Review

Hydroxyethylstarch revisited for acute brain injury treatment

https://doi.org/10.4103/1673-5374.300978

Date of submission: April 2, 2020

Date of decision: May 7, 2020

Date of acceptance: September 28, 2020

Date of web publication: December 12, 2020

Martin A. Schick[1, 2, #], Malgorzata Burek[3, #], Carola Y. Förster[3, #], Michiaki Nagai[4], Christian Wunder[5, *], Winfried Neuhaus[6, *]

Abstract

Infusion of the colloid hydroxyethylstarch has been used for volume substitution to maintain hemodynamics and microcirculation after e.g., severe blood loss. In the last decade it was revealed that hydroxyethylstarch can aggravate acute kidney injury, especially in septic patients. Because of the serious risk for critically ill patients, the administration of hydroxyethylstarch was restricted for clinical use. Animal studies and recently published *in vitro* experiments showed that hydroxyethylstarch might exert protective effects on the blood-brain barrier. Since the prevention of blood-brain barrier disruption was shown to go along with the reduction of brain damage after several kinds of insults, we revisit the topic hydroxyethylstarch and discuss a possible niche for the application of hydroxyethylstarch in acute brain injury treatment.

Key Words: acute subarachnoid hemorrhage; astrocyte; chronic kidney disease; delayed cerebral ischemia; microglia; neurovascular unit; osmotic pressure; pericyte; stroke; traumatic brain injury

The Colloid Hydroxyethylstarch for Volume Substitution

Since the 1960s, hydroxyethylstarch (HES) has commonly been used as a safe artificial colloid for volume substitution to restore hypovolemia and microcirculation after e.g., severe blood loss. HES is a branched and variegated molecule based on glucose, which is modified by hydroxyethylation (mainly) at the C2 and C6 carbon atoms in order to prevent rapid hydrolysis by available α-amylase in the plasma and enable long lasting effects *in vivo*. HES is a polydisperse solution, and the nomenclature of e.g. 130/0.4 HES stands for an average mean molecular weight of 130 kDa. 0.4 means that 40% of the glucose subunits are modified by hydroxyethylation (Jungheinrich and Neff, 2005). Currently, HES 130/0.4 or HES 130/0.42 with carrier solution either 0.9% sodium chloride (NaCl) or a balanced solution are applied in clinical routine. Alternatively to colloid solutions such as HES or albumin, crystalloid solutions such as saline, Ringer's solution or Sterofundin® ISO could be used for volume substitution.

PubMed and Google Scholar were used as databases using topic related key words such as HES, hydroxyethylstarch, blood-brain barrier, brain endothelial cells, stroke, brain injury, TBI, traumatic brain injury, SAH.

The microvasculature volume expansion by HES, being essential for its beneficial effects, was explained by the Starling equation that tried to describe the fluid exchange between intravascular space and the interstitium with hydraulic conductivity of the endothelium, surface area, hydrostatic pressure and the osmotic pressure (OP) in the capillary. The OP was measurable and built the theoretical construct to develop colloid solutions to increase the OP, and therefore bind water intravascularly and/ or trace water back from the interstitium to the bloodstream to resuscitate hypovolemia. This volume expanding effect of HES is well measurable in young and healthy patients, however, in the case of critical ill patients the starling equation is under discussion. The propagandized volume effect of HES (four times higher than the effects of crystalloids) seems to be overestimated in critically ill patients when advanced hemodynamic monitoring is used. A major drawback for the application of HES in the clinical routine was the VISEP study (Brunkhorst et al., 2008), which reveals a negative effect of HES 200/0.4 on kidney function in septic patients. In regard to this, we and others figured out in the last ten years, that HES is incorporated in the proximal tubules cells of the kidney and can induce acute kidney injury (AKI). This effect is not dependent from the size of HES nor its origin (corn- or potato-derived HES) or its carrier solution, just the total applied amount of HES was found to be the key parameter (Bruno et al., 2014). Even in healthy animals, we showed that HES alone induced AKI, which may not be seen in human, because of the lack of e.g nephrobiopsy in routine pathological processes. Nowadays and in the last decade, superiority of HES over crystalloids was not confirmed, but studies with HES revealed its negative

[1]Department of Anesthesiology and Critical Care, Medical Center-University of Freiburg, Freiburg, Germany; [2]Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]Department of Anaesthesia and Critical Care, University Hospital Würzburg, Würzburg, Germany; [4]Department of Internal Medicine, General Medicine and Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan; [5]Robert-Bosch-Krankenhaus, Department of Anesthesiology and Intensive Care Medicine, Stuttgart, Germany; [6]Competence Unit Molecular Diagnostics, Center Health and Bioresources, Austrian Institute of Technology GmbH, Vienna, Austria

***Correspondence to:** Winfried Neuhaus, winfried.neuhaus@ait.ac.at; Christian Wunder, Christian.Wunder@rbk.de.

https://orcid.org/0000-0002-6552-7183 (Winfried Neuhaus)

#These authors contributed equally to this work.

