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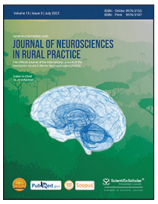

Systematic Review

Role of albumin-induced volume expansion therapy for cerebral vasospasm in aneurysmal subarachnoid hemorrhage: A systematic review

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ABSTRACT

Objectives: This study reviews the effect of albumin-induced volume expansion therapy on symptomatic vasospasm and clinical outcome in aneurysmal subarachnoid hemorrhage (aSAH).

Materials and Methods: Computer searches carried out from the Scopus, Medline, Embase, Web of Science, the Cochrane Library, and Internet documents; hand searching of medical journals; and review of reference lists. Randomized controlled trials (RCT) and observational studies (OSs) comparing albumin therapy in combination or alone with crystalloid therapy for the treatment of cerebral vasospasm in aSAH were included in the study. Risk-of-bias assessment was conducted using ROB2.0 and ROBINS-I tools for RCTs and Oss, respectively.

Results: Out of a total of 1078 searches, one RCT (published in two articles) and one observational (retrospective) study were included for final analysis. In RCT, albumin was used for volume expansion therapy with a baseline crystalloid regime and comparison made between hypervolemic and normovolemic groups and it showed no beneficial effects on symptomatic vasospasm and clinical outcomes based on the Glasgow outcome scale. Furthermore, the use of albumin showed a tendency for sodium retention with lowering of glomerular filtration rate, limiting the amount of total fluid required for targeted central venous pressure values, and thereby avoiding fluid overload manifestations. The retrospective study results between albumin versus non-albumin groups (crystalloids only) supported improved outcomes in the former group with lower in-hospital mortality. Cardiorespiratory complications were equivocal in RCT and increased in non-albumin group in the retrospective study. Risk-of-bias assessment analyses revealed "some concerns" in RCT and "serious" limitation in OS due to its retrospective design.

Conclusion: Albumin-induced volume expansion therapy for cerebral vasospasm does not have substantiative evidence to improve cerebral vasospasm and clinical outcomes in aSAH. Studies with well-designed RCTs are required to compare the use of albumin for volume expansion therapy versus standard fluid management using crystalloids to mitigate the scarcity of published data.

Keywords: Albumin, Subarachnoid hemorrhage, Cerebral vasospasm, Volume expansion therapy, Symptomatic vasospasm, Aneurysms

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating neurosurgical emergency with exceedingly high morbidity and mortality of over 50% if untreated.[1,2] Accounting for 5% of all strokes, aSAH occurs more frequently in people of working age, contributing to potential loss of quality-adjusted life years with a disproportionately high economic impact.[3,4] Poor outcome (death or dependence) occurs in approximately 70% of patients and is attributed to secondary ischemia in approximately 30% of all patients with poor outcome.[5] Over the past few decades, the clinical outcome in patients with aSAH has improved with refinements in neurosurgical techniques and advanced neurocritical care management.[6] However, to date, there is no effective management modality to counter cerebral ischemia associated with cerebral vasospasm despite the beneficial effects of anti-vasospasm management including nimodipine and volume expansion therapy.[7,8]

In aSAH, symptomatic vasospasm (also termed as delayed cerebral ischemia-DCI) has been frequently associated with excessive natriuresis and intravascular volume contraction.[9] The development of decreased cerebral blood flow (CBF) after aSAH is typically attributed to two causes.[10] First, within hours of onset, a primary generalized reduction in cerebral oxidative metabolism occurs in conjunction with a coupled decrease in CBF.[9,10] The primary cause of this

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phenomenon is thought to be the toxic effects of SAH blood products on cerebral metabolism, although hydrocephalus, cerebral edema, and increased intracranial pressure may also contribute to decreased CBF.[10] Second, in the next 2 weeks, cerebral vasospasm may manifest due to a further decrease in CBF and this may cause an additional reduction in cerebral metabolism.[10] The topographically heterogeneous reduction in CBF in the late stages of aSAH seems to contribute to focal[10-12] neurological deficits and severe angiographic vasospasm. To mitigate this hypoperfusion, post-operative hypervolemic therapy has been rationalized and was routinely practiced in the past that included the use of isotonic crystalloids and colloids including dextran, hypertonic saline, and human albumin.[12,13]

