



Review Article

Evaluation of Human Serum Albumin in Neurocritical Care: A Narrative Review of Current Applications and Treatment Challenges



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Abstract

Human serum albumin (HSA) is a multifunctional carrier protein that helps maintain vascular barrier integrity and intravascular fluid homeostasis and has long been used in the management of critically ill patients, including those with acute brain injury. HSA is thought to exert neuroprotective effects through four complementary mechanisms: oncotic/volume expansion and hemodilution, antioxidant and anti-inflammatory effects, HSA-nitric oxide-mediated antithrombotic activity, and glycocalyx stabilization, although the precise pathways remain incompletely understood. Despite its biological rationale, the clinical efficacy of HSA in severe neurological disorders remains inconclusive, and few guidelines provide specific recommendations for its use in neurological care. This uncertainty stems primarily from the complex etiology and heterogeneous pathophysiology of neurological disorders, as well as inconsistent findings across existing studies. This narrative review aims to summarize the current evidence on HSA use in traumatic brain injury, acute ischemic stroke, and aneurysmal subarachnoid hemorrhage, identify existing knowledge gaps, and provide insights for future research and clinical practice. We screened records from PubMed, Embase, the Cochrane Library, CNKI, and Yiggle, as well as ClinicalTrials.gov, ChiCTR, and ChinaDrugTrials. A total of 29 human and animal studies were included. Collectively, available evidence supports a biological rationale for HSA therapy in neurocritical care, yet its clinical benefit remains incompletely established and substantial challenges persist. Prospective randomized controlled trials are warranted to clarify the efficacy and safety of HSA and determine whether preliminary encouraging findings can inform standardized guidelines and expert consensus recommendations, particularly regarding optimal concentration, timing, and patient selection.

Introduction

Elevated intracranial pressure (ICP) is a common pathological feature of various neurological disorders. Beyond etiological treatment, osmotic therapy is widely used to control ICP. Human serum albumin (HSA), a major constituent of the endothelial glycocalyx, plays an important role in preserving vascular barrier integrity and attenuating fluid and protein extravasation. Accounting for approximately 75–80% of plasma oncotic

pressure, HSA is a major determinant of intravascular fluid homeostasis.¹ Fluid therapy is fundamental to the management of acute brain injury, including volume resuscitation, ICP management, and prevention of delayed cerebral ischemia (DCI). For more than 70 years, HSA has been used in the management of craniocerebral injuries,² and its use for brain edema dates back to 1948.³ In 1994, Asgeirsson *et al.*⁴ introduced the “Lund concept,” emphasizing reduction of extracellular edema (rather than intracellular edema) and proposing that ischemia was not the primary trigger of edema formation. The authors suggested that secondary brain injury could be mitigated by maintaining normal oncotic pressure and correcting hypoalbuminemia through HSA infusion.⁴

Potential neuroprotective effects are a proposed rationale for HSA use in neurocritical care. Although the underlying pathways are not fully understood, several mechanistic hypotheses have been proposed: 1) HSA may increase plasma oncotic pressure and intravascular volume, resulting in hemodilution, reduced ischemic

Keywords: Human serum albumin; Neurocritical care; Brain injury; Traumatic brain injury; Acute ischemic stroke; Aneurysmal subarachnoid hemorrhage.

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tissue edema and infarct volume, and improved neurological function; 2) HSA acts as an antioxidant by scavenging reactive oxygen species via its cysteine-34 residue (thereby reducing oxidative stress) and may exert anti-inflammatory effects by modulating cytokines such as tumor necrosis factor- α , interleukin-1, and interleukin-6, collectively providing neuroprotection and vascular endothelial protection in ischemic regions; 3) HSA binds nitric oxide to form an HSA-nitric oxide adduct, which may enhance antithrombin III activity while inhibiting the prothrombotic effects of histones, thereby reducing cerebral vessel occlusion; and 4) HSA's interaction with the glycocalyx may reduce hydraulic conductivity across the vascular barrier, resist glycocalyx degradation, and help maintain vascular integrity and normal capillary permeability, contributing to overall neuroprotection. These mechanisms collectively highlight the multifaceted potential of HSA to provide neuroprotection (Fig. 1).⁵⁻¹² However, because of the complex etiology and pathophysiology of neurological disorders, few guidelines provide specific recommendations for HSA use in these conditions.

In this review, studies on the use of HSA in traumatic brain injury (TBI), acute ischemic stroke (AIS), and aneurysmal subarachnoid hemorrhage (aSAH) were retrieved from PubMed, Embase, the Cochrane Library, CNKI, and Yiigle from their inception to May 23, 2025. Ongoing clinical trials were identified through ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and ChinaDrugTrials. A total of 29 studies were included. This review aimed to summarize current applications and treatment challenges of HSA in neurocritical care.

In this review, "neurocritical care" refers to the specialized area of critical care that manages acute, life-threatening neurological disorders (such as TBI, AIS, and aSAH) using advanced neuromonitoring, intracranial pressure management, and other intensive care strategies aimed at preserving neurological function and improving outcomes.

We conducted a comprehensive literature search across five electronic databases: PubMed, Embase, the Cochrane Library, CNKI, and Yiigle from their inception to May 23, 2025. Search terms were combined using Boolean operators and adapted to the syntax of each database, covering three core domains: intervention terms, including "human serum albumin"[Title/Abstract] OR "HSA"[Title/Abstract]; disease terms, including "traumatic brain injury"[Title/Abstract] OR "TBI"[Title/Abstract] OR "acute ischemic stroke"[Title/Abstract] OR "AIS"[Title/Abstract] OR "subarachnoid hemorrhage"[Title/Abstract] OR "SAH"[Title/Abstract]; and neurocritical care-related terms, including "intensive care"[Title/Abstract] OR "ICU"[Title/Abstract] OR "intracranial pressure"[Title/Abstract]. In addition to published studies, we manually searched three clinical trial registries (ClinicalTrials.gov, ChiCTR, and ChinaDrugTrials) to identify ongoing registered trials investigating HSA in the target populations. Only English- or Simplified Chinese-language publications were considered.

