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ORIGINAL WORK

Effect of an Albumin Infusion Treatment Protocol on Delayed Cerebral Ischemia and Relevant Outcomes in Patients with Subarachnoid Hemorrhage

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Abstract

Background: An institutional management protocol for patients with subarachnoid hemorrhage (SAH) based on initial cardiac assessment, permissiveness of negative fluid balances, and use of a continuous albumin infusion as the main fluid therapy for the first 5 days of the intensive care unit (ICU) stay was implemented at our hospital in 2014. It aimed at achieving and maintaining euvolemia and hemodynamic stability to prevent ischemic events and complications in the ICU by reducing periods of hypovolemia or hemodynamic instability. This study aimed at assessing the effect of the implemented management protocol on the incidence of delayed cerebral ischemia (DCI), mortality, and other relevant outcomes in patients with SAH during ICU stay.

Methods: We conducted a quasi-experimental study with historical controls based on electronic medical records of adults with SAH admitted to the ICU at a tertiary care university hospital in Cali, Colombia. The patients treated between 2011 and 2014 were the control group, and those treated between 2014 and 2018 were the intervention group. We collected baseline clinical characteristics, cointerventions, occurrence of DCI, vital status after 6 months, neurological status after 6 months, hydroelectrolytic imbalances, and other SAH complication. Multivariable and sensitivity analyses that controlled for confounding and considered the presence of competing risks were used to adequately estimate the effects of the management protocol. The study was approved by our institutional ethics review board before study start.

Results: One hundred eighty-nine patients were included for analysis. The management protocol was associated with a reduced incidence of DCI (hazard ratio 0.52 [95% confidence interval 0.33–0.83] from multivariable subdistribution hazards model) and hyponatremia (relative risk 0.55 [95% confidence interval 0.37–0.80]). The management protocol was not associated with higher hospital or long-term mortality, nor with a higher occurrence of other unfavorable outcomes (pulmonary edema, rebleeding, hydrocephalus, hypernatremia, pneumonia). The intervention group also had lower daily and cumulative administered fluids compared with historic controls ($p < 0.0001$).

Conclusions: A management protocol based on hemodynamically oriented fluid therapy in combination with a continuous albumin infusion as the main fluid during the first 5 days of the ICU stay appears beneficial for patients

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with SAH because it was associated with reduced incidence of DCI and hyponatremia. Proposed mechanisms include improved hemodynamic stability that allows euvolemia and reduces the risk of ischemia, among others.

Keywords: Subarachnoid hemorrhage, Intracranial aneurysm, Aneurysm, Ruptured, Albumins, Colloids, Fluid therapy

Introduction

Subarachnoid hemorrhage (SAH) treatment in the intensive care unit (ICU) after early surgical or endovascular control of the ruptured aneurysm focuses on prevention of complications that negatively affect the patients' neurological and vital outcomes [1]. Delayed cerebral ischemia (DCI) is the most feared among such complications [2]. It typically occurs between days 3 and 14 after the initial bleeding, with a peak incidence around day 7 [1, 2]. There is evidence of a multifactorial etiology for DCI, including cerebral microcirculation failure due to the interaction of circulatory, inflammatory, and thrombotic phenomena. It is believed that genetic and/or physiological variability also has a role, as it determines different degrees of susceptibility to cerebral circulation failure and varying tolerance to ischemia [1, 3]. Consequently, several strategies and drugs have been proposed and evaluated to prevent DCI for different therapeutic purposes, as its multifactorial etiology gives a rationale for several potential therapeutic targets [1, 4].

The most recent management guidelines for SAH from the American Heart Association are from 2012, and those from the European Stroke Association date from 2013 [1, 5]. Guidelines state that clinicians faced with treating patients with SAH use the recommendations only as a starting point, after which they ought to use the tools they deem appropriate to improve patient outcomes [1]. Both guidelines note that SAH research on DCI prevention has been a rapidly growing field of research since the beginning of the century (even more so over the past decade) and is the reason why several therapies have been proposed and are under scrutiny. Each clinician may apply different approaches based on risk profiles or apply a structured approach for all patients. Different fluids and strategies for their administration are used for DCI prevention. All seek to maintain normovolemia and cerebral circulation, two elements that play a fundamental role in the multifactorial pathophysiology of DCI [3]. Human albumin (HA) is one of the types of fluids that has attracted interest in the treatments of SAH. According to an international survey conducted in 2014, of 362 intensivists, mostly from academic institutions and hospitals with more than 500 beds, 83% reported that HA was not included in institutional treatment protocols for patients with SAH. However, 46% reported using HA in patients with SAH outside the management protocol [6].