In patients with aSAH, human albumin and isotonic saline administered either concomitantly or in alternating fashion have been conventionally used as the solutions of choice to maintain normovolemia (NV) or hypervolemia (HV).[13-15] Studies with acute focal ischemia in rat models showed that albumin treatment has markedly reduced cerebral infarction volume.[16] While in the clinical setting, human albumin treatment benefits have also been studied in patients with acute ischemic stroke, traumatic brain injury, intracerebral hemorrhage, and aSAH.[16-18] Dose-dependent neuroprotective effects of human albumin have been reported in ischemic stroke.[2] Suarez *et al*.[15,19,20] conducted a pilot study on albumin use in subarachnoid hemorrhage study to explore the optimal safe dosage regimen and also documented that human albumin may reduce DCI and cerebral infarction with improvement in CBF, leading to better clinical outcomes. There is an obvious scarcity of literature with no published systematic review on the role of albumin for volume expansion therapy to treat cerebral vasospasm in aSAH. In this systematic review, we aim to focus on the use of human albumin to achieve an optimal fluid management regime to explore its potential beneficial role to improve cerebral perfusion and clinical outcome in patients with aSAH.

MATERIALS AND METHODS

Objective

The objective of this study was to determine the effects of albumin-induced volume expansion therapy on the development of symptomatic vasospasm or DCI on clinical outcomes in all patients with aSAH using database search strategy for randomized controlled trials (RCTs) and/or observational studies (OSs) from June 1, 1990, to June 30, 2022.

Search strategy

We undertook a systematic review based on a predefined protocol in accordance with the International Platform of Registered Systematic Review and Meta-analysis Protocols.[21] We searched Embase, MEDLINE, Web of Science, Scopus, and the Cochrane Library for these keywords: "Subarachnoid Hemorrhage, aneurysm, SAH, albumin, and volume expansion." Boolean operators were used as appropriate (PICOT table and the Search Strategy in Appendix A and B). We restricted our inclusion of articles to those written in English.

Study selection (inclusion/exclusion) criteria

Two investigators (Ali A. and Babu A.) independently selected and analyzed studies according to the eligibility criteria. Disagreements between the investigators concerning the decision to include or exclude a study were resolved by consultation with the senior author (Shaikh N). Eligible studies had to meet the following criteria: (1) The study must be RCTs or OSs; (2) the study must include use of human albumin only for volume expansion therapy and/or baseline standard crystalloid solution; there will be comparison groups to assess effects of volume expansion therapy with use of albumin; (3) the study must report events of interest in each group, such as symptomatic vasospasms, and/or cerebral infarctions and/or clinical outcome scales Glasgow outcome scale (GOS) and/or modified Rankin scale (MRS) along with volume overload medical complications; (4) the patients in the studies must be adult (≥18 years); (5) aneurysmal SAH must be documented by computed tomography (CT) or lumbar puncture and angiography in all patients and ruptured aneurysms secured with microsurgical clipping and/or endovascular coiling; (6) articles were excluded if they have reported overlapping data or have not reported events of interest or in combination, animal studies, reviews, comments, conference abstracts, and pilots' studies; and (7) studies were also excluded if they used colloids other than albumin (such as dextran), alone or in combination with baseline crystalloids.

Data extraction

EPPI-Reviewer™ (https://eppi.ioe.ac.uk/) online licensed platform has been used for the literature searches, database input, study selection, handling of missing data, and synthesis of summary statistics. Two investigators (Ali A. and Babu A.) independently extracted the following information from each eligible article: Name of the first author, study design, study period, use of albumin, fluid management regimens, comparative groups, hemodynamic variables, follow-up time, and baseline clinicodemographic characteristics of patients (e.g., mean ages of participants, number of participants, aneurysm treatment modalities, complications, and severity assessment).

