials using endovascular methods or agents including cilostazol or anticoagulants (5).

Precision medicine is an individualized diagnosis and treatment of aSAH in that, it takes into account genetic, environmental, and lifestyle factors of a patient. It includes genetic risk evaluation, high-tech imaging, and early diagnosis biomarkers, and customized surgical and pharmacological interventions to enhance the results and decrease complications (6). This review will analyze the new treatment methods and the relevance of precision critical care in the treatment of aneurysmal subarachnoid

hemorrhage (aSAH) and consider personalized treatment methods that have the potential to enhance patient outcomes and inform future studies (6,7).

Methodology

To find pertinent research on aneurysmal subarachnoid hemorrhage (aSAH), a thorough literature search was carried out on PubMed and Google Scholar.The following search terms, alone and in combination, were used: “Aneurysmal Subarachnoid Hemorrhage,” “Emerging Therapeutics,” “Critical Care,” “Intensive Care,” “Intracranial Aneurysm,” “Unruptured Intracranial Aneurysm,” and “Cerebral Ischemia.” And Only the English language was searched with publications dating back to January 2015 and March 2025 (2).

Peer-reviewed original research publications, clinical trials, observational studies, expert consensus statements, and clinical guidelines were among the acceptable sources. Editorials, conference abstracts, case reports, and articles written in languages other than English were not included. With a focus on therapeutic interventions, preventive medicine tactics, pharmaceutical innovations, and multimodal monitoring approaches in aSAH, the retrieved studies were examined and arranged based on study design (3).

After independently checking the titles and abstracts for relevancy, two reviewers evaluated the full texts. Discussion and agreement were used to settle disagreements. To find more pertinent studies, the reference lists of the included articles were also reviewed.This was a narrative review; therefore, there were neither quality assessment tools nor risk-of-bias scoring tools. Instead, the choice was aimed at providing a reasonable overview of the latest data and professional views. Despite the possibility of author bias that is always present in narrative reviews, this was minimized through the application of broad search terms, pre-set inclusion criteria, and independent screening by multiple reviewers (4,5).

Discussion

The treatment of aneurysmal subarachnoid hemorrhage is typically done with oral nimodipine, which is a calcium channel blocker, that works by restricting calcium influx into smooth muscle cells, improving cerebral perfusion, restricting vasoconstriction (6,7). Nimodipine can cross the blood brain barrier and in this way, it yields an anti-apoptotic effect on neurons and glial cells, making it neuroprotective. There are many randomized control trials which show that nimodipine has a prophylactic effect and it can improve the neurological outcomes and delay cerebral ischemia by up to 50% unassociated with vasospasm (6,8,9). Currently, oral nimodipine is what is usually given for most patients, soon after their diagnosis for a duration of 21 days, favorably showing positive outcomes in reducing cerebral infarction, overall recovery and decrease in death (8,9). However, this cannot be said for all patients, such as those who are critically ill or intubated.

So, intravenous nimodipine is being considered, for example, recently developed GTx-104, shows an advancement in dose delivery, lessening critical hypotension, and more stable plasma concentrations. Phase 3 STRIVE-ON trial data underlined the advantage of IV nimodipine, by demonstrating 29% increase in advantageous outcome in 90 days, fewer readmissions in ICU, and reduced use of ventilator, thus showing that it increases cerebral perfusion and reduces secondary brain injury (10,11). IV nimodipine shows an advantage compared to oral nimodipine as it improves bioavailability and reduces variability in systemic absorption, in preclinical and clinical studies (4). Yet, there is a high risk of hypotension with IV nimodipine, so careful monitoring is required (8).

Other challenges with IV nimodipine, specifically EG-1962 is the limitation on the current evidence for it. Most randomized controlled trials were limited by small sample sizes and sometimes early termination. The reliability of the findings can also be questioned because of incomplete outcome data and absence of blinded outcome assessment. And while there is a great reduction in vasospasm, there are no improvements in delayed cerebral ischemia or functional recovery. This means that there should be a larger sample size, and more evidence is required to conclude that IV nimodipine can provide clinical benefit beyond the radiographic markers (12). Besides calcium channel blockers, there are other therapies being investigated. For example, Clazosentan, an endothelin receptor antagonist, showed a reduction in angiographic vasospasm but clinical outcomes seem incompatible in treatment (13).