A retrospective study of 140 patients with SAH published in 2004 suggested better outcomes at 3 months with the use of albumin and reported a trend toward lower measured frequency of vasospasm (prior to definition of DCI) in the group that received albumin [7]. In 2012, a phase II clinical trial was published to evaluate the safety of different doses of albumin in patients with SAH [8]. It reported that dosages of up to 1.25 g/kg/day and for up to 7 days are safe, without being associated with complications that limit the use of the medication, although they did report the occurrence of pulmonary edema (PE) in three patients (11%), of whom two were in a 2.5-g/kg/day intervention arm. HA was considered the definitive cause of this adverse event in one of them and probable in the other two. However, the study was not powered to assess the effect of HA on other mid-term and long-term clinical outcomes of interest [8]. In other clinical settings, such as surgery, sepsis, and shock, HA has been used as an infusion and reported to be beneficial in maintenance of euvolemia in concentrations ranging from 4 to 20% [9, 10].

Based on these previous reports and after consensus among experienced intensive care physicians, in 2014, a hospital treatment protocol for SAH was established at our institution, a tertiary care university hospital in Cali, Colombia. This protocol indicates an initial cardiovascular evaluation (pro-Brain Natriuretic Peptide, [proBNP] + and echocardiography, a continuous infusion of HA during the first 5 days of admission, and a preference to guide fluid administration by hemodynamic parameters instead of fluid balances. This study aimed at assessing the effect of this institutional protocol based on early HA infusion on the incidence of DCI, mortality, and other outcomes of interest. Our hypothesis was that HA could have a beneficial effect in the prevention of DCI by facilitating hemodynamic stability and reducing renal fluid losses.

Methods

Design and Participants

This was a quasi-experimental study with historical controls based on electronic clinical records. We included adult patients of either sex with SAH diagnosed by head computed tomography (CT) scan or lumbar puncture who were treated in the ICU of a tertiary care university hospital in Cali, Colombia, between 2011 and 2018. We excluded patients who died in the first 24 h

after admission and patients with severe SAH defined as World Federation of Neurosurgical Societies WFNS scale (WFNS) scores 4 and 5, without aneurysm control because of palliative approach. Currently, all patients with SAH receive this protocol, but prior to its implementation, HA was not applied as part of the standard management. This background gave rise to the possibility of developing the research project presented here. Institutional ethics review board approval was obtained before the study start (institutional review board approval number: No.2-040-2020; January 29, 2020), and no informed consent was indicated.

Standard of Care

All aspects of management other than the institutional protocol corresponded to the standard of care for patients with SAH, both in the control group and in the intervention group. This included the following: CT angiography or digital subtraction angiography for the diagnosis of aneurysms, early neurosurgical or endovascular interventions according to indication, oral nimodipine to improve neurological outcome at a dosage of 60 mg every 4 h for 21 days, use of transcranial Doppler monitoring in the ICU, and use of CT in case of neurological deterioration. Fluid administration is usually guided by monitoring tools, such as cardiac output, central pressures, or transpulmonary preload and afterload indices, or by urinary output and vital signs.

During the control period, all patients had arterial blood pressure and central venous pressure monitoring. The use of pulmonary artery catheter monitoring and its interpretation and derived treatment was decided by discretion of the treating physician and was typically used in patients with high-grade SAH or in hemodynamically unstable patients. Cardiac evaluation with an echocardiogram was performed only in unstable patients or those with a clinical suspicion of cardiac compromise. Fluid therapy was based on crystalloid solutions (0.9% saline or Ringer lactate) and boluses of crystalloids at treating physician preference; the goal was to avoid negative fluid balances and to keep central venous pressure over 5 mmHg during the early phase or if vasospasm was detected. The use of colloids was permitted but was unusual.

Managements Protocol with Albumin Infusion

The 5% albumin infusion is prepared in the institutional pharmacy and consists of a mixture of 100 ml of 20% albumin (20 g of HA, 200 g/l Baxter solution) plus 300 ml of normal saline, which results in a 400-ml iso-oncotic and nearly isotonic solution to be used as the main intravenous fluid at a fixed dosage for 5 days, around 60 g/day [11]. This dosage was determined based on the safety profile of HA reported by the Albumin in Subarachnoid Hemorrhage (AliSAH) study [8], the physiological effect of HA in volemia as expressed in other settings [12], our goal of achieving and maintaining hemodynamic stability after fluid administration during the early phases of SAH, its implementation advantages, and the experience of the department with the use of HA in this setting (a detailed rationale for the use of 5% HA for infusion is provided in the Discussion section).

The infusion was stopped if hemodynamic monitoring showed clear signs of hypervolemia or PE. Negative fluid balances were tolerated if cardiovascular function variables indicated euvolemia. In the event of DCI, the increase in preload and the increase in systemic blood pressure were prioritized. The use of other fluids is not recommended, although it is permitted if the treating physician deems it necessary. The goal is to maintain euvolemia, mainly evaluated by invasive monitoring; therefore, positive fluid balance and central venous pressure are not a goal anymore. Euvolemia in patients with PiCCO® Transpulmonary monitoring was determined by a normal Global End-Diastolic volume Index (GEDI) value between 680 and 800 ml/m^2. Other parameters, such as systolic volume variability or pulse pressure variability, were used as indicators of potential response to a volume challenge but not as indicators of euvolemia. Indications for transcranial Doppler, vasopressors, and inotropes remained unchanged with respect to the historic control period.