Outcome measures

The primary outcome was symptomatic vasospasm and cerebral infarctions. The secondary outcomes measured

with clinical outcome scales GOS and/or MRS including mortality and hemodynamics complications associated with volume overload including pulmonary edema, congestive heart failure, and hyponatremia. In each study included, all outcome measures were scrutinized, and results were analyzed as per clinical outcomes defined. Symptomatic vasospasm or DCI is defined as a focal neurological deficit or deterioration in the level of consciousness, with either confirmation of infarction on a computed tomography (CT) scan or exclusion of other possible causes of deterioration, such as rebleeding, hydrocephalus, electrolyte disorder, infection, seizure, and cerebral infarction. The clinical outcome scale has been documented during clinical follow at least once anytime during or at the end or before concluding the study. New cerebral infarction was assessed with CT or magnetic resonance imaging (MRI) scan, excluding procedure-related infarctions. Cerebral infarction was defined as a new infarct on CT or MRI scans that were not visible on the day following the operation or intervention.

Risk-of-bias assessment

Risk-of-bias assessments have been conducted using ROB2.0[22] (for RCT) and ROBINS-I[23] (for OS) and it has been projected as a traffic-light plot using the online platform robvis™ to create figures for the quality of risk-of-bias assessment (https://mcguinlu.shinyapps.io/robvis/).

RESULTS

Description of studies included

Out of a total of 1078 imports, we narrowed down the search to identify one single-center RCT and one retrospective study meeting the inclusion criteria [Figure 1]. The RCT was carried out in the Columbia Presbyterian Medical Center, New York, USA, but its results were reported in two separate publications with a focus on different clinical outcome measures, and therefore, we tabulated their results separately. Initial results of patients (n = 43), recruited between June 1991 and July 1993, were published by Mayer *et al*.,[20] and later on, Lennihan *et al*.[16] reported his results on the total cohort (n = 84) of patients (including the previous 43 patients) recruited until October 1994 at the completion of the trial. The former reported outcome with symptomatic vasospasm and complications of volume expansion therapy while the latter added mean CBF, cerebral infarctions, and GOS in clinical outcome measurements. CBF was measured on study day 0 (before treatment assignment), study day 1, and then approximately every 3 days until aSAH day 14. All patients with an established diagnosis of ruptured cerebral aneurysms entered the study on the day after surgical clipping of their aneurysm, done within 7 days of the SAH in all cases [Table 1]. At the time of randomization, patients were classified, based on the number of days since aSAH and the Hunt/Hess Grade, into one of four strata, as follows: (1) SAH Day 0–3 and Hunt/Hess Grade I or II, (2) SAH Day 0–3 and Hunt/Hess Grade III or IV, (3) SAH Day 4–7 and Hunt/Hess Grade I or II, and (4) SAH Day 4–7 and Hunt/Hess Grade III or IV. After stratification, subjects were randomized to receive either HV or NV therapy. They only used 5% albumin (used in boluses of 250 mL every 2 h) for volume expansion therapy along with a baseline crystalloid solution regimen (80 mL/h 5% dextrose and 0.9% saline) to achieve targeted cardiac filling pressures (central venous pressure [CVP] and pulmonary artery diastolic pressure [PADP]) and then compared HV versus NV groups for clinical outcomes [Table 2].

In Suarez *et al*. study,[15] patients' data were collected in retrospect from May 1998 to May 2000, and albumin was used for volume expansion to keep a target of CVP at >8 mm Hg before May 1999, and subsequently, albumin use was stopped due to a change in the hospital policy. In the old protocol (before May 1999), if bolus administration of normal saline (500 mL) failed to achieve CVP >8 mm Hg, patients received human albumin (5 or 25%, 12.5 g). After May 1999, patients with aSAH have been treated with crystalloids only. All other aspects of care were unchanged; this has allowed authors to compare clinical data before and after implementation of the new policy with/without the use of albumin to achieve targeted volume expansion. They compared the results between two groups (albumin vs. non-albumin) for their outcome measures based on symptomatic vasospasm, volume overload medical complications, and clinical outcome using GOS. In addition, they also measured the duration of hospital stay with total hospital and radiological costs in two groups.