We initially screened the titles and abstracts of all retrieved records to identify potentially eligible studies. When few clinical or observational studies were available, we also considered animal studies. Full-text articles for the remaining records were then retrieved and independently assessed for final eligibility.

Eligible studies were required to investigate HSA administration in the management of TBI, AIS, or aSAH in a neurocritical

care context; report relevant primary endpoints; provide complete full-text data; and be published in English or Simplified Chinese. We excluded studies that did not specifically address the neurocritical care population or intervention, including those focusing on nonsevere neurological conditions, alternative interventions, or study designs such as case reports, reviews, and commentaries. These criteria were intended to ensure relevance to advanced care protocols and outcomes in neurocritical care.

Studies were initially identified from PubMed ($n = 119$), Embase ($n = 44$), the Cochrane Library ($n = 18$), CNKI ($n = 67$), Yiigle ($n = 26$), ClinicalTrials.gov ($n = 4$), ChiCTR ($n = 0$) and ChinaDrugTrials ($n = 0$). After 118 duplicates were removed, 160 records underwent title and abstract screening, of which 124 were excluded; 36 full-text articles were retrieved and evaluated for eligibility. During full-text screening, studies were primarily excluded because of an ineligible population ($n = 4$) or intervention ($n = 3$). SAH-related articles were separately evaluated for aneurysm relevance. Finally, 29 studies met the inclusion criteria. The studies identified in the original search were subsequently rechecked for registration records, publication status, and newly published results on September 21, 2026, and the relevant content of this review was updated accordingly.

Application of HSA in TBI

In TBI, elevated ICP is a common pathological manifestation, often accompanied by Cushing's triad (hypertension, bradycardia, and respiratory depression).¹³ Maintaining volume homeostasis and plasma oncotic pressure through HSA administration has been proposed as one strategy for ICP reduction, although evidence regarding its safety and efficacy remains controversial (Tables 1 and 2).^{5,14-41}

Emerging data from preclinical and clinical studies suggest potential therapeutic effects of HSA in TBI. Ginsberg *et al.*¹⁴ reported in a rat model of brain injury that 2.5 g/kg HSA increased local cerebral blood flow and reduced metabolism/blood flow uncoupling, suggesting potential benefit in acute brain injury. Another animal study by Is *et al.*¹⁵ reported that intracerebroventricular HSA administered within 12 hours after severe head trauma reduced cytotoxic edema in a rat impact-acceleration injury model, suggesting a potential therapeutic window for further investigation. In a Chinese multicenter prospective randomized controlled trial, Huang *et al.*¹⁶ reported that half-dose mannitol combined with moderate- or high-dose albumin (20–40 g/d) significantly reduced ICP compared with full-dose mannitol, half-dose mannitol, and alternating use of mannitol and furosemide in patients with severe TBI ($P < 0.05$).

Some studies have reported favorable prognostic findings associated with HSA. A meta-analysis by Wiedermann included four studies, one of which was a randomized controlled trial, encompassing a total of 320 patients with head injury, including 165 treated with HSA. The meta-analysis reported lower mortality among patients with severe TBI treated with hyperoncotic HSA (20–25%) according to the Lund concept than among controls (14.5% vs. 38.1%, $P = 0.002$).¹⁷ In a subsequent commentary, Wiedermann summarized potential benefits of albumin in fluid management for TBI, including increased oncotic pressure, improved fluid balance and hemodynamic stability, and anti-inflammatory effects. He also noted that maintaining normal