Exposures and Outcomes

The primary outcomes were the incidence of DCI according to the medical diagnosis reported in the clinical history and death during ICU and hospital stay. DCI is defined as proposed by Vergouwen et al.: "The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 h, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies" [13].

Secondary outcomes were neurological status measured with the Glasgow Outcome Scale Extended (GOSE) after 6 months, death at 6 months (recorded from publicly available national registries), and occurrence of hospital complications, such as PE, hyponatremia, rebleeding, hydrocephalus, or vasospasm. PE and rebleeding were determined based on diagnoses by treating physicians; hyponatremia was defined as a sodium level < 135 mEq/l, and hypernatremia was defined as a

sodium level > 150 mEq/l; hydrocephalus was determined based on ventricular enlargement in radiologic reports and clinical signs; and vasospasm was determined when reported after routine assessment with transcranial Doppler or, less frequently, when detected in an angiographic study.

The volume of fluids administered and eliminated daily during the ICU stay was also an end point of interest based on the rationale of the use of HA. These were recorded as daily and cumulative volumes during the first 5 days of the ICU stay.

Sample Size

We used the Fleiss method with values of alpha = 0.05 (type I error) and beta = 0.2 (type II error) and considered an absolute risk reduction of 20% or a relative risk (RR) of 0.33 with a frequency of DCI of 30% in nonexposed patients. The resulting sample size needed to detect this effect was 124 patients (62 exposed and 62 unexposed), which was considered achievable before data collection started. This calculation was made in the virtual calculator of the Open Epi online software (sample size-cohort/RCT).

Data Collection

Patients were identified through hospital administrative records. To assess the quality of the data, an exploratory analysis was done to identify extreme, strange, and missing data. To validate the data extraction process, a random sample of 10% of the data was compared with the source documents with no further need to review.

Statistical Analysis

All statistical analyses were conducted in Rstudio software version 1.3.10. The Shapiro–Wilk test was used to assess the distribution of continuous variables and determined the use of the mean and standard deviation or median and interquartile range (IQR) for their description. Nominal and ordinal variables are described with absolute and relative frequencies. The effects of the intervention are reported in measures of association with crude and/or adjusted risk difference and RR and hazard ratio (HR), accordingly. All association measures are presented with 95% confidence intervals (95% CI). For the hypothesis tests, alpha = 0.05 was considered as the level of significance, and the p value is reported for all comparisons.

The effect of the intervention on the main outcomes was assessed with consideration of baseline prognostic features and treatments, including age, clinical and radiological severity, the type of aneurysm control, and other treatments received. The primary analysis was conducted with logistic regression to obtain adjusted risk ratios. Variable selection for multivariable models followed the "purposeful variable selection" strategy described by Bursac et al. [14] and Kleinbaum et al. [15, 16] to assess and control for confounding effects, in which each covariate is assessed in separate models and selected based on initial significance ($p < 0.2$) and kept in the model if it modifies estimates of effect (confounding) in a reiterative process.

We noted that the death of patients during the ICU stay could lead to a biased measure of DCI incidence because of competing risks (higher mortality in one group can lead to lower DCI occurrence because fewer patients/survivors are at risk). To overcome this limitation, we conducted two post hoc analyses. One analysis was based on the cumulative incidence function (CIF), which uses Gray's test [15, 17–21], and time-to-event multivariable regression models based on the hazard function: the cause-specific hazard function (CSHF) and the hazard subdistribution function (HSDF) [17]. A second post hoc analysis used the creation of a composite outcome: DCI or death in the ICU. This outcome used a logistic regression model to assess the effect of the intervention.

For the analysis of neurological status at 6 months, the eight-category GOSE was dichotomized as follows: undesirable outcome = GOSE < 5 (primary analysis) and undesired outcome = GOSE < 4 (sensitivity analysis). The evaluation of this outcome with two different dichotomization points as a sensitivity analysis allows us to verify the detection of an effect of the intervention, reducing the possibility that the result is an artifice of the cutoff point, in addition to allowing comparison with studies in the literature, in which both cutoff points are frequent. To assess the differences in volumes administered, daily and cumulative (up to day 5) volumes, as well as daily fluid balances (input and output) each day, were also compared between groups. For all these comparisons of continuous variables, the nonparametric Mann–Whitney U-test was used.

Results

A total of 189 patients with SAH met the selection criteria and were included for analysis. The median age was 58 years old (IQR 48–66), and most were women (72.2%). Sixty-three patients (~ 1/3) were treated in the ICU during the period prior to implementation of the institutional albumin infusion protocol (historical controls), and 126 patients were treated with the albumin infusion protocol (intervention group). The median daily albumin dosage received in the intervention group 48.7 g (IQR 33.7–59.7) or 0.69 g/kg/day (IQR 0.51–0.86).