Funding: *This work was supported by a grant from the Forschungskommission der Medizinischen Fakultät, Albert-Ludwigs-Universität Freiburg (SCHI1123/17, to MAS).*

How to cite this article: *Schick MA, Burek M, Förster CY, Nagai M, Wunder C, Neuhaus W (2021) Hydroxyethylstarch revisited for acute brain injury treatment. Neural Regen Res 16(7):1372-1376.*

effects like AKI and coagulopathy (Skhirtladze et al., 2014; Futier et al., 2020).

Acute Brain Injury and Hydroxyethylstarch

Acute subarachnoid hemorrhage (SAH) exhibits a lethality of 35% and survivors show only 30% of regain self-dependence. In this context, we differentiate between "early brain injury", manifesting during the first 3 days after bleeding, and "delayed cerebral ischemia (DCI)". DCI is a syndrome after SAH, caused by cerebral vasospasms and cerebral hypoperfusion. Another devastating acute disease in the brain is ischemic stroke that remains the second leading cause of death and disability worldwide (Vos et al., 2015). Within the ischemic cerebrovascular bed, there are two major zones of injury: the core ischemic zone and the "ischemic penumbra" (ischemic, but still viable cerebral tissue). In the core zone, which is an area of severe ischemia, the loss of oxygen and glucose results in rapid depletion of energy stores. Severe ischemia can result in necrosis of neurons and also of supporting cellular elements (glial cells) within the severely ischemic area. Brain cells within the penumbra, a rim of mild to moderately ischemic tissue lying between tissue that is normally perfused and the area, in which infarction is evolving, may remain viable for several hours (Thirugnanachandran et al., 2018). That is because the penumbral zone is supplied with blood by collateral arteries anastomosing with branches of the occluded vascular tree. However, even cells in this region will die, if cerebral edema occurs and reperfusion is not established during the early hours, since the diffusion length for oxygen remains too long and collateral circulation is inadequate to maintain the permanent neuronal demand for oxygen and glucose indefinitely (Heiss, 2012; Wu et al., 2018).

The protection or stabilization of the blood-brain barrier (BBB) might play the key role to reduce neuroglial deficiency after cerebral ischemia induced by vasospasms after SAH and to reduce edema in the penumbra after stroke. To prevent DCI, the so called "triple H-therapy" has been established: Hypervolemia, hypertension and haemodilution. To establish the triple-H goals, HES has been used extensively in these patients. Interestingly, critical ill patients with neurological disorders show different results in regard to HES induced AKI. For example, despite of the enormous amounts of administered HES (> 1 L HES/patient per day) to prevent cerebral vasospasm in the treatment of SAH, no increased incidence of AKI was detected (Kunze et al., 2016; Bercker et al., 2018). However, no benefit in the neurological outcome of this therapy of SAH patients was detectable (Vergouwen, 2011). On the contrary, in the SAFE study, the volume substitution with another colloid (albumin) in patients with traumatic brain injuries resulted in a higher mortality rate compared to crystalloids (Myburgh et al., 2007). The use of HES for critically ill patient are contradicted or highly restricted by different agencies like Federal Drug Agency, the European Medicines Agency or Health Canada.

In this context, finding answers to following questions would be essential: (1) How are the pharmacokinetic properties of HES within the brain, can HES be uptaken by glial or neuronal cells? (2) Is HES capable of protecting the BBB and thus reduces the neurological damage during SAH/DCI or stroke? (3) Is there a cross-talk between the kidney and the BBB? (4) Is it justifiable to apply HES under SAH/DCI or stroke conditions to stabilize the microvasculature in the brain, although the risk of HES for AKI is known?

Blood-Brain Barrier Functionality and Hydroxyethylstarch

In general, only few data are available about the effects of HES on BBB functionality. With regard to the effects of HES on the BBB and its permeation into the central nervous system (CNS), some reports support the idea that HES does not permeate across the BBB, but can stabilize the function of the BBB in comparison to detrimental effects of physiological 0.9% NaCl solution (Gerhartl et al., 2020a). Some animal studies showed that BBB leakage by different stimuli such as hyperosmolar mannitol treatment, sepsis induction by cecal ligation and puncture, temporary middle cerebral artery occlusion, severe brain injury or hyperthermia was prevented by HES. Additionally, the inhibition of neutrophil migration by HES may be an advantage in DCI (Trentini et al., 2019). One study using transmission electron microscopy revealed with morphometric analysis of HES treated animals after severe brain injury that HES accumulated in brain capillary endothelial cells–the main sealing component of the BBB–but was not uptaken by other cells of the neurovascular unit such as pericytes or astrocytes (Somova et al., 2013). This led to the hypothesis, that HES does not reach the brain parenchyma. In this regard, HES could not be found in brains of healthy animals after its injection. Moreover, even in patients with defect BBB function after SAH or head trauma, no HES was found in the cerebrospinal fluid, supporting the assumption that HES cannot enter the brain tissue (Dietrich et al., 2003).