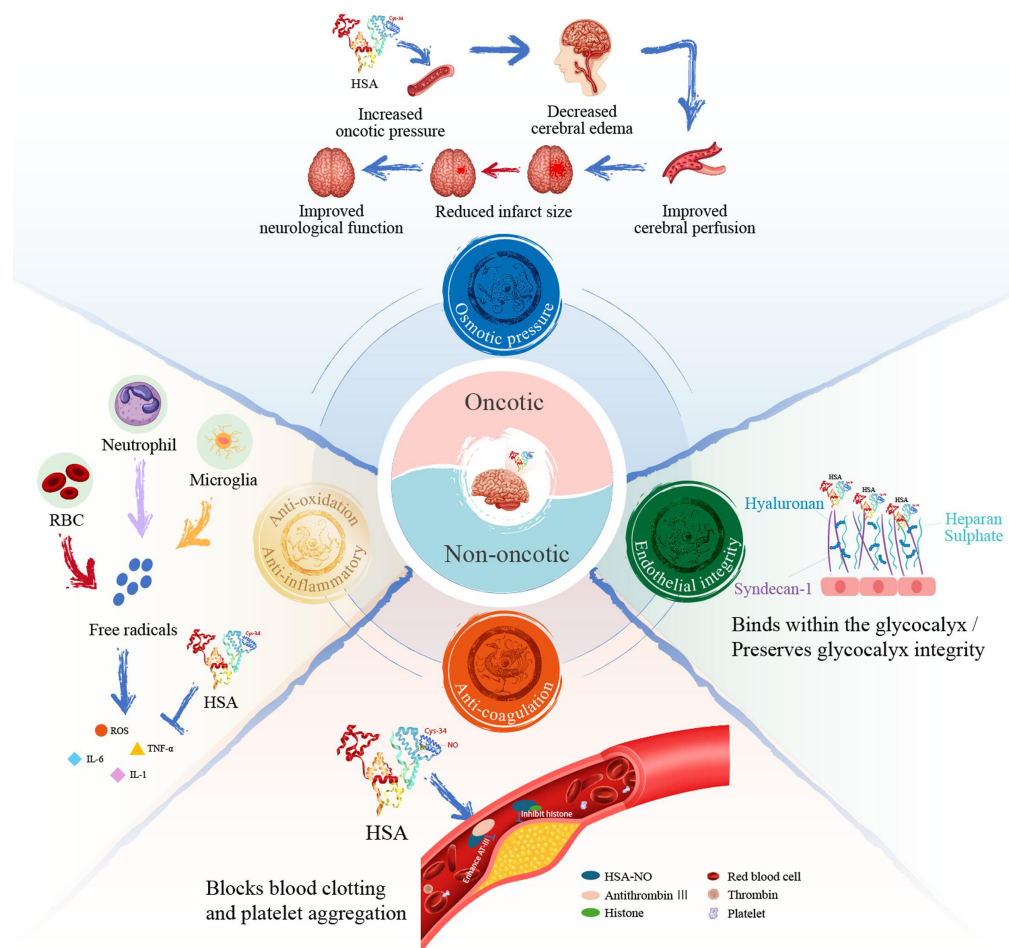


Fig. 1. Potential mechanisms of neuroprotective effects of albumin. The figure is inspired by the Chinese Tai Chi symbol, representing the balance and integration of albumin's various mechanisms. The oncotic and non-oncotic functions are depicted as two opposing forces within the Tai Chi symbol. Additionally, the four potential mechanisms underlying the neuroprotective effects of albumin are illustrated as the Four Emblems in Tai Chi, each corresponding to a distinct neuroprotective pathway. AT III, antithrombin III; HSA, human serum albumin; IL, interleukin; NO, nitric oxide; RBC, red blood cell; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α .

serum albumin levels may be associated with hemodynamic stability and reduced cerebral edema.⁴²

Conversely, other evidence raises concerns about HSA administration in TBI. In the Saline versus Albumin Fluid Evaluation (SAFE) randomized trial, the TBI subgroup had higher mortality with 4% HSA than with normal saline (24.5% vs. 15.1%; relative risk [RR], 1.62; 95% confidence interval [CI], 1.12–2.34; $P = 0.009$).¹⁸ A post hoc analysis of the SAFE trial also found higher mortality among patients with severe TBI resuscitated with 4% HSA than among those resuscitated with normal saline (33.2% vs. 20.4%; RR, 1.63; 95% CI, 1.17–2.26; $P = 0.003$).¹⁹ Another post hoc analysis suggested that HSA resuscitation was associated with increased ICP during the first week, which may have contributed to the higher mortality.²⁰ In healthy sheep, Iguchi *et al.*²¹ reported that increases in ICP were related to the tonicity of the albumin solution rather than albumin itself and found no physiological benefit of albumin-based volume expansion under nonhypovolemic conditions.

The SAFE trial and its post hoc TBI analyses indicate that 4% HSA resuscitation is associated with higher mortality in patients with TBI. In contrast, the safety and efficacy of hyperoncotic HSA (20–25%) remain uncertain because robust, high-quality data are lacking. Wiedermann suggested that hyperoncotic HSA (20–25%) may not carry the same prognostic risk.¹⁷ Additionally, two recent abstracts presented at the European Society of Intensive Care Medicine annual congress reported no significant association between albumin administration and in-hospital mortality among neurocritical care patients, including one study on hyperoncotic albumin (25%).^{43,44} However, these preliminary observations are insufficient to support recommending hyperoncotic HSA over 4% HSA or any other fluid therapy. Large, well-designed, double-blind randomized controlled trials are needed to clarify the safety and efficacy of hyperoncotic HSA in TBI. Outside research settings, its use should be considered cautiously, with continuous ICP monitoring and careful assessment of potential benefits and risks.

Table 1. Summary of animal studies on the use of HSA

Study	Animal model/sample	Groups	HSA regimen	Main outcomes	Key findings	Limitations
Traumatic brain injury						
Ginsberg <i>et al.</i> , 2001 ¹⁴	SD rats (n=45)	Vehicle control (n=22); HSA treatment (n=23)	25%; 2.5 g/kg, intravenous injection	LCBF, LCMRglu, and LCMRglu/LCBF at 60 min	HSA preserved contralateral LCBF and reduced metabolism/blood-flow uncoupling after brain injury	No head-to-head comparison with other therapies
Is <i>et al.</i> , 2005 ¹⁵	SD rats (n=64)	8 groups (n=8/group): C, T, A1, A12, A1+A12, TA1, TA12, TA1+TA12	20%; 2 µL intraventricular injection (0.2 µL every 25 s)	Specific gravity of brain tissue	HSA administered within 12 h increased the specific gravity of edematous tissue ($P < 0.001$), suggesting reduced cytotoxic edema	Preliminary study; further experimental validation is needed before clinical application
Iguchi <i>et al.</i> , 2018 ²¹	Merino sheep (n=6)	Crossover: normal saline, hypotonic HSA, and isotonic HSA	4%; intravenous infusion	Change in ICP and CVP to 24 h	Hypotonic HSA increased ICP ($+8.5 \pm 2.1$ mmHg; $P < 0.01$) and CVP; isotonic HSA and saline did not significantly change ICP	Healthy sheep; findings may not generalize to critically ill or hypovolemic trauma patients
Acute ischemic stroke						
Belayev <i>et al.</i> , 2001 ⁵	SD rats (n=47)	Saline (n=9); Alb at 2 h (n=9), 3 h (n=10), 4 h (n=10), or 5 h (n=9)	25%; 1.25 g/kg, intravenous infusion	Infarct volume, brain edema, neurological score	Neurological scores improved and cortical, subcortical, and total infarct volumes were reduced when HSA was started up to 4 h after MCAO	No molecular mechanistic validation; the proposed mechanism was inferred theoretically
Nimmagadda <i>et al.</i> , 2008 ²²	SD rats (n=14)	Albumin (n=8); saline (n=6)	25%; 2.5 g/kg, intravenous infusion	Small-artery blood flow	HSA rapidly increased microvascular flow, reaching 38% of the pre-thrombotic level at 10 min and 61-67% at 50-60 min	Small sample (n=14)
Park <i>et al.</i> , 2008 ²³	SD rats (n=21)	Reteplase + albumin (n=12); reteplase + saline (n=9)	25%; 2.5 g/kg, intravenous infusion	Microvascular flow downstream of thrombosis	Reteplase plus HSA increased microvascular flow to 58% of the pre-thrombotic level ($P = 0.013$) and remained higher at subsequent time points	Prior comparison experiments were not conducted contemporaneously, limiting statistical comparability
Belayev <i>et al.</i> , 2002 ²⁴	SD rats (n=18)	LCSM: saline (n=3), HSA	25%; 1.25 g/kg (LCSM) or 2.5	Cortical vessel diameter,	HSA increased arterial diameter,	Very small treatment and control groups in