Table 1 displays the baseline clinical features and the treatments received in each group. There was a higher proportion of patients with high-grade SAH, as well as a

Table 1 Baseline clinical features and treatments received

Baseline clinical features	All patients $N=189$		Historic controls $n=63$		Intervention group $n=126$	
Age, mean (SD)	56.7	(13.0)	53.7	(11.9)	58.3	(13)
Age, median (IQR)	57	(48–65)	54	(47–61)	58	(51–67)
Age, min–max	22–93	–	22–77	–	26–93	–
Women, *n* (%)	136	(72.0)	45	(71.4)	91	(72.2)
WFNS scale, *n* (%)						
1	63	(33.3)	24	(38.1)	50	(39.7)
2	46	(24.3)	26	(41.3)	20	(15.9)
3	13	(6.9)	1	(1.6)	12	(9.5)
4	35	(18.5)	10	(15.9)	25	(19.8)
5	21	(11.1)	2	(3.2)	19	(15.1)
High WFNS (4–5), *n* (%)	56	(29.6)	12	(19.0)	44	(34.9)
Modified Fisher scale, *n* (%)						
1	16	(8.5)	9	(14.3)	7	(5.6)
2	23	(12.2)	9	(14.3)	14	(11.19
3	41	(21.7)	14	(22.2)	27	(21.4)
4	109	(57.7)	31	(49.2)	78	(61.9)
APACHE, II median (IQR)	9	(6–14)	9	(6–12.5)	10	(6–15)
Treatments						
Mechanical ventilation, *n* (%)	104	(55.0)	29	(46.0)	75	(59.5)
Type of aneurysm control, *n* (%)						
Endovascular	94	(49.7)	31	(49.2)	63	(50.0)
Surgical	80	(42.3)	28	(44.4)	52	(41.3)
None	15	(7.9)	4	(6.3)	11	(8.7)
Cardiac output monitoring, *n* (%)	130	(68.8)	36	(57.1)	94	(74.6)

APACHE II, Acute Physiology and Chronic Health Evaluation II; *IQR*, interquartile range; *SD*, standard deviation; *WFNS*, World Federation Neurosurgical Societies

slightly higher age in the intervention group. This likely explains the higher use of hemodynamic monitoring and higher need for invasive mechanical ventilation in that group. Both groups were comparable regarding other known prognostic factors, including type of aneurysm control, a relevant cointervention to consider.

DCI

Delayed cerebral ischemia occurred in 75 patients (39.7%) in total, with a lower incidence in the intervention group (34.9%) than in the control group (49.2%) (crude RR 0.71; 95% CI 0.50–1.00). The adjusted analysis (adjusted by initial severity between the groups; WFNS/modified Fisher) suggested a lower risk of DCI associated with the intervention (adjusted RR 0.63 [95% CI 0.46–0.88], multivariable analysis) (Table 2).

The post hoc CIF analysis to compare the DCI incidence between groups, considering the competing risk with death, is shown in Fig. 1. The graph suggests a lower cumulative incidence of DCI in the intervention group compared with the control group (Gray's test: $p=0.027$). However, no significant difference is observed in mortality (Gray's test: $p=0.091$). The multivariable HSDF model suggested a large reduction in the incidence of DCI associated with the intervention group compared with historic controls (HR 0.52 [95% CI 0.33–0.83], $p=0.0057$; adjusted by WFNS, modified Fisher scale, and age), as did the CSHF model (HR 0.48 [95% CI 0.30–0.78], $p=0.0029$). In both models, the association was adjusted for age and WFNS and modified Fisher scale scores. For the CSHF, the proportional hazard test resulted in a p value of 0.41, indicating proportionality over time of follow-up.

ICU and Hospital Mortality

Overall mortality in the ICU was 19%. No differences were identified in the effect of the interventions studied on this outcome (adjusted RR 0.92; 95% CI 0.51–1.70). The HSDF and CSHF models considering the presence of competing risks did not detect differences in death in the ICU between groups either (HSDF HR 0.67 [95%CI 0.26–1.73]; CSHF HR 0.52 [95%CI 0.19–1.40]). There were no differences in hospital mortality (24.3% overall) between the groups (adjusted RR 1.23; 95% CI 0.67–2.26).

Table 2 Effect of the intervention on clinical outcomes (crude and adjusted estimates)

Clinical outcomes	Control group		Intervention group		Crude RR	95% CI	Adjusted RR	95% CI
	n = 63		*n* = 126					
	n	%	*n*	%				
DCI	31	49.2	44	34.9	0.71	0.50–1.00	0.63	0.46–0.88[a]
Death in ICU	11	17.5	25	19.8	1.14	0.60–2.16	0.93	0.51–1.70[b]
DCI or death in ICU	38	60.3	55	43.7	0.72	0.55–0.96	0.65	0.50–0.84[a]
Hospital death	12	19.0	3.4	27.0	1.42	0.79–2.54	1.25	0.69- 2.30[c]
Death at 6 months	13	20.6	37	29.4	1.42	0.82–2.48	1.23	0.71–2.15[c]
GOSE at 6 months < 4 (21 losses)	19	33.3	46	41.4	1.24	0.81–1.91	1.04	0.69–1.59[d]
GOSE at 6 months < 5 (21 losses)	21	36.8	48	43.2	1.17	0.79–1.75	1.02	0.69–1.50[d]