Clinical outcomes

Mayer *et al*. study results were published after 7 days of the total study period with data collection beginning at 12:00 a.m. on post-operative day-1. DCI developed in 29% (n = 7) of cases in NV versus 26% (n = 5) in HV group. These patients were switched to HV therapy (in NV group) with/without vasopressors (dopamine/norepinephrine/phenylephrine) for 20 days and HV patients were treated with vasopressor only for 16 days but the proportions of total patient-days with pressors for the two groups were not significantly different. Hyponatremia (n = 2) and pulmonary edema (n = 1) reported in HV group only.

In Lennihan *et al*. reported results, DCI seen in eight patients each in HV (additional three patients) and NV (additional one patient) groups while hyponatremia was reported in two more patients in NV groups [Table 3] as compared to earlier reported results. In addition, cerebral infarctions were reported in two patients in each group, with no significant difference in mean CBF values in NV (47 mL/100gm/min) versus HV group (45 mL/100gm/min). Clinical outcome

Table 1: Characteristics of included studies.

Study parameters	Lennihan *et al*. 2000	Mayer *et al*. 1998	Suarez *et al*. 2004
Design	RCT		Retrospective study
Population	82	43	140 (Subgroup *n*=84)
Age (years)	48.4±12.9	48±11	56±13
Female	48	21	91
Aneurysm location	Anterior circulation	Anterior circulation	Not specified
Aneurysm securing method	Clipping	Clipping	Both clipping and coiling
Dose of albumin (Boluses if cardiac filling pressures falls≤set targets)	250 mL of 5% albumin solution every 2 h	250 mL of 5% albumin solution every 2 h	5 or 25% of albumin boluses as per need to achieve targeted CVP >8 mm Hg
Study groups	Hypervolemic group (PADP ≤14 mm Hg or CVP ≤8 mm Hg)	Hypervolemic group (PADP ≤14 mm Hg or CVP ≤8 mm Hg)	Albumin group (received only albumin boluses to maintain targeted CVP >8 mm Hg
Comparator	Normovolemic group (PADP ≤7 mm Hg or CVP ≤5 mm Hg)	Normovolemic group (PADP ≤7 mm Hg or CVP ≤5 mm Hg)	Non-albumin group received only boluses of 0.9% saline to maintain targeted CVP >8mm Hg
Baseline fluid management	Crystalloid infusion - 80 mL/h 5% dextrose and 0.9% saline	Crystalloid infusion - 80 mL/h 5% dextrose and 0.9% saline solution	Crystalloid infusion of normal saline (maintenance fluid regime not specified)
Outcome measurements	CBF GOS	Symptomatic Vasospasm (DCI)	GOS (dichotomized as good [scores 1–3] and poor [scores 4–5])
Duration of albumin treatment therapy (days)	14	7	14
Duration of follow-up	12 months (3-, 6- and 12-month duration)	7 days	3 months

RCT: Randomized controlled trial, CVP: Central venous pressure, PADP: Pulmonary artery diastolic pressure, CBF: Cerebral blood flow, GOS: Glasgow Outcome scale, DCI: delayed cerebral ischemia. *Values are numbers±standard deviations

Table 2: Fluid management, hemodynamic, and laboratory parameters.

Parameters*	Mayer *et al*. 1998			Lennihan *et al*. 2000		
	NV group (*n*=24)	HV group (*n*=19)	*P*-value (0.05)	NV group (*n*=41)	HV group (*n*=41)	*P*-value (0.05)
PADP (mm Hg)	13±4	12.5±2.5	NS	12.0	14.2	0.002
CVP (mm Hg)	7.1±2.9	8.5±2.1	0.02	7.0	8.3	0.002
MAP (mm Hg)	105±11	101±11	NS	101.31	101.25	0.922
Fluid intake (L)	3.93±1.07	4.92±1.42	0.003	3.6	4.1	0.006
Fluid output (L)	4.07±1.32	4.90±1.48	0.004			
Cumulative fluid balance	−0.13±1.21	+0.02±1.11	NS	+0.01	−0.04	0.810
Sodium input (mEq)	481±150	606±193	0.005			
Sodium output (mEq)	508±183	597±196	0.02			
Cumulative sodium balance	−36±184	+9±164	NS			
5% Albumin input (L)	4.0±0.8	1.38±0.79	0.0001			
Serum albumin (g/dL)	1.1±1.3	5.3±0.8	0.005			
Renin activity (ng/mL/h)	1.1±1.3	0.4±0.3	0.004			
Mean GFR (mL/min)	138±38	124±36	NS			
Hematocrit (%)				28.7	31.0	0.056