Table 1. Summary of animal studies on the use of HSA (*continued*)

Study	Animal model/sample	Groups	HSA regimen	Main outcomes	Key findings	Limitations
		(n=4); LDPI: saline (n=5), HSA (n=6)	g/kg (LDPI), intravenous infusion	erythrocyte flow, cortical perfusion	improved erythrocyte perfusion in veins and capillaries, and partially removed adherent thrombotic material	both LCSM and LDPI experiments
Eady <i>et al.</i> , 2012 ²⁵	SD rats (n=79)	Saline, DHA, Alb, and DHA-Alb groups treated at 2-7 h after MCAO	25%; 1.25 g/kg, intravenous infusion	Neurological score and infarct volume	DHA-Alb improved neurological scores and reduced infarct volume even when treatment was started 7 h after MCAO, equaling or exceeding Alb or DHA alone	Limited molecular mechanistic validation; the synergistic mechanism remains speculative
Yao <i>et al.</i> , 2010 ²⁶	SD rats (n=10)	Saline (n=5); HSA (n=5)	25%; 1.25 g/kg, intravenous infusion	VEGF expression	HSA reduced VEGF upregulation at 6 h and 1 day after MCAO compared with saline ($P < 0.05$)	The mechanism by which HSA regulates early ischemic VEGF expression remains unclear
Subarachnoid hemorrhage						
Xie <i>et al.</i> , 2017 ³⁵	SD rats (n=180)	Sham (n=60); SAH + saline (n=60); SAH + Alb (n=60)	20%; 1 g/kg, intravenous injection	Mincle expression	HSA attenuated Mincle upregulation and subsequent microglial inflammatory responses, with effects similar to genetic Mincle knockdown.	Possible interactions with SAP130 or other proteins remain unclear.
Xie <i>et al.</i> , 2017 ³⁶	SD rats (n=92)	Sham, saline, low-dose Alb, and high-dose Alb (n=23/group)	20%; 0.63 or 1.25 g/kg, intravenous infusion	Mincle and SAP130 expression	HSA bound directly to Mincle and disrupted its association with SAP130	Endovascular perforation model has high variability and mortality; only young male rats were studied

Alb, albumin; CVP, central venous pressure; DHA, docosahexaenoic acid; Group A1, albumin used 1 hour after anesthesia; Group A12, albumin used 12 hours after anesthesia; Group A1+A12, albumin used 1 and 12 hours after anesthesia; Group C, control group; Group T, brain injury group; Group TA1, albumin used 1 hour after brain injury; Group TA12, albumin used 12 hours after brain injury; Group TA1+TA12, albumin used 1 and 12 hours after brain injury; HSA, human serum albumin; ICP, intracranial pressure; LCBF, local cerebral blood flow; LCMRglu, local cerebral glucose utilization; LCSM, laser confocal scanning microscope; LDPI, laser Doppler perfusion imaging; MCAO, middle cerebral artery occlusion; Mincle, macrophage-inducible C-type lectin; SAH, subarachnoid hemorrhage; SD rats, Sprague-Dawley rats; VEGF, vascular endothelial growth factor.

Application of HSA in AIS

Studies have examined associations between HSA levels and neurological deficits in patients with AIS and the potential value of HSA levels for predicting stroke recurrence.⁴⁵ This review

focuses on the therapeutic applications of HSA in AIS. Overall, preclinical and clinical studies have yielded mixed findings regarding HSA therapy for AIS.

In animal studies, Belayev *et al.*⁵ used a rat model and reported that a moderate dose (1.25 g/kg) of HSA improved neurological