CI, confidence interval; *DCI*, delayed cerebral ischemia; *GOSE*, Glasgow Outcome Scale Extended; *ICU*, intensive care unit; *RR*, relative risk; *WFNS*, World Federation Neurosurgical Societies

[a] Adjusted by modified Fisher scale score

[b] Adjusted by WFNS scale score and type of aneurysm control (surgical or endovascular)

[c] Adjusted by WFNS scale score and age

[d] Adjusted by WFNS scale score and modified Fisher scale score

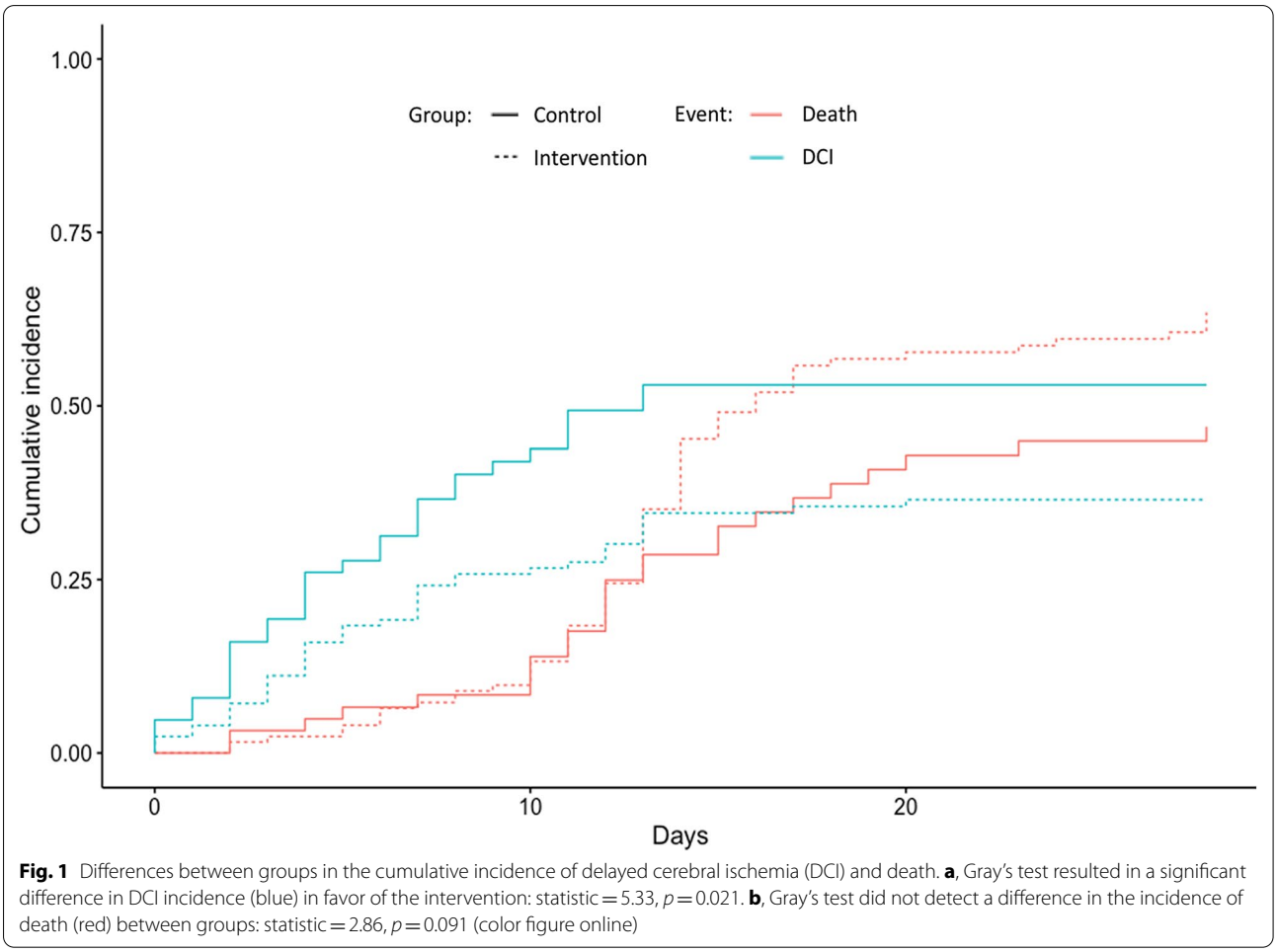

Fig. 1 Differences between groups in the cumulative incidence of delayed cerebral ischemia (DCI) and death. **a**, Gray's test resulted in a significant difference in DCI incidence (blue) in favor of the intervention: statistic = 5.33, $p = 0.021$. **b**, Gray's test did not detect a difference in the incidence of death (red) between groups: statistic = 2.86, $p = 0.091$ (color figure online)

Vital and Neurological Status 6 Months After SAH

Follow-up data on mortality were available for all patients, but for neurological status, we had 21 losses to follow-up 6 months after SAH. The estimate of the effect of the intervention on this outcome was also underpowered. The multivariable analysis considered prognostic variables and resulted in death at 6 months (RR 1.23; 95% CI 0.71–2.15). The evaluation of neurological status was unavailable for 21 patients (11.1%) without follow-up after discharge, six in the historical control group (9.5%), and 15 in the intervention group (11.9%).