*NS: Statistically non-significant. ±Values are mean±standard deviation, Or calculated average values during the study period. ¶*P* values refer to the 5% significance level. MAP: Mean arterial pressure, GFR: Glomerular Filtration rate, CVP: Central venous pressure, PADP: Pulmonary artery diastolic pressure, HV: Hypervolemic, NV: Normovolemic

based on GOS was not significantly different between the two groups at day 14 or 3 months, and there was only a little change in outcome between 3, 6, and 12 months post-ictus.

In a retrospective study (Suarez *et al*)., the results compared albumin versus non-albumin groups, and the latter experienced more symptomatic vasospasm and had poor

Table 3: Clinical outcome analysis.

Clinical outcomes and complications	Mayer *et al*. (1998)		Lennihan *et al*. (2000)		Suarez *et al*. (2004)	
	NV group (*n*=24)	HV group (*n*=19)	NV group (*n*=41)	HV group (*n*=41)	Albumin group (*n*=37)	Non-albumin group (*n*=47)
Mean cerebral blood flow (mL/100 g/min)			47 (Basline-52.3)	45 (Baseline-48.9)		
Symptomatic vasospasm/delayed cerebral ischemia	7 (29)	5 (26)	8 (20)	8 (20)	7 (19)	13 (28)
Cerebral infarctions			4 (10)	7 (17)		
Hyponatremia (<135 mEq/L)	0 (0)	2 (11)	2 (5)	2 (5)		
Pulmonary edema/congestive heart failure	0 (0)	1 (5.2)	0	1 (3)	6 (16)	9 (19)
Cerebral edema (Radiographic)			7 (17)	6 (15)		
GOS at 3-months			29 (74)	30 (75)	68%	39%
1 (Minimal deficits)						
2 (Moderate deficits)			2 (5)	3 (7)		
3 (Severe deficits)			5 (13)	5 (13)		
4 (Vegetative)			0 (0)	0 (0)		
5 (Dead)			3 (7)	2 (5)	5%	21%

Values are presented as *n* (%) and proportions. DCI: Delayed cerebral ischemia, HV: Hypervolemic, NV: Normovolemic

GOS scores with higher in-hospital mortality. There was no difference, however, in the incidence of cardiorespiratory complications between the two groups. The proportion of patients with good outcome at 3 months was significantly higher in the albumin versus non-albumin subgroup [Table 3]. After adjusting for age, sex, race, and GCS score <8, their logistic regression analysis showed that albumin administration was an independent predictor of better outcome at 3 months after aSAH but the use of albumin was not an independent predictor of in-hospital deaths.

Effects of intervention

In single-center RCT (collective data), there is no change in the clinical outcome including symptomatic vasospasm (DCI), cerebral infarctions, and GOS in HV versus NV groups with albumin-induced volume expansion therapy. However, it tends to marginally increase the rate of cardiorespiratory complications due to HV. Interestingly, Mayer *et al*. have also reported that albumin with its properties as colloidal agent is contributing to paradoxical reduction in glomerular filtration rate (GFR) and independently enhancing renal sodium retention with no effect on renin-aldosterone activity [Table 2]. These properties of albumin may limit the amount of total fluid required to maintain targeted cardiac filling pressures (CVP/PADP) and, hence, may help minimize the frequency of volume overload complications. The retrospective study by Suarez *et al*. showed a statistically significant trend with improved symptomatic vasospasm and better GOS scores with lower mortality in the albumin group but had no difference in cardiorespiratory complications due to volume expansion between the two comparison groups. However, in RCT, there was no subgroup analysis to report clinical outcome and complications in those patients who received albumin versus non-albumin groups, limiting a homogenous comparison for our review. In terms of the overall quality of risk-of-bias assessment analyses, the RCT revealed "some concerns" (based on ROB2.0) as it did not aim to compare vividly albumin versus crystalloid volume-expansion therapies while the OS has been judged as having "serious" limitations (based on ROBINS-I) due to its retrospective design [Figure 2].