There were two trials done CONSCIOUS-1 & CONSCIOUS-2 Trials, CONSCIOUS-1 Phase II trial showed that clazosentan greatly reduced angiographic vasospasm when compared to the placebo, the CONSCIOUS-2 Phase III trial showed no improvement in neurological outcome despite decrease in vasospasm. This indicates that vasospasm alone is not the main cause of delayed cerebral ischemia (14). But when clazosentan is implemented into a multimodal treatment approach, it can have potential in ameliorating the result, as Japanese cohorts so (9). Another drug, Rho-Kinase (ROCK) Inhibitors (e.g., Fasudil), reveals similar findings.The vasospasm reduction was achieved but there was no improvement in the neurological outcome since vasospasm is only one part of secondary brain injury (14).

Cilostazol has shown some promise in randomized control trials but before routine use can be indicated, further investigations need to be done. Others, such as milrinone, and targeted anti-inflammatory drugs show favorable effects in decreasing vasospasm or DCI incidence in preliminary trials, large, multicenter randomized controlled trials (RCTs) display constant practical results, but are still investigational (15).

According to the 2023 AHA/ASA guidelines, neuroprotective and anti-inflammatory medications may be beneficial following an aneurysmal subarachnoid hemorrhage; however, there is not enough data to support their clinical application. Many neuroprotective drugs, such as magnesium sulfate, statins, erythropoietin, and free radical scavengers like tirilazad, have been assessed in clinical trials but none present a favorable outcome (16,17). For example, Magnesium trials (IMASH, MASH-2) showed no benefit in decreasing delayed cerebral ischemia. Statins seemed promising early on, but the same was noted.

Small RCTs showed some potential neuroprotection with erythropoietin but enough evidence is needed to be convinced of a benefit. Furthermore, anti-inflammatory drugs such as corticosteroids and interleukin inhibitors have demonstrated promising outcomes in experimental models, but there is insufficient clinical data to support their routine use in treatment. Though these agents have potential, the guideline emphasizes that for now they should be limited to clinical trials only (7). Another strategy, a lumbar cerebrospinal fluid drainage, shows prophylactic lumbar drainage, like from EARLYDRAIN randomized controlled trial, decreased secondary infarction rates and bettered six-month outcomes (18,19). Altogether, this highlights a multimodal approach in treatment, combining nimodipine and other interventions to personalize treatment in high-risk patients (18). Advances in precision critical patient care move towards a patient specific management. There are several innovations which indicate personalized, early interventions prevent brain damage by implementing continuous monitoring of real time changes.

Monitoring ICP and having external ventricular drains reduce the risk of herniation, identifying areas of ischemia before an infarction develops using CT perfusion and MR perfusion, Transcranial Doppler Ultrasonography which measure cerebral blood flow velocities to detect vasospasm early, particularly in high-risk phases (19).

Cerebral micro dialysis is a multimodal approach where levels of glucose, lactate, pyruvate, glutamate, and glycerol, are measured and can provide warning signs of metabolic crisis. Since increased lactate/pyruvate ratio is linked to cerebral ischemia and increased glutamate and glycerol levels show excitotoxicity, understanding these changes can guide physicians to personalized therapy because it gives them an idea of the brain's metabolic status (20).

Biomarkers directed plans of action, such as CSF biomarkers endothelin-1 (ET-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) and the hope of omics technologies, including genomics, proteomics, and metabolomics, propel an idea of targeted therapy (4,10). Moreover, Hemodynamic management can differ from patient to patient. Traditionally, there's a fixed blood pressure threshold for patients after aSAH, however research shows this is not optimal since different patients respond differently after a hemorrhage. Personalized blood pressure and fluid targets are preferred and is a shift from triple H therapy (hypertension, hypervolemia, hemodilution) (6). Evidence shows that high-volume, specialized neurocritical care units establish great results, so it is important to have trained staff, proper infrastructure and orderly teams (12).

There is evidence from clinical trials which show these things are possible. Beside nimodipine, the ISAT trial showed that there are advantages in endovascular aneurysm treatment, the SAHaRA trial set the safe hemoglobin transfusion thresholds. As mentioned before, the EARLYDRAIN trial showed the advancement in outcomes (9,13). Multimodal approaches show a significant improvement in outcome of certain patients who had a poor chance, with discharges at 3 months (18). Nevertheless, there are several key challenges in executing precision critical care.

Firstly, there's a variability in patient response because of genetic polymorphisms like ApoE and not all patients with vasospasm develop DCI and some develop DCI without vasospasm (18). DCI can also be caused by many processes such as vasospasm, micro thrombosis, cortical spreading depolarizations, neuroinflammation, and cerebral autoregulation disruption. Consequently, a single drug is not advantageous (18). This means that standard protocols cannot be recommended for all patients and emphasizes the need for patient specific care plans. Secondly, a multimodal approach like multimodal neuromonitoring, cerebral oxygenation (PbtO2) probes, continuous EEG, CT perfusion, and advanced endovascular rescue therapies means increased healthcare cost since they require advanced imaging, significant staff expertise in interpretation of data and specialized units.