function and reduced infarct volume in cortical and subcortical regions; these effects were observed even when treatment was initiated 4 hours after stroke onset, suggesting a therapeutic window of up to 4 hours. Nimmagadda *et al.*²² reported that high-dose HSA rapidly and consistently improved microvascular hemodynamics after cortical arteriole thrombosis, suggesting an intravascular effect of HSA in AIS. The same research group reported that HSA combined with thrombolytic therapy improved microvascular blood flow in a rat model, suggesting potential translational implications for combining high-dose HSA with thrombolysis in AIS.²³ Another study by Belayev *et al.*²⁴ found that HSA treatment increased arterial diameter, improved erythrocyte perfusion, and partially removed adherent thrombotic material, supporting a potential role of HSA in reducing blood stasis, thrombosis, and cell adhesion. In a rat stroke model, Eady *et al.*²⁵ reported that moderate doses (0.63 and 1.25 g/kg) of the docosahexaenoic acid-albumin (DHA-Alb) complex improved neurological scores and reduced infarct volume. Specifically, all doses of the DHA-Alb complex reduced cortical, striatal, and total infarct volumes by 65–70%, 52–63%, and 60–64%, respectively. These findings suggested greater neuroprotection with the DHA-Alb complex than with albumin or DHA alone, with a therapeutic window of up to 7 hours.²⁵ Vascular endothelial growth factor is a key contributor to stroke-related brain edema. Yao *et al.*²⁶ reported that, compared with saline, HSA significantly reduced vascular endothelial growth factor upregulation in the cortex at 6 hours and 1 day after middle cerebral artery occlusion in Sprague-Dawley rats ($P < 0.05$).

Several clinical studies have evaluated HSA in patients with ischemic stroke. A multicenter, randomized, double-blind, placebo-controlled study in China ($n = 134$) assessed the efficacy and safety of albumin combined with endovascular therapy in patients with AIS due to anterior circulation large-vessel occlusion. Compared with placebo, albumin (25% daily for the first 4 days) reduced infarct volume growth from baseline to day 5 (median growth, 7.5 mL vs. 16.5 mL; adjusted median difference, -8.63 ; 95% CI, -13.85 to -5.07 ; $P = 0.003$), with subgroup analyses suggesting larger effects in women, patients with a National Institutes of Health Stroke Scale (NIHSS) score < 15 , and those receiving intravenous thrombolysis. The albumin group also showed favorable trends in functional outcomes, including the modified Rankin Scale and the proportion of patients achieving early neurological improvement, although statistical significance was not achieved.²⁷ In an observational study involving 80 patients with acute severe ischemic stroke in China, HSA treatment was associated with improved clinical outcomes, as evidenced by a higher Glasgow Coma Scale score (11.1 ± 3.5 vs. 9.9 ± 2.5 ; $P = 0.033$) and a lower incidence of complications ($P < 0.05$). However, the treatment group also exhibited a lower Scandinavian Stroke Scale score, indicating that the study conclusions should be interpreted with caution.²⁸ The AMASS trial, a prospective, single-center, open-label pilot trial conducted in China, provided preliminary safety and feasibility data for endovascular treatment combined with intra-arterial HSA infusion in patients with AIS. During the dose-escalation phase ($n = 27$), two deaths and two mild infusion-related adverse events were reported, with no cases of symptomatic intracerebral hemorrhage (sICH). In the subsequent dose-expansion phase ($n =$

15), one death and one case of sICH occurred, with no adverse events attributed to HSA. A post hoc analysis found smaller infarct volumes at 24 hours in the HSA group than in controls.²⁹

Multiple studies have also examined the potential prognostic value of HSA. The Albumin in Acute Stroke (ALIAS) Initial Study, a multiple-tier, open-label, dose-escalation trial in the United States and Canada, showed that 25% HSA was tolerated at doses up to 2.05 g/kg without major dose-limiting complications.³⁰ High-dose HSA (1.37–2.05 g/kg) was associated with an 81% higher probability of a favorable outcome at 3 months than low-dose HSA (0.34–1.03 g/kg) and a 95% higher probability than historical controls without HSA treatment.³¹ Although the ALIAS phase 3 trial failed to demonstrate a clinical benefit of high-dose 25% HSA for AIS,⁴⁶ a post-stratified analysis reported better outcomes with HSA infusion within 2 hours after stroke onset than with later infusion in patients with large cardioembolic stroke (adjusted odds ratio [OR], 9.369; 95% CI, 1.040–84.405; $P = 0.0461$).³² However, this post hoc finding should be interpreted cautiously because of the small sample size (only six patients in the early albumin group) and potential selection bias. More importantly, the null phase 3 result cannot be attributed solely to the treatment window; several other clinically and mechanistically relevant factors may have contributed. First, broad inclusion of patients with mild-to-moderate stroke (median baseline NIHSS score, 11) may have diluted the treatment effect, as preclinical and post hoc data suggested a larger effect in severe, large-vessel, cardioembolic stroke.^{32,46} In addition, differences in baseline comorbidities between animal models and patients with AIS, who are typically middle-aged or older and may have concomitant conditions, could attenuate treatment effects.⁴⁶ Second, high-dose HSA causes substantial plasma volume expansion, which may impair cardiopulmonary function by increasing cardiac preload and causing blood pressure fluctuations. In the phase 3 trial, albumin increased the incidence of pulmonary edema (13.1% vs. 1.2%) and symptomatic intracranial hemorrhage (4.1% vs. 1.7%), adverse events that may have offset potential neurovascular benefits.⁴⁶ Third, high rates of concurrent reperfusion therapies, including intravenous thrombolysis and endovascular thrombectomy, in the study population may have introduced treatment interactions.⁴⁶ Any or all of these factors may have contributed to the trial's null result.

Supporting a potential neuroprotective role of HSA, Dziedzic *et al.*³³ reported that lower serum albumin levels were associated with adverse outcomes in 759 patients with AIS; higher serum albumin levels were associated with a lower risk of adverse outcomes (OR, 0.43; 95% CI, 0.26–0.70).

Although animal and clinical studies suggest potential neuroprotective effects of HSA in AIS and possible improvements in microvascular hemodynamics and clinical outcomes (Tables 1 and 2), the discrepancy between early promising signals and the negative ALIAS phase 3 results highlights the complexity of HSA therapy. Further high-quality clinical studies are therefore warranted to evaluate the effect of HSA on outcomes in AIS.