DISCUSSION

Volume expansion therapy for cerebral vasospasm

The mechanisms involved in the development of cerebral vasospasm associated with aSAH are still not fully understood.[1,7-10] Multifactorial mediators of cerebral vasospasm include those derived from endothelium, smooth muscle cell, by-products of blood breakdown in basal cisterns, and platelet activating factors.[24-26] Calcium channel antagonists like nimodipine have been well-documented to improve prognosis in aSAH (absolute risk reduction of 5%) but its mechanism of action remained controversial whether it is either by neuroprotection or by improving vasospasm or both.[7,8] Except for the limited effect of nimodipine in improving clinical outcome in aSAH, there is no other effective therapeutic or preventive modality to counter cerebral vasospasm or improving neuroprotection in patients with aSAH.[7,27] The rationale to use volume expansion therapy has been justified due to SAH-associated volume contraction with increased risks of cerebral vasospasm and the reports suggesting clinical improvement in acutely

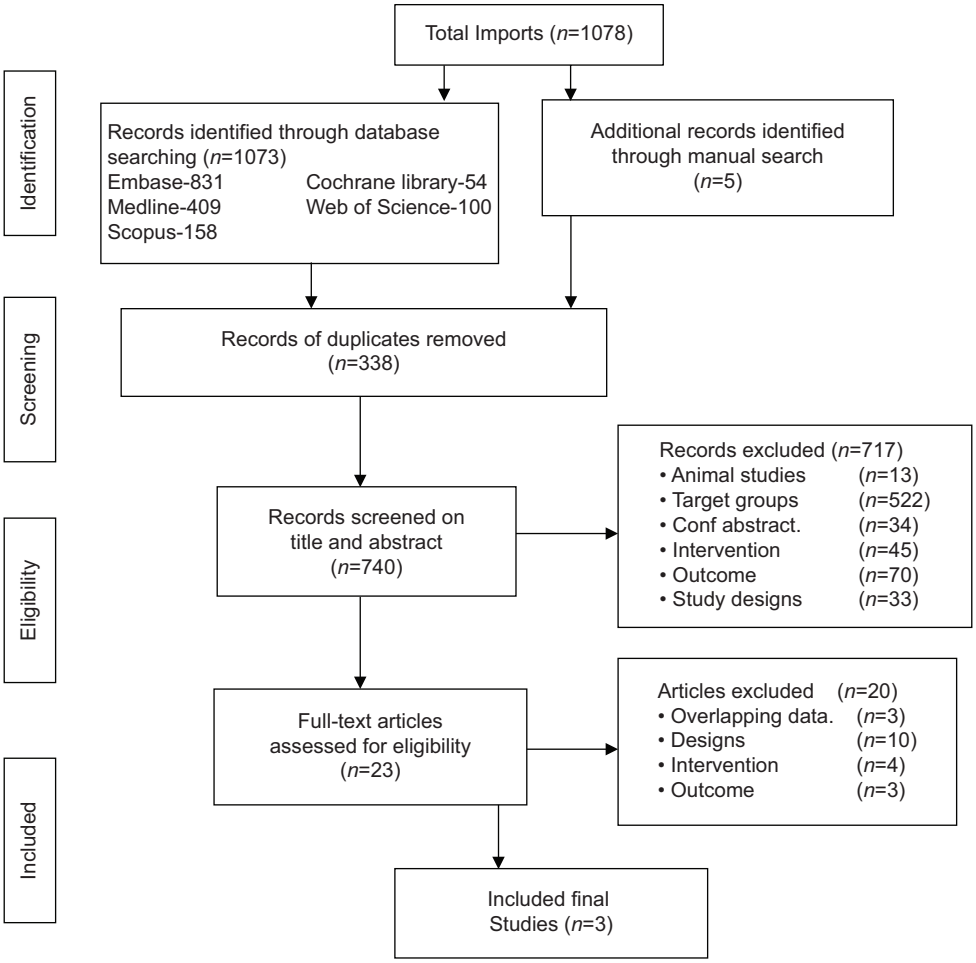

Figure 1: PRISMA flow diagram 2020 for new systematic reviews showing literature searches and selection of studies.[21]