In order to assess, whether HES can protect the BBB and subsequently the CNS in case of acute brain injury, the underlying mechanisms need to be better understood. In **Figure 1**, we have illustrated some mechanisms that may be related to the restorative effect of HES on the BBB. During acute brain injury, brain capillary endothelial cells experience an increase in intracellular calcium levels and reactive oxygen species (ROS) associated with the activation of kinases such as ERK1/2 and signaling pathways that ultimately lead to the break-up of tight junctions and increased autophagy (Neuhaus et al., 2017; Andjelkovic et al., 2020; Kim et al., 2020; Orellana-Urzúa et al., 2020). Appropriately, we measured that HES can reduce ROS formation in kidney proximal tubules cells and thus may have had an influence on autophagy activity by reducing ROS levels under the threshold necessary for autophagocytotic processes (unpublished data). With regard to the calcium level, we found that the plasma calcium level was significantly reduced after application of HES during pediatric neurosurgery even postoperatively on the intensive care unit (retrospective study HES: 16.4 ± 9.2 (SD) mL/KG/BW, not yet published). Thus, HES might interact with calcium levels, but the detailed mechanisms are still unknown. However, these data could be of high relevance, considering that the calcium level in plasma and that of the interstitial fluid in the CNS are in a dynamic equilibrium, and that one major task of the BBB is the maintenance of the homeostasis between blood and brain. In this regard, Sharma et al. (2017) reported that the serum calcium level correlated positively with neuropsychological and cognitive performance suggesting that a plasma calcium level modulating effect by HES might also affect neuronal function in the CNS (Lam et al., 2016; Sharma et al., 2017). Although there are no further mechanistic studies on the effects of HES on the BBB directly, experiments about the influence of HES on cell-cell junction regulating mediators could be used to discuss possibly related underlying mechanisms. For example, HES was able to diminish brain edema formation in a rat model of severe brain injury (Somova et al., 2013). Moreover, it was shown that HES attenuated NO formation in capillaries during severe TBI, and inhibited NO production is linked to reduced short-term tight junction degradation (Shi et al., 2016; Choi et al., 2019). In addition, HES blocked neuroinflammation in a rat sepsis model (Feng et al., 2010) which coincided with less Evans Blue permeability into the CNS. Since cytokines can increase BBB permeability (Harazin et al., 2018) and HES decreased proinflammatory cytokine levels, HES might restore BBB tightness by mildening the neuroinflammatory process. In this regard, HES also reduced intercellular adhesion molecule-1 expression – an essential surface protein for cell adhesion – which could contribute to less immune cell penetration into