This also further creates difficulty since many centers lack these guidelines to deliver recommended individualized therapy (19). When treating patients with aneurysmal subarachnoid hemorrhage, it is also important to understand that there is a socioeconomic burden past the early stages of management. Long-term morbidity is common and there are often disabilities that limit the person from returning to their normal work lifestyle and independence. This means there is a greater dependance upon healthcare usage and upon social support systems, translating to significant increase in overall costs (19).

Artificial intelligence (AI), advanced imaging, and biomarkers may be used in the future to inform the personalized therapy developed by aSAH management. AI driven methods could help in timely interventions such as recognizing a secondary brain injury, predicting a DCI risk. Such biomarkers as GFAP, S100B, as well as microRNAs can assist in the adequate and timely risk assessment. Genetic factors, including variants in eNOS, MMP-9, and estrogen receptor genes can do the same and help create a personalized strategy in managing the patient (20).

Another demand for further research is the development of powerful prognostic tools to help guide personalized treatment. An example of this is the SAHOT score but further clarification and confirmation is imperative for a broad application for all kinds of patients. Additionally, there is a need for patient reported outcomes, as survival alone is not enough measure of success. An overall idea of the quality of life of the patient, their social, functional and mental wellbeing, can help determine the best approaches with different patients and improve the long-term quality of life (20).

Basically, aneurysmal subarachnoid hemorrhages are an urgent emergency whose mortality rates are always high and whose resultant impairments are irreversible even after decades of advancements in treatment. Currently, oral nimodipine and cerebrospinal fluid management is the protocol, but there are barriers such as patient-to-patient variability, lack of infrastructure and other limitations in the healthcare system that call for continuous changes. Novel agents, such as IV nimodipine, anti-inflammatory agents, neuroprotective drugs, seem promising for a better improvement in neurological recovery and reduce secondary brain injury, but much evidence is required to adopt them into the standard care and management (18,19,20).

The other valuable practice is the precision critical care (including multimodal neuromonitoring, intracranial pressure, cerebral oxygenation, continuous EEG, and advanced imaging) that allows

opening the gateway to the personalization of treatment of each patient individually, focusing on blood pressure and fluids and predicting early complications. This can be extremely helpful in overall outcome but calls for specialized infrastructure and highly trained personnel, underlining the gap between evidence and clinical practice. Looking forward, the world of artificial intelligence such as enhanced imaging, genetic risk profiling and use biomarkers calls for a truly individualized approach to treatment. These emerging technologies and tools have the ability to help the patient with perfect intervention. This can be done through collective, multicenter research, investments in healthcare, and significance in affordability and accessibility to ensure that it is accessible to a varied population of patients. With a collaborative effort, the field will be able to roll out of the incremental gains to life modifying neurological improvements in survival and long-term recovery (19,20)

Conclusion

Aneurysmal Subarachnoid Hemorrhage (aSAH) is a serious neurological crisis with high morbidity and mortality rates whose management requires urgent patient stabilization, prompt diagnosis and timely treatment. Although Early Brain Injury (EBI), Delayed Cerebral Ischemia (DCI) and cerebral vasospasm are the most complicated and perilous outcomes of (aSAH), they pose significant treatment issues, even with the current progress in neurocritical care. Such developments have not only changed their emphasis towards the prevention of vasospasm but a wider perspective that is more precise and does not focus on one pathway of pathophysiology.

The management of aSAH requires a multidisciplinary patient-focused methodology based on experience in neurosurgery, endovascular therapy and neurological management. The development of neuroimaging, genetic profiling, surgical and endovascular therapies, and pharmacological interventions has also enhanced the detection of this disease, its risk factors, and clinical outcomes. The only pharmacological treatment that has continued to demonstrate results in enhancement of neurological outcome is Nimodipine among others. Intraventricular nimodipine has shown a lower risk of angiographic vasospasms compared to oral nimodipine. Clazosentan, an endothelin receptor has shown potential in reducing vasospasms. Apart from nimodipine and clazosentan, fasudil and cilostazol have also shown favourable results.Examples of other agents are statins, magnesium, and anticoagulants, but they are indefinite and underline the need to have therapeutic advancement.

The studies are supposed to close the gaps in comprehending aSAH pathophysiology and measures that are likely to promote better outcomes in the long run. Key research topics that need our scrutiny and priority are -developing biomarker-driven and personalized treatment strategies, along with the integration of non-invasive, real-time neuromonitoring technology in clinical practice. We can proceed to investigate and innovate these fields of imaging, surgical work, endovascular work and prevention measures to have hope of bettering the results and life quality of the affected patients with this devastating condition.

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