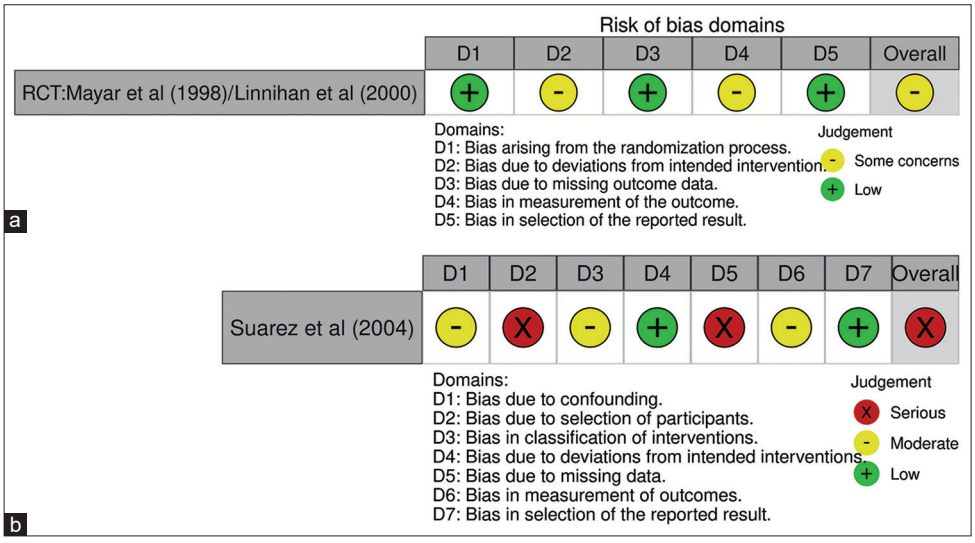

Figure 2: Traffic-light plot for risk of bias assessment, using ROB2.0 tool (a) for randomized controlled trial and ROBINS-1 and (b) tool for observational study.[22,23]

symptomatic patient after HV therapy.[9,28,29] The natural clinical course of aSAH has been associated with decreased cerebral perfusion and it also contributes to the development of cerebral vasospasm.[14,28] In our review, the findings of RCT trial conclude that HV therapy has failed to increase CBF as compared to patients in NV group. Volume expansion therapy has contributed to achieve targeted blood volume parameters, but there is no effect on clinical outcome based on GOS scores. However, this volume expansion therapy has been associated with an increase in volume-overload complications such as hyponatremia and pulmonary edema. Conversely, the findings in the retrospective study favors the use of albumin-induced volume expansion therapy with the improved clinical outcome with less complications associated with volume overload.

Use of albumin in volume expansion therapy

Over the past 50 years of intensive care clinical practice, albumin has had a good safety profile with its time-honored use for volume expansion therapy, and its clinical use is partially based on the notion that serum hypoalbuminemia is associated with an increased mortality rate in critically ill patients.[30-33] Albumin is a 67-kD protein that is responsible for 80% of the colloidal osmotic pressure of plasma and supplies most of the acid/base buffering action of the plasma proteins.[27,34] It is a very important component of the body because it also serves as a vehicle for metabolites, a factor in lipid metabolism, and performs many other functions that are still being elucidated.[31,33] In patients with acute ischemic strokes, preliminary data from pilot studies have shown that 25% of human albumin has a neuroprotective effect in a dose-dependent manner.[2,35-37] In the RCT results, the use of 5% albumin has also been associated with a significant effect on cumulative sodium balance (but not on blood volume) by lowering GFR and promoting sodium retention. This sodium-retention effect of albumin-induced volume expansion therapy has also been seen in hypovolemic trauma patients and burn victims.[34,38] The possible mechanisms for albumin reduction of the GFR and attenuation of renal sodium excretion include the following: (1) Elevation of oncotic pressure, causing reduced net glomerular hydrostatic pressure; (2) reduction of the glomerular filtration fraction; (3) promotion of sodium reabsorption in the distal nephron; or (4) contamination of albumin with vasoactive peptides that affect glomerular filtration.[14,34,38] This sodium retention effect by decreasing GFR, use of albumin, has potential to mitigate the harmful effects of fluid overload and minimizing its associated complications including pulmonary edema and hyponatremia. This finding seems to align with results from the retrospective study (Suarez *et al*.) in our review, showing less cardiorespiratory complications in the albumin group. However, the substantiative evidence for the use of albumin-induced volume expansion to improve symptomatic vasospasm and enhance clinical outcome remained uncertain.