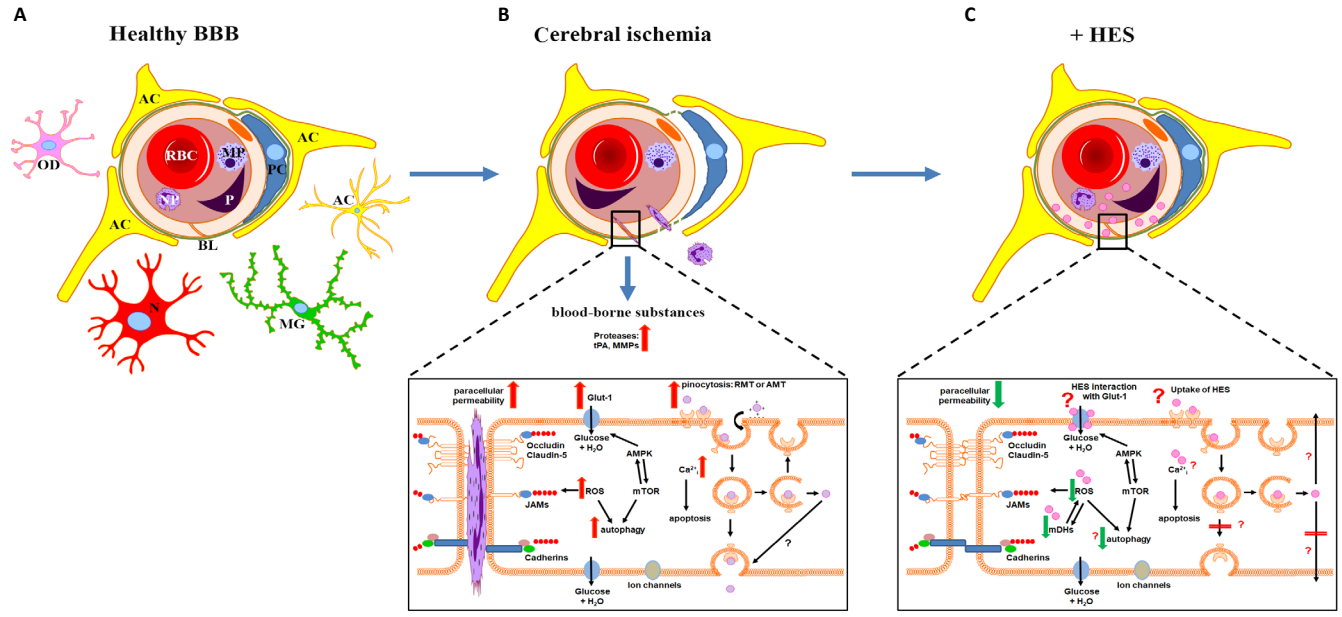

Figure 1 | **Summary of proposed mechanistic processes responsible for blood-brain barrier (BBB) breakdown during cerebral ischemia and hypotheses about effects of hydroxyethylstarch (HES) in BBB restoration.**

(A) In the healthy BBB brain capillary endothelial cells form the main component of the barrier. Intercellular gaps are sealed by tight junction strands, which prevent an unspecific permeation of mainly hydrophilic compounds into the central nervous system (CNS). A huge array of mechanisms control the transcellular transport across the BBB and subsequent entry of substances into the CNS. Transporter proteins could be classified in ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters with 48 or almost 400 member proteins, respectively. These transporters regulate the transcellular permeation of compounds by preventing (efflux) or enabling their entry (influx). Most prominent efflux transporters are ABCB1 (P-gp, P-gylcoprotein), ABCG2 (BCRP, breast cancer resistance protein) and ABCCs (MRPs, multidrug resistance associated proteins), whereas especially nutrient transporters such as SLC2A1 (GLUT-1) or SLC7A5 (LAT-1) belong to the best studied influx carriers. Bigger molecules such as peptides, proteins, particles or even cells can use receptor–or adsorption mediated transcytosis (RMT, AMT) pathways. Microenvironmental stimuli can strongly regulate the function of brain capillary endothelial cells. These stimuli could be molecules secreted, for example, by neighboring cells such as astrocytes (AC) or pericytes (PC) or physical forces such as shear stress induced by blood flow. Brain capillary endothelial cells share the same basal lamina (BL) with pericytes, whereas astrocytes are separated by an additional extracellular matrix layer and cover the majority of the surface of blood capillaries from the CNS side (Abbott et al., 2006, 2010). Within the neurovascular unit the interaction of brain capillary endothelial cells is also proposed with further CNS cells such as microglia (MC), oligodendrocytes (OD) and neurons (N), whereas the interplay with cells in blood such as red blood cells (RBC), macrophages (MP), neutrophils (NP) or platelets (P) is recognized as important but understudied. (B) During cerebral ischemia it was shown that BBB permeability is increased in several phases based on different mechanisms. It is proposed that BBB disruption is causally linked to brain edema formation and development of sequelae after stroke and traumatic brain injury. Therefore, it was hypothesized that the BBB could be a promising target for therapeutic strategies against brain injuries (Thal and Neuhaus, 2014). Some of the mechanisms include opening of the tight junctions which could be linked to phosphorylation of the myosin-light chains, increase of intracellular calcium (Ca^{2+})$_i$ and formation of reactive oxygen species (ROS). But also active transporter systems are regulated leading to an altered transcellular permeability, pericytes can lose their close contacts to brain capillary endothelial cells which is proposed to be correlated with an increased transcellular transcytosis rate, and immune cell entry is enabled preferentially at the post-capillary venules. Released tissue-type plasminogen activator (t-PA) and subsequently activated matrix metalloproteinases (MMPs) degrade proteins including tight junction proteins such as Occludin. Due to the lowered availability of glucose during cerebral ischemia, brain endothelial cells upregulate the expression and functionality of glucose transporters such as SLC2A1 (Glut-1) which can also contribute to brain edema formation by the suggested co-transport of water molecules (MacAulay and Zeuthen, 2010). Moreover, ion channel functionality is changed disturbing ion and water homeostasis (O'Donnell, 2014). Concordantly to these detrimental processes autophagy in brain endothelial cells is increased under ischemic conditions (Kim et al., 2020). (C) In relation to these adverse molecular mechanisms at the BBB under ischemic conditions, data of effects of HES (symbolized with pink circles) in different *in vitro* and *in vivo* models suggest that HES might have the potential to counteract BBB damage. For example, HES can decrease activity of mitochondrial dehydrogenases (mDHs), ROS formation and stabilize paracellular permeability (Gerhartl et al., 2020a). Yet unpublished data from our own lab suggested that autophagy or single steps of autophagy could be modified by HES. Another important point, which should be investigated in detail in the near future, is the interplay of HES with glucose dependent processes. HES is based on modified glucose units, and thus possibly interact with uptake and metabolic pathways of glucose maybe competing about the same interaction and binding sites with glucose itself. This might lead to an altered glucose uptake and/or metabolism such as glycolysis or subsequent respiratory chain which is also linked to the formation of ROS. Moreover, the interplay of AMP-activated protein kinase (AMPK) as intracellular energy sensor within the cell and the mechanistic target of rapamycin (mTOR) could be concerned and presents a link to autophagy. However, the detailed mechanisms and interactions have still to be resolved.