Secondary Outcomes

Table 3 displays the frequency of secondary outcomes in each group and the effect of intervention in absolute and relative effect measures. PE was detected in 19 patients (10.1%), with a frequency of 4.8% in the control group compared to 12.7% in the intervention group. No difference was detected between groups; however, the study had low power (40.7%) to detect differences of this magnitude on this outcome. We found a reduced risk of hyponatremia in the intervention group versus the control group (27.0% vs. 49.2%) (RR 0.71; 95% CI 0.55–0.91). No cases of hypernatremia were detected in the control group, and six occurred in the intervention group, so an RR could not be calculated, and the measured risk difference for hypernatremia was 4.54% (95% CI 1.04–8.48), which is considered statistically significant in favor of the control.

The intervention also had an effect on the volume of fluids used, with consistently lower administered volumes during the first 5 days of the ICU stay in the intervention group compared with the historic controls (see Table 4). This marked reduction in administered fluid volumes was not accompanied by differences in median fluid balances between groups. These results suggest that the intervention helped to maintain similar fluid balances with lower fluid volumes administered.

Discussion

Summary of Findings

This study evaluated the effect on clinical outcomes of a management protocol based on a fluid administration strategy oriented by hemodynamic goals and the use of a continuous infusion of isotonic, iso-oncotic albumin for the first 5 days of the ICU stay. The intervention was associated with a reduced incidence of DCI and was not associated with a higher incidence of other relevant complications or unfavorable outcomes. The intervention was also associated with a significant reduction in the occurrence of hyponatremia and led to lower volumes of fluids used during the first 5 days of the ICU stay. We hypothesize that this fluid administration strategy oriented by hemodynamic goals in combination with a stabilizing effect of HA may have led to reduced renal loss of sodium and water, reduced risk of hyponatremic hypovolemia, and reduced incidence of DCI given the improved hemodynamic stability.

Strengths and Limitations

A critique of the quasi-experimental design with historic controls is that clinical outcomes tend to improve over time because of advances that are difficult to measure or to compensate for in analysis. Nevertheless, our study found a benefit of the implemented intervention only in those outcomes theorized to be modified by it, without a similar improvement in other clinical outcomes that might be expected to improve over time (and for which this study had adequate statistical power), such as rebleeding, vasospasm, pneumonia, or death. Additionally, it is worth noting that treatments for SAH changed little during the study period (no new guidelines), and the

Table 3 Secondary clinical outcomes

Secondary outcomes	Control group		Intervention group		RD	95% CI RD	RR	95% CI RR
	n = 63		*n* = 126					
	n	%	*n*	%				
PE	3	4.8%	16	12.7%	7.9%	−0.09, −15.8	2.7	0.8–8.8
Hyponatremia	31	49.2%	3. 4	27.0%	−22.2%	−36.8, −7.6	0.4	0.2–0.8
Hypernatremia	0	0.0%	6	4.8%	4.8%	1.04, 8.5	Info	NA-Inf
Vasospasm	27	42.9%	41	32.5%	−10.3%	−25.0, 4.4	0.6	0.3–1.3
Rebleeding	9	14.3%	21	16.7%	2.4%	−8.4, 13.2	1.2	0.5–3.2
Hydrocephalus	18	28.6%	42	33.3%	4.8%	9.1, 18.6	1.3	0.6–2.6
Pneumonia	9	14.3%	24	19.1%	4.8%	−6.3, 15.8	1.4	0.6–3.7

Hyponatremia = serum sodium < 135 mEq/; hypernatremia = serum sodium > 145 mEq/l

CI, confidence interval; *RD*, risk difference; *NA*, not applicable; *INF*, infinity; *PE*, pulmonary edema; *RR*, relative risk

Table 4 Daily administered liquids accumulated and water balances of the first 5 days