Limitation of available data

Despite the use of albumin-induced volume expansion in published literature, there is an obvious scarcity of data to prove its efficacy and beneficial effects for clinical outcome in comparison to a controlled group (the use of crystalloids) for cerebral vasospasm in aSAH.[2,15,22,39] In this systematic review, the comparative analysis for the use of albumin versus non-albumin (crystalloid alone) for volume expansion therapy is limited because the RCT results did not include this subgroup analysis while the study by Suarez *et al*. lacks sufficient evidence due to its retrospective design. The small sample size and heterogeneity of data between RCT and retrospective study also prevented us from meta-analysis. This systematic review (with one RCT and one OS) remained insufficient in the synthesis of any robust evidence and, thereby, underscores the need for conducting well-designed studies to explicitly define the role of albumin-induced volume expansion therapy in aSAH in future.

CONCLUSION

This systematic review found only one RCT and one retrospective study in which albumin was used exclusively for volume expansion therapy to treat cerebral vasospasm and has provided an insight to explore its beneficial use in clinical practice. The RCT results remained inconclusive with the tendency for slightly higher cardiorespiratory complications with HV therapy while the retrospective study supported the beneficial use of albumin-induced volume expansion with improvement in symptomatic vasospasm and clinical outcome with less volume overload complication and in-hospital mortality. The use of albumin with its sodium retention effect may have a role in minimizing the volume overload manifestations. This review emphasizes the need for future trials aiming to compare albumin-induced volume expansion therapy versus the standard fluid management with crystalloid therapy in cerebral vasospasm for aSAH.

Declaration of patient consent

Patients' consent not required as there is no patients' data in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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APPENDIX A

PICOTS table of systematic review.

Population	All adult patients who have established diagnosis of aneurysmal subarachnoid hemorrhages and has received treatment for securing ruptured aneurysms
Intervention	Volume expansion therapy with intravenous human albumin
Comparator	Hypervolemic therapy with crystalloid fluids therapy alone or in combination with albumin
Outcomes	Primary outcome: • Symptomatic Vasospasm/Delayed cerebral Ischemia • Clinical outcome measured on clinical scales (GOS and/or MRS) Secondary outcome: • Volume overload complications include pulmonary edema/congestive heart failure and hyponatremia.
Timing	42 years (June 1, 1990, to June 30, 2022)
Setting	Intensive care units

DCI: Delayed cerebral ischemia, GOS: Glasgow Outcome scale, MRS: Modified Rankin scale

APPENDIX B

Search Terms

Aneurysm, subarachnoid hemorrhage, albumins, human, colloids, colloidal solutions, crystalloids, normal saline, vasospasm, symptomatic vasospasm, cerebral, complications, neuroprotection, calcium channel blockers, calcium antagonist, nimodipine, nicardipine, clinical outcome, Glasgow outcome scale, GOS, Modified Rankin Scale, MRS, National Institute of Health Stroke Scale, NIHSS, Transcranial Doppler, TCD, CT scan, CT angiography, delayed cerebral infarctions, DCI, delayed ischemic neurological deficits, DINDS, observational, cohort, randomized control trials, controlled clinical trials, random, interventional, central venous pressure, CVP, mean arterial pressure, MAP, hypervolumia, normovolumia, fluid management, pulmonary edema, fluid overload, complications, neuroprotection.