Application of HSA in aSAH

In patients with aSAH, cerebral vasospasm and associated reductions in cerebral blood flow are important contributors to poor outcomes.⁴⁷ A retrospective study by Dicipinigitis *et al.*³⁴

Table 2. Summary of clinical studies on the use of HSA

Study	Design/population	Groups	HSA regimen	Primary outcome	Key findings	Limitations
Traumatic brain injury						
Huang <i>et al.</i> , 2008 ¹⁶	Randomized controlled trial; severe TBI (n=451)	Five regimens (A-E; n=80-101); HSA-containing group E, n=87	20-40 g/d HSA + 125 mL 20% mannitol; intravenous infusion	ICP	Half-dose mannitol plus moderate- or high-dose HSA reduced ICP more than the comparator regimens ($P < 0.05$)	No HSA-only group; direct neuroprotective effects of HSA remain unclear
Wiedermann <i>et al.</i> , 2022 ¹⁷	Meta-analysis; patients with head injury (n=320)	Lund concept/ICP-targeted with HSA (n=165); CPP-targeted controls (n=155)	20-25%; intravenous infusion	Mortality risk ratio	Hyperoncotic HSA under the Lund concept was associated with lower mortality (RR = 0.42; 95% CI, 0.24-0.73; $P = 0.002$)	Few clinical studies, small total sample, and low-quality evidence limit generalizability
Finfer <i>et al.</i> , 2004 ¹⁸	Randomized controlled trial; ICU patients (n=6,997)	HSA (n=3,497); saline (n=3,500)	4%; intravenous infusion	28-day all-cause mortality	In the TBI subgroup, mortality was 24.5% with HSA vs. 15.1% with saline (RR = 1.62; 95% CI, 1.12-2.34; $P = 0.009$)	TBI comprised only 7% of the trial population; the excess number of deaths was small
Myburgh <i>et al.</i> , 2007 ¹⁹	Post hoc analysis; TBI (n=460)	HSA (n=231); saline (n=229)	4%; intravenous infusion	24-month mortality	Mortality was 33.2% with HSA vs. 20.4% with saline (RR = 1.63; 95% CI, 1.17-2.26; $P = 0.003$)	Post hoc subgroup analysis; a chance finding remains possible and the mechanism is unclear
Cooper <i>et al.</i> , 2013 ²⁰	Post hoc analysis; TBI with ICP monitoring (n=321)	HSA (n=164); saline (n=157)	4%; intravenous infusion	Mean ICP change through day 14	At week 1, HSA was associated with higher mean ICP and higher mortality (34.4% vs. 17.4%; $P = 0.006$)	Restricted to the SAFE TBI subgroup; findings may not generalize to other populations
Acute ischemic stroke						
Ginsberg <i>et al.</i> , 2006 ³⁰	Open-label dose-escalation trial; AIS, NIHSS ≥ 6 (n=82)	Six HSA dose groups	25%; 0.34-2.05 g/kg, intravenous infusion	Neurological and cardiac safety	Dose-related increases in plasma albumin and mild hemodilution occurred; mild/moderate pulmonary edema occurred in 13.4%, and doses up to 2.05 g/kg were tolerated	Small sample and no control group limit efficacy assessment
Palesch <i>et al.</i> ,	Open-label dose-	Six HSA dose	25%; 0.34-	Favorable	After adjustment for	Nonrandomized

Table 2. Summary of clinical studies on the use of HSA (*continued*)

Study	Design/population	Groups	HSA regimen	Primary outcome	Key findings	Limitations
2006 ³¹	escalation trial; AIS, NIHSS ≥ 6 (n=82)	groups	2.05 g/kg, intravenous infusion	outcome at 3 months	tPA, the three highest doses were associated with a higher probability of favorable outcome than lower doses (RR = 1.81; 95% CI, 1.11-2.94)	open-label design with no untreated concurrent control group
Khatri <i>et al.</i> , 2018 ³²	Post-stratified phase 3 analysis; large cardioembolic stroke, NIHSS ≥ 15 (n=189)	HSA (n=100); saline (n=89)	25%; 2 g/kg, intravenous infusion	Favorable outcome (mRS 0-1)	HSA within 2 h was associated with a higher probability of favorable outcome at 3 months (OR = 9.369; 95% CI, 1.040-84.405; $P = 0.0461$)	Very small early-treatment subgroup; prognostic imbalance and confounding are possible
Dziedzic <i>et al.</i> , 2004 ³³	Prospective study; AIS (n=759)	Adverse outcomes (n=266); nonadverse outcomes (n=493)	NA	mRS at 3 months; serum albumin level	Serum albumin was lower in patients with adverse outcomes and independently predicted adverse outcome risk (OR = 0.43; 95% CI, 0.26-0.70)	Single-center design and 3-month follow-up limit generalizability and long-term assessment
Sun <i>et al.</i> , 2009 ²⁸	Prospective observational study; severe AIS (n=80)	HSA (n=44); control (n=36)	20%; 50 mL, intravenous infusion	Neurological impairment, GCS, and complications	HSA was associated with better neurological impairment and GCS scores and fewer complications than control (all $P < 0.05$)	Small sample and no blinded assessment
Du <i>et al.</i> , 2026 ²⁹	Phase 1, prospective, nonrandomized open-label pilot; AIS with LVO (n=57)	HSA (n=42); external control (n=15)	20%; 0.25-0.60 g/kg, intra-arterial infusion	Symptomatic intracranial hemorrhage	No sICH occurred in the dose-escalation phase; one case occurred in dose expansion. Post hoc analysis showed smaller 24-h infarct volume with HSA	Single-center, nonrandomized pilot with a small sample and limited power for efficacy assessment
Liu <i>et al.</i> , 2026 ²⁷	Randomized, double-blind, placebo-controlled phase 2 study; AIS with LVO (n=134)	HSA (n=66); placebo (n=68)	25%; 0.5 g/kg, intravenous infusion for 4 days	Change in infarct volume at day 5	HSA reduced infarct-volume growth vs. placebo (7.5 vs. 16.5 mL; adjusted difference, -8.63 mL; 95% CI, -13.85 to -5.07; $P = 0.003$);	Chinese-only population; imaging assessment and treatment imbalances; limited power for