	Control group		Intervention group		Difference[a]	*p-value*[b]
	n = 63		*n* = 126			
	Median	RIC	Median	RIC		
Fluids administered						
Day 1	1530	810 to 2421	1059	525 to 1564	471	0.001
Day 2	3510	2861 to 4588	2325	1886 to 2749	1185	< 0.0001
Day 3	3896	2985 to 4710	2540	2064 to 3059	1356	< 0.0001
Day 4	3669	2996 to 4794	2553	2048 to 3210	1116	< 0.0001
Day 5	3313	2529 to 4160	2655	2112 to 3365	658	0.001
Up to day 2	4915	3804 to 7012	3323	2778 to 4215	1592	< 0.0001
Up to day 3	9032	7389 to 11,582	6058	4897 to 7365	2974	< 0.0001
Up to day 4	12,889	10,642 to 15,439	8558	7179 to 10,232	4331	< 0.0001
Up to day 5	16,830	14,036 to 20,360	11,205	9596 to 13,019	5625	< 0.0001
Water balances						
Balance day 2	322.5	426 to 1227	−121	−1018 to 732	444	0.015
Balance day 3	−88	−1525 to 1055	−150.2	−798 to 612	62	0.529
Balance day 4	−104	−1158 to 691	−295	−974 to 618	191	0.983
Balance day 5	−109	−823 to 648	−25	−771 to 686	−84	0.921

[a] Difference between unexposed and exposed patients

[b] *p* value from the Mann–Whitney *U*-test

cointerventions received were similar between groups and were assessed in multivariable analyses [1, 4, 5].

Caution should be exercised when attempting to assess an intervention using a nonrandomized design, as there is a risk of confounding by clinical indication. However, the intervention was established as part of clinical practice in an institutional management protocol that created two groups of patients who were expected to have had the same spectrum of severity of the disease, without the risk of confounding by indication [22]. Strict and judicious records led to no missing data regarding clinical features on admission, cointerventions, and clinical events, which allowed for a profound analysis of other sources of confounding.

The outcome DCI was chosen because it is the event on which we expected the intervention to have a beneficial effect. Moreover, it is an important clinical outcome for patients, and it is routinely screened and recorded in clinical practice. DCI has been associated with long-term neurological status and death and is used extensively in the SAH literature [4, 13, 23]. The benefit of the intervention on this outcome was detected with the a priori analysis and verified with two sensitivity analyses (post hoc) that considered the risk of bias due to competing risks with death. All analyses suggested a large reduction in DCI incidence (relative effect sizes between 25 and 50%), which gives us confidence in this finding.

This study was limited by its retrospective nature in the assessment of neurological status at 6 months because of the variability and questionable reliability of the neurological examination and its report in clinical records and also because of many losses to follow-up, which although balanced between groups, underpowered the comparison. The assessment of the effect of the intervention on the incidence of PE was also limited because a standard definition of PE is lacking and we relied on clinician diagnosis alone. PE is a threat in the treatment of SAH; it is more frequent in severe cases and when the cardiovascular system is affected on admission [24, 25]. PE has been associated with the use of HA, although at higher doses than in our study [8]. Our incidence of PE was low, which underpowered the comparison of this outcome between groups, even though it was within the range that is described in the literature. PE was not associated with increased mortality or length of ICU stay.

Relevance to Clinical Practice and Research

The administration of HA to facilitate fluid resuscitation in patients with SAH is controversial because its effect has not been demonstrated in phase III clinical trials, and some studies in patients with other critical neurological diseases have suggested potential risks associated with its use [6, 26]. In preclinical studies with animal models of SAH, albumin has shown neuroprotective effects related to a decrease in inflammatory markers and an increase in

neuroplasticity markers, suggesting short-term and long-term benefits [27–29]. These studies have also reported greater recovery of sensorimotor and cognitive performance in animals receiving albumin compared to crystalloid fluids [28, 29]. A quasi-experimental study with historic controls was also conducted by Suarez et al. [7] in 2004, who compared 63 patients treated with HA with 77 patients treated after the use of HA was restricted in their management protocol (very similar to our study, but with HA as the historical control). They reported lower mortality and better functional outcomes in the group of patients with HA [7]. Other reports of observational studies that have evaluated HA in SAH used it to induce hypervolemia, an approach that did not produce better results [30] or that was even associated with worse neurological and functional outcomes [31]. However, we propose that the hypervolemia approach was the harmful element in those studies and not HA, which was used as a tool for greater therapeutic intensity in more severe patients [31]. Dilutional hypervolemia is not currently recommended because it is associated with worse clinical outcomes in SAH [4].

HA has been widely used for volume expansion in the treatment of SAH. Mayer et al. [9] reported that HA was effective in inducing hypervolemia in the short term (hours), but in the long term (days), monitoring showed a decrease of circulating volume of about 10% in a population of critically ill patients. Studies from the ICU and surgery settings report the use of 20% or 25% HA boluses consistent with the objective of inducing hypervolemia, and preclinical studies and a phase II trial have used HA in the same concentration on SAH to exert neuroprotection. The institutional protocol we report uses HA for maintenance of euvolemia, which is why 5% HA (as reported by Mayer et al. [9] in patients with SAH) was chosen for continuous infusion to avoid the sudden and large changes in circulating volume that can occur with bolus administration of higher concentrations of HA. In the setting of early SAH, patients are subjected to acute hormonal and metabolic stress, including increased natriuretic peptides, serum levels of catecholamines, and other stress mediators [32]. In this setting, large changes of intravenous volume can lead to sudden increases of central venous return, triggering further hormonal response with increased natriuretic peptide release and a renal response that leads to loss of sodium and water (increased diuresis), which can potentially lead to hypovolemia, hyponatremia, and cerebral hypoperfusion with or without vasospasm [33]. By contrast, with a constant low amount of intravenous fluids and isotonic HA concentration, such variations can be avoided, leading to gradual decrease of sympathetic tone and proBNP levels, which prevents natriuresis [9]. HA was chosen because of its reliable and long-lasting effect on volemia [34], which allowed us to give a small amount of HA solution as the only fluid for patients' metabolic needs. The dosage of 50 ml/hour (~60 g/day) was selected based on the assumption of a blood volume expansion by albumin estimated at 1.3 to 1.5 times the amount of infused albumin [12], keeping in consideration the safety profile shown in the Albumin in Subarachnoid Hemorrhage study [8].