the CNS. Further proposed mechanistic details are summarized in **Figure 1**.

In addition to the acute processes during a cerebral ischemic insult, the processes following reperfusion must also be considered in order to evaluate a therapeutic strategy. Various cellular and molecular mechanisms are involved in the complex process of reperfusion injury, including e.g., activation and modulation of the complement, immune and coagulation systems. It is known that all these systems can be influenced in different ways by the application of HES. In the last decades experimental animal studies revealed that HES can reduce reperfusion injury by reduction of leucocytes adherence and therefore e.g., reduction of vascular injury (Kaplan et al. 2000). However, clinical trials were not able to recapitulate these beneficial experimental results or revealed even adverse neurological outcome (Mast and Marx, 1991). In this context it is important to consider the respective HES dosage in the interpretation of the outcomes. Generally, it can be postulated that high HES concentrations might lead to vascular instability *in vivo*. The indication of the above mentioned clinical study for HES application was mainly hemodilution, and to investigate whether adjusting this parameter with HES can reduce cerebral damage after stroke. It is now well known that volume substitution with significant amounts of HES can reduce the vascular glycocalyx (Hippensteel et al., 2019; Li et al., 2020) and therefore induce vascular instability (Alphonsus and Rodseth, 2014). Therefore, it could be postulated that the applied HES concentrations were too high in order to be successful in stroke therapy. Another endothelium-stabilizing

proposed mechanism mediated by HES could be the inhibition of the plasmatic coagulation system (Rasmussen et al., 2016) and the coating of platelets (Deusch et al., 2003). By coating platelets HES could decrease the attachment of neutrophils and monocytes, and therefore attenuate their increased production of e.g., superoxide after attachment to platelets, which was shown to be more than twice of the amount without attachment. This kind of diminution of ROS formation might contribute to a stabilized endothelial barrier (Rodrigues and Granger, 2015). In summary, it could be speculated that all these known adverse side effects of HES may be superior in case of TBI or stroke to reduce microembolism, stabilize the vascular endothelium and may prevent or reduce damages to the BBB and consequently also to neurons or glial cells.

Possible Cross-Talk between Kidney and the Blood-Brain Barrier

When considering the use of HES in acute brain injury, the possible cross-talk between kidney and the BBB should be included. In the case that HES treatment damages the kidney and at the same time rescues the BBB, later detrimental sequalae effects that are triggered in the kidney can abolish the beneficial effects on the BBB. In this context, it is known that patients with chronic kidney disease or AKI show frequently neurological disorders, such as cerebrovascular disease, cognitive impairment and neuropathy. This indicates that there is a substantial cross-talk between the kidney and the brain (Lu et al., 2015). For example, patients with chronic kidney disease show an increased prevalence of microbleeds in the brain compared to age-matched controls. The presence of microbleeds elevates the risk of cognitive decline and stroke. AKI is characterized by abrupt reduction of kidney function, systemic inflammation, oxidative stress and dysregulation of sodium, potassium and water channels. Systemic factors can affect the endothelial cells of the brain and lead to changes in the BBB integrity (Lu et al., 2015). Several studies on BBB function in kidney disease have been published (O'Kane et al., 2006; Nongnuch et al., 2014). It was shown that acute kidney injury leads to inflammation, BBB disruption and functional changes in the mouse brain (Liu et al., 2008). Another study showed that brains of rats with surgical 5/6 nephrectomy (rat model of chronic renal failure) as well as rat brain endothelial cells incubated with serum from nephrectomised rats showed a significant decrease of influx and efflux drug transporters at mRNA and protein levels (Naud et al., 2012). Nevertheless, BBB integrity and function was not changed due to this chronic renal failure as the brain permeability for drugs was unchanged (Naud et al., 2012). Ischemia/reperfusion injury is a major cause of AKI. To gain more insights into the cross-talk between kidney and brain, we constructed an *in vitro* co-culture model based on human proximal tubule kidney cells and brain microvascular endothelial cells (BMECs). Human kidney cells underwent oxygen/glucose deprivation for 4 hours and then were cultured along with BMECs. In addition, BMECs were left untreated or were treated with kidney injury toxins, indole-3-acetic acid and indoxyl sulfate. To validate this *in vitro* model of kidney-brain interaction, we isolated brain microvessels from mice subjected to bilateral renal ischemia (30 minutes)/reperfusion (24 hours) injury and measured the mRNA and protein expression as in the *in vitro* studies described above. Both *in vitro* and *in vivo* systems showed similar changes in the expression of drug transporters, cellular receptors and tight junction proteins (unpublished results, Förster, Burek, personal communication).