Table 2. Summary of clinical studies on the use of HSA (*continued*)

Study	Design/population	Groups	HSA regimen	Primary outcome	Key findings	Limitations
					functional outcomes did not differ significantly	functional outcomes
Subarachnoid hemorrhage						
Dicpinigaitis <i>et al.</i> , 2024 ³⁴	Retrospective study; aSAH (n=276)	Low serum albumin (n=98); normal albumin (n=178)	NA	DCI and in-hospital mortality	Low serum albumin was associated with higher DCI (18.4% vs. 8.4%; OR = 2.45) and in-hospital mortality (27.6% vs. 16.3%; OR = 1.95)	Retrospective design and limited sample size
Suarez <i>et al.</i> , 2004 ³⁷	Retrospective study; aSAH (n=140)	HSA (n=63); non-HSA (n=77)	5% or 25%; 1.5-6 g/kg, intravenous infusion	Favorable outcome at 3 months (GOS $\geq$ 4)	Favorable outcomes were more frequent with HSA (68% vs. 39%; OR = 3.2; 95% CI, 1.1-11.0)	Retrospective, nonrandomized design and small sample may introduce bias
Suarez <i>et al.</i> , 2015 ³⁸	Dose-escalation study; SAH (n=47)	Three HSA dose groups	25%; 0.625, 1.25, or 1.875 g/kg	TCD vasospasm, DCI, and cerebral infarction	Observed rates of vasospasm, DCI, and cerebral infarction decreased across higher HSA dose groups	Study stopped early after 47 patients because of severe cardiovascular side effects in dose tier 3
Gempeler <i>et al.</i> , 2023 ³⁹	Quasi-experimental study; SAH (n=189)	HSA intervention (n=126); historical control (n=63)	20%; ~60 g/d, intravenous infusion	DCI, ICU mortality, and hospital stay	The HSA protocol was associated with lower DCI (HR = 0.52; 95% CI, 0.33-0.83) and hyponatremia (RR = 0.55; 95% CI, 0.37-0.80)	Historical-control design; incomplete records, unreliable assessments, and substantial follow-up loss
Ibrahim <i>et al.</i> , 2013 ⁴⁰	Propensity-score matched analysis; aSAH (n=123)	Colloid (n=41); non-colloid (n=82)	NA	DIND, delayed infarction, NIHSS, and mRS	Colloid use was not associated with lower DIND or infarction and was associated with worse NIHSS and mRS scores	Blood volume was not directly measured; CT interpretation showed substantial interobserver disagreement
NCT06548477 (ongoing) ⁴¹	Single-center, open-label prospective randomized trial; aSAH (planned n=84)	Human albumin-induced volume expansion (n=42); crystalloid only (n=42)	20%; 1.25 g/kg per 24 h	Dichotomized mRS (0-2 vs. 3-6)	Ongoing; results not published	Not published

AIS, acute ischemic stroke; aSAH, aneurysmal subarachnoid hemorrhage; CI, confidence interval; CPP, cerebral perfusion pressure; CT, computed tomography; DCI, delayed cerebral ischemia; DIND, delayed ischemic neurological dysfunction; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HR, hazard ratio; HSA, human serum albumin; ICU, intensive care unit; ICP, intracranial pressure; LVO, large vessel occlusion; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RR, relative risk; SAFE, Saline versus Albumin Fluid Evaluation; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage; TBI, traumatic brain injury; TCD, transcranial color Doppler; tPA, tissue plasminogen activator.

found that patients with aSAH who had low serum albumin levels (< 3.4 g/dL) had a significantly higher risk of DCI than those with normal serum albumin levels (18.4% vs. 8.4%; OR, 2.45; 95% CI, 1.17–5.10; $P = 0.017$). Hypervolemic therapy, including HSA administration, has been used in neurocritical care with the aim of improving neurological outcomes. Although animal studies provide a rationale for this approach, clinical data are conflicting.

Animal studies have suggested that HSA may inhibit macrophage-inducible C-type lectin (Mincle) signaling in aSAH (Table 1). Xie *et al.*³⁵ reported that HSA attenuated Mincle upregulation and subsequent microglial inflammatory responses in rats with aSAH, with effects similar to genetic knockdown of Mincle. Another study reported that HSA directly bound to Mincle and disrupted its association with the proinflammatory nuclear protein SAP130 in rats with aSAH.³⁶ In patients with aSAH, several studies have reported associations between HSA use and clinical outcomes (Table 2). A retrospective analysis by Suarez *et al.*³⁷ involving 140 patients with aSAH and confirmed ruptured aneurysms who underwent clipping or endovascular treatment found a higher rate of favorable outcomes at 3 months among HSA-treated patients (68% vs. 39%; OR, 3.2; 95% CI, 1.1–11.0). The ALISAH dose-escalation study by Suarez *et al.*³⁸ reported lower incidences of vasospasm, DCI, and cerebral infarction across higher HSA dose groups, as assessed by transcranial color Doppler, suggesting a possible effect of high-dose HSA on cerebral blood flow and adverse events. A quasi-experimental study by Gempeler *et al.*³⁹ found that a hemodynamic-guided fluid therapy regimen combined with continuous HSA infusion during the first 5 days of ICU stay was associated with a lower incidence of DCI (hazard ratio, 0.52; 95% CI, 0.33–0.83) and hyponatremia (RR, 0.55; 95% CI, 0.37–0.80). However, Ibrahim *et al.*'s matched cohort study found no benefit of HSA-based colloids in preventing delayed cerebral ischemia and reported worse neurological outcomes with colloid use, suggesting potential risks in aSAH fluid management.⁴⁰ An ongoing single-center, open-label, prospective, parallel-group randomized controlled study (NCT06548477) is evaluating the efficacy and safety of human albumin in patients with aSAH.⁴¹