Administration of Hydroxyethylstarch at Acute Brain Injury

In this regard, the question arose for which kind of neurological diseases the stabilization of the BBB by HES treatment could be most beneficial and practically feasible, because especially the controlled delivery of HES to the BBB would be a major factor for the success. A lot of disease states, that compromise the brain, have a preserved vessel architecture and a challenged endothelial layer of the capillaries with changes in BBB integrity in common: Stroke, traumatic brain injury, ischemia-reperfusion after cardiopulmonary resuscitation and severe bleedings, neurosurgery, radiotherapy, systemic inflammation, and all entities of severe hypoxia. However, the challenge remains, to apply HES locally in the vasculature of interest and to benefit from the protective qualities on the BBB integrity without having to deal with the systemic disadvantages of HES in critically ill patients (i.e., kidney injury, coagulopathy etc.). In this context, stroke seems to be the ideal model and disease state to investigate the effect of HES. Acute ischemic stroke is caused by the sudden shut down of the perfusion of a confined brain region. Modern therapies aim to apply mechanical thrombectomy as soon as possible to re-open the vessel of interest and reduce the penumbra area (Sarraij et al., 2020). With the intervention catheter being in the vasculature of interest, it would be easy to apply HES locally in order to reduce brain oedema in the penumbra after the elapsed ischemia-reperfusion injury and to restore BBB integrity in the compromised brain region.

Conclusion

In summary, the discussed data confirmed that kidney injury is a factor influencing BBB functionality which should not be neglected when thinking of HES treatments to stabilize the BBB. A lot of *in vitro* (e.g., based on oxygen/glucose deprivation) and *in vivo* (e.g., temporary middle cerebral artery occlusion) models are well established, which could be used to investigate the effects of HES on BBB integrity in stroke (Kleinschnitz et al., 2011; Neuhaus et al., 2017; Gerhartl et al., 2020b), before the straightforward translational transfer in human treatment will be possible. But despite evidence on the adverse effects of HES on the kidney, the well-documented contraindications and warnings, and the overall recommendation from scientific and regulatory bodies that the use of HES should be avoided in the intensive care unit or operating room, Gerhartl et al. (2020a) showed so far unexpected potential benefits for its use demonstrating tightening effects on the BBB *in vitro*. If confirmed in translational approaches, the use of HES to tighten the BBB might represent a niche for its use in specific cases, especially in diseases where no adverse effects of HES are reported. Nevertheless, to date the use for HES in neurological disorders should be subjected only to clinical trials.

Author contributions: *MAS has written and revised the manuscript, MB has written and revised the manuscript, CYF has written and revised the manuscript, MN has written and revised the manuscript, CW has written and revised the manuscript, WN has drawn the illustration, has written and reivsed the manuscript. All authors approved the final manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Financial support: *This work was supported by a grant from the Forschungskommission der Medizinischen Fakultät, Albert-Ludwigs-Universität Freiburg (SCHI1123/17, to MAS).*
Copyright license agreement: *The Copyright License Agreement has been signed by all authors before publication.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

References

Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ (2010) Structure and function of the blood-brain barrier. Neurobiol Dis 37:13-25.

Abbott NJ, Rönnbäck L, Hansson E (2006) Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci 7:41-53.

Alphonsus CS, Rodseth RN (2014) The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia 69:777-784.

Andjelkovic AV, Stamatovic SM, Phillips CM, Martinez-Revollar G, Keep RF (2020) Modeling blood-brain barrier pathology in cerebrovascular disease in vitro: current and future paradigms. Fluids Barriers CNS 17:44.

Bercker S, Winkelmann T, Busch T, Laudi S, Lindner D, Meixensberger J (2018) Hydroxyethyl starch for volume expansion after subarachnoid haemorrhage and renal function: Results of a retrospective analysis. PLoS One 13:e0192832.

Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, et al. (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 10;358:125-139.

Bruno RR, Neuhaus W, Roewer N, Wunder C, Schick MA (2014) Molecular size and origin do not influence the harmful side effects of hydroxyethyl starch on human proximal tubule cells (HK-2) in vitro. Anesth Analg 119:570-577.