Current clinical evidence suggests a potential benefit of HSA in patients with aSAH, but the findings are derived primarily from retrospective cohort studies and preliminary analyses, and clinical trial data are conflicting. Consequently, the efficacy and safety of HSA in patients with aSAH require further evaluation in high-quality studies.

Discussion

Current guidelines do not generally recommend routine HSA use in neurocritical care, although some discuss albumin in specific fluid-management contexts. Existing national and international guidelines and consensus statements do not advocate routine HSA

use in TBI,^{2,48,49} whereas the Lund concept provides a theoretical rationale for maintaining oncotic pressure, including through 20% albumin administration.⁴ In an early-phase study, high-dose HSA was associated with a higher probability of favorable outcomes,³¹ and a post hoc analysis reported better outcomes with earlier administration after stroke.³² Ongoing studies are evaluating HSA as an adjunctive neuroprotective therapy after endovascular reperfusion for large-vessel occlusion.⁵⁰ The Japanese Society of Transfusion Medicine and Cellular Therapy Guidelines on Albumin Products recommend albumin for maintaining circulating blood volume during vasospasm after aSAH.⁴⁸ The Expert Consensus on the Use of Human Serum Albumin in Critically Ill Patients, published in China in 2021, states that HSA may be administered in patients with cerebral hemorrhage and may improve neurological outcomes.²

Current evidence suggests that HSA concentration may influence outcomes, but this hypothesis requires further validation. The studies included in this review used HSA concentrations of 4%, 20%, and 25%. Notably, most negative outcomes, including those in the SAFE trial, were observed with 4% hypotonic HSA,^{18–20} whereas many positive findings involved 20–25% hyperoncotic HSA. One study reported that the colloid osmotic pressure of 4% HSA was approximately half that of normal human serum (13.6 ± 0.6 vs. 27.5 ± 2.7 mmHg), whereas that of 20% HSA was approximately eight times higher (196.0 ± 12.3 mmHg).⁵¹ In healthy sheep, 4% HSA increased ICP when the solution was hypotonic, suggesting that solution tonicity may influence ICP.²¹ Together, these observations raise the hypothesis that HSA concentration and tonicity may contribute to heterogeneous outcomes in neurocritical care; however, this relationship remains unproven. Accordingly, 20–25% HSA cannot currently be recommended over 4% HSA solely on the basis of the available evidence. Further studies are required to evaluate the impact of HSA concentration on outcomes in patients with TBI. Many positive clinical findings in AIS and aSAH involved 20–25% HSA, whereas the study reporting poor outcomes with HSA-containing colloids did not provide concentration-specific data.⁴⁰ A recent prospective cohort study found an association between serum albumin levels and neurological outcomes in AIS, with each 1 g/L increase in serum albumin below 42.2 g/L associated with a lower risk of poor outcomes (OR, 0.88; 95% CI, 0.847–0.913).⁵² However, this association between serum albumin levels and outcomes does not directly establish a concentration-response relationship for infused HSA. In addition, in-hospital mortality was higher among patients with low serum albumin levels (27.6% vs. 16.3%; OR, 1.95; 95% CI, 1.08–3.54; $P = 0.027$).³⁴ That study suggested that serum albumin may be a cost-effective laboratory marker for identifying patients at risk of DCI.

Limitations

Several limitations of the present review warrant consideration when interpreting our findings, primarily because most retrieved articles were animal studies, retrospective studies, or post hoc analyses. First, the translational value of the underlying preclinical evidence is limited. The animal models included in this review may not fully replicate the complexity of human neurological disorders, particularly with respect to comorbidities and disease heterogeneity. Second, the overall quality and strength of the available evidence remain suboptimal. Most included clinical studies were retrospective studies or post hoc analyses, and high-quality randomized controlled trials are lacking. Third, data gaps remain in key clinical domains. For TBI, prospective randomized controlled trials are needed to determine the benefits and risks of HSA.¹⁷ For AIS, uncertainty regarding the mechanisms of HSA further limits interpretation of its applicability. For aSAH, available data are insufficient to draw definitive conclusions about the efficacy of HSA in mitigating cerebral vasospasm, and further investigation is needed. Given the limited scope, heterogeneity, and variable quality of the included studies, the findings should be interpreted cautiously. A randomized controlled trial in neurocritical care is currently underway to further evaluate HSA and clarify its potential clinical applications (NCT06548477).

Conclusions

For patients with TBI, current evidence regarding HSA use in neurocritical care remains inconclusive. For patients with AIS and aSAH, evidence from larger randomized controlled trials or well-designed real-world studies is needed before positive clinical findings can inform guidelines or expert consensus recommendations. Overall, HSA has a plausible therapeutic rationale in neurocritical care, but important evidence gaps remain and require further rigorous investigation.

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Conflict of interest

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manuscript, independent of the funding source.

Author contributions

Conceptualization (SJ, YL, SY, CW), methodology (SJ, CW), data curation (SJ, YL, SY, CW), formal analysis (SJ, YL, SY, CW), validation (SW), and writing – review and editing (SJ, YL, SY, SW, CW). All authors have approved the final version and publication of the manuscript.

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