Choi S, Saxena N, Dhammu T, Khan M, Singh A, Singh I, Won J (2019) Regulation of endothelial barrier integrity by redoxdependent nitric oxide signaling: Implication in traumatic and inflammatory brain injuries. Nitric Oxide 83:51-64.

Deusch E, Gamsjäger T, Kress HG, Kozek-Langenecker SA (2003) Binding of hydroxyethyl starch molecules to the platelet surface. Anesth Analg 97:680-683.

Dieterich HJ, Reutershan J, Felbinger TW, Eltzschig HK (2003) Penetration of intravenous hydroxyethyl starch into the cerebrospinal fluid in patients with impaired blood-brain barrier function. Anesth Analg 96:1150-1154.

Feng X, Zhang F, Dong R, Wang H, Liu J, Liu X, Li W, Yao J, Xu J, Yu B (2010) Effects of hydroxyethyl starch (130 kD) on brain inflammatory response and outcome during normotensive sepsis. Int Immunopharmacol 10:859-564.

Futier E, Garot M, Godet T, Biais M, Verzilli D, Ouattara A, Huet O, Lescot T, Lebuffe G, Dewitte A, Cadic A, Restoux A, Asehnoune K, Paugam-Burtz C, Cuvillon P, Faucher M, Vaisse C, El Amine Y, Beloeil H, Leone M, et al. (2020) Effect of hydroxyethyl starch vs saline for volume replacement therapy on death or postoperative complications among high-risk patients undergoing major abdominal surgery: the FLASH randomized clinical trial. JAMA 323:225-236.

Gerhartl A, Hahn K, Neuhoff A, Friedl HP, Förster CY, Wunder C, Schick M, Burek M, Neuhaus W (2020a) Hydroxyethylstarch (130/0.4) tightens the blood-brain barrier in vitro. Brain Res 1727:146560.

Gerhartl A, Pracser N, Vladetic A, Hendrikx S, Friedl HP, Neuhaus W (2020b) The pivotal role of micro-environmental cells in a human blood-brain barrier in vitro model of cerebral ischemia: functional and transcriptomic analysis. Fluids Barriers CNS 17:19.

Harazin A, Bocsik A, Barna L, Kincses A, Varadi A, Fenyvesi F, Tubak V, Deli MA, Vecsernyes M (2018) Protection of cultured brain endothelial cells from cytokine-induced damage by α-melanocyte stimulating hormone. PeerJ 6:e4774.

Heiss WD (2012) The ischemic penumbra: how does tissue injury evolve? Ann N Y Acad Sci 1268:26-34.

Hippensteel JA, Uchimido R, Tyler PD, Burke RC, Han X, Zhang F, McMurty SA, Colbert JF, Lindsell CJ, Angus DC, Kellum JA, Yealy DM, Linhardt RJ, Shapiro NI, Schmidt EP (2019) Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care 23:259.

Jungheinrich C, Neff TA (2005) Pharmacokinetics of hydroxyethyl starch. Clin Pharmacokinet 44:681-699.

Kaplan SS, Park TS, Gonzales ER, Gidday JM (2000) Hydroxyethyl starch reduces leukocyte adherence and vascular injury in the newborn pig cerebral circulation after asphyxia. Stroke 31:2218-2223.

Kim KA, Kim D, Kim HJ, Shin YJ, Kim ES, Akram M, Kim EH, Majid A, Baek SH, Bae ON (2020) Autophagy-mediated occludin degradation contributes to blood-brain barrier disruption during ischemia in bEnd.3 brain endothelial cells and rat ischemic stroke models. Fluids Barriers CNS 17:21.

Kleinschnitz C, Blecharz K, Kahles T, Schwarz T, Kraft P, Göbel K, Meuth SG, Burek M, Thum T, Stoll G, Förster C (2011) Glucocorticoid insensitivity at the hypoxic blood-brain barrier can be reversed by inhibition of the proteasome. Stroke 42:1081-1089.

Kunze E, Stetter C, Willner N, Koehler S, Kilgenstein C, Ernestus RI, Kranke P, Muellenbach RM, Westermaier T (2016) Effects of fluid treatment with hydroxyethyl starch on renal function in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 28:187-194.

Lam V, Albrecht MA, Takechi R, Prasopsang P, Lee YP, Foster JK, Mamo JCL (2016) Serum 25-hydroxyvitamin D is associated with reduced verbal episodic memory in healthy, middle-aged and older adults. Eur J Nutr 55:1503-1513.

Li X, Sun S, Wu G, Che X, Zhang J (2020) Effect of hydroxyethyl starch loading on glycocalyx shedding and cerebral metabolism during surgery. J Surg Res 246:274-283.

Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov M, Sun Z, Crow M, Ross CA, Mattson MP, Rabb H (2008) Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol 19:1360-1370.

Lu R, Kiernan MC, Murray A, Rosner MH, Ronco C (2015) Kidney-brain crosstalk in the acute and chronic setting. Nat Rev Nephrol 11:707-719.

MacAulay N, Zeuthen T (2010) Water transport between CNS compartments: contributions of aquaporins and cotransporters. Neuroscience 168:941-956.

Mast H, Marx P (1991) Neurological deterioration under isovolemic hemodilution with hydroxyethyl starch in acute cerebral ischemia. Stroke 22:680-683.

Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S (2007) Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 357:874-884.

Naud J, Laurin LP, Michaud J, Beauchemin S, Leblond FA, Pichette V (2012) Effects of chronic renal failure on brain drug transporters in rats. Drug Metab Dispos 40:39-46.

Neuhaus W, Krämer T, Neuhoff A, Gölz C, Thal SC, Förster CY (2017) Multifaceted mechanisms of WY-14643 to stabilize the blood-brain barrier in a model of traumatic brain injury. Front Mol Neurosci 10:149.

Nongnuch A, Panorchan K, Davenport A (2014) Brain–kidney crosstalk. Crit Care 2014;18:225.

O'Donnell ME (2014) Blood-brain barrier Na transporters in ischemic stroke. Adv Pharmacol 71:113-146.

O'Kane RL, Vina JR, Simpson I, Zaragoza R, Mokashi A, Hawkins RA (2006) Cationic amino acid transport across the blood–brain barrier is mediated exclusively by system y+. Am J Physiol Endocrinol Metab 291:E412-419.

Orellana-Urzúa S, Rojas I, Líbano L, Rodrigo R (2020) Pathophysiology of ischemic stroke: role of oxidative stress. Curr Pharm Des doi: 10.2174/1381612826666200708133912.

Rasmussen KC, Secher NH, Pedersen T (2016) Effect of perioperative crystalloid or colloid fluid therapy on hemorrhage, coagulation competence, and outcome: A systematic review and stratified meta-analysis. Medicine (Baltimore) 95:e4498.

Rodrigues SF, Granger DN (2015) Blood cells and endothelial barrier function. Tissue Barriers 3:e978720.

Sarraj A, Savitz S, Pujara D, Kamal H, Carroll K, Shaker F, Reddy S, Parsha K, Fournier LE, Jones EM, Sharrief A, Martin-Schild S, Grotta J (2020) Endovascular thrombectomy for acute ischemic strokes: current US access paradigms and optimization methodology. Stroke 51:1207-1217.

Sharma A, Schray A, Bartolovic M, Roeach-Ely D, Aschenbrenner S, Weisbrod M (2017) Relationship between serum calcium and neuropsychological performance might indicate etiological heterogeneity underlying cognitive deficits in schizophrenia and depression. Psychiatry Res 252:80-86.

Shi Y, Zhang L, Pu H, Mao L, Hu X, Jiang X, Xu N, Stetler RA, Zhang F, Liu X, Leak RK, Keep RF, Ji X, Chen J (2016) Rapid endothelial cytoskeletal reorganization enables early blood-brain barrier disruption and long-term ischaemic reperfusion brain injury. Nat Commun 7:10523.

Skhirtladze K, Base EM, Lassnigg A, Kaider A, Linke S, Dworschak M, Hiesmayr MJ (2014) Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth 112:255-264.

Somova LM, Moldavanov MA, Plekhova NG, Shumatov VB (2013) Morphological validation of hydroxyethylstarch use during the acute period of severe brain injury. Bull Exp Biol Med 155:403-407.

Thal SC, Neuhaus W (2014) The blood-brain barrier as a target in traumatic brain injury treatment. Arch Med Res 45:698-710.

Thirugnanachandran T, Ma H, Singhal S, Slater LA, Davis SM, Donnan GA, Phan T (2018) Refining the ischemic penumbra with topography. Int J Stroke 13:277-284.

Trentini A, Murganti F, Rosta V, Cervellati C, Manfrinato MC, Spadaro S, Dallocchio F, Volta CA, Bellini T (2019) Hydroxyethyl Starch 130/0.4 binds to neutrophils impairing their chemotaxis through a mac-1 dependent interaction. Int J Mol Sci 20:817.

Vergouwen MD; Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage (2011) Vasospasm versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. Neurocrit Care 15:308-311.

Vos T; Global Burden of Disease Study 2013 Collaborators (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386:743-800.

Wu S, Yuan R, Wang Y, Wei C, Zhang S, Yang X, Wu B, Liu M (2018) Early prediction of malignant brain edema after ischemic stroke. Stroke 49:2918-2927.

C-Editors: Zhao M, Li JY; T-Editor: Jia Y