However, the reduction in the incidence of DCI in our intervention group may be the result of other aspects of the institutional management protocol in addition to the continuous infusion of HA. A more recent randomized clinical trial published by Anetsberger et al. [35] that assessed the effect of therapy guided by hemodynamic monitoring goals with transpulmonary thermodilution, found a relative reduction of DCI risk similar to ours. Therefore, the guidance of fluid therapy with specialized invasive monitoring in patients with SAH may be independently associated with better outcomes. Additionally, optimized cardiac support is known to affect neurological outcome [36]. It is then plausible that one or more of the components of our management protocol had individual effects that, added or in interaction, gave rise to the results we report.

Recently, endothelial glycocalyx has been linked to pathophysiology of DCI in SAH [37]. Glycocalyx is essential for proper endothelial function, when damaged leukocyte and platelet adhesion might increase [37, 38]. Albumin is related to the homeostasis of the endothelial surface, as it is necessary for preservation of its integrity [39]. In SAH, endothelial and glycocalyx damage are related to subsequent DCI [40], and hypervolemia has been related to endothelial damage via the release of natriuretic peptide and the shedding of glycocalyx [41]. Early administration of HA may contribute to restoration of glycocalyx integrity and endothelial recovery and lead to better vessel wall function, improving both vessel reactivity and the interaction with blood components of inflammation and hemostasis.

Future Directions

From its conception, the purpose of this study was to inform the institutional decision to maintain or change this management protocol of hemodynamically oriented fluid administration with HA infusion and cardiac evaluation. We also had the purpose to contribute to the justification of developing and financing randomized clinical trials that assess the effects of HA in patients with SAH. We hope this report is also useful as an example of the dosage and administration of HA in patients with SAH.

We propose three hypotheses that should continue to be studied in clinical trials and high-quality observational studies: (1) Initial cardiac evaluation provides guidance

of fluid management and use of vasoactive or inotropic agents to reduce the risk of DCI and unfavorable short-term and long-term outcomes. (2) Fluid, vasoactive, and inotropic management guided by hemodynamic monitoring goals with transpulmonary thermodilution in patients with high-grade SAH or hemodynamic instability allows for optimization of cerebral perfusion. (3) HA provides a stabilizing hemodynamic effect that reduces the risk of complications.

There is a special interest in determining whether the early phenomena of the pathophysiology of the disease influence the development or severity of delayed phenomena, such as DCI [4]. As both types of phenomena are strongly associated with the initial severity of the hemorrhage, it is difficult to make this distinction. Our intervention of study was administered during the first 5 days after the hemorrhage (so it could be classified as an "early" intervention) and was associated with the reduction of a characteristically delayed phenomenon. This might be due to a long-lasting effect of HA in circulation and tissues that still provides protection against delayed phenomena. Nonetheless, this result calls for further study of the relationship between early and delayed phenomena, which could identify potential preventive targets.

Future studies on patients with SAH treated in the ICU should consider the presence of competing risks to avoid bias. Also, future studies on SAH should prioritize outcomes that are important for the patients, and characteristics or variables that reflect how a patient feels, functions, or survives (mortality and long-term neurological status and quality of life).

Conclusions

The institutional management protocol based on a hemodynamically oriented fluid administration strategy using a continuous albumin infusion appears beneficial for patients with SAH, as it reduced the incidence of DCI and hyponatremia. It was also associated with a large reduction in volumes of fluids administered during the first 5 days of the ICU stay. Proposed mechanisms may involve improved hemodynamic stability that allows for the maintenance of euvolemia and reduces the risk of ischemia, among others. Increased use of cardiac output monitoring to guide fluid administration alone may lead to improved outcomes. As such, the individual effects of HA are to be assessed in randomized clinical trials and other studies that allow for the assessment of the effect of HA independent of the fluid therapy strategy.

Supplementary Information
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Author's Contribution
All authors made contributions to drafts of the manuscript and approved the final report. Conceiving the research question and developing the research protocol: JHM-M, AG, LG, AO, NJ, DR. Data collection: LG, LB, SE, AO, NJ. Statistical analysis: AG, JHM-M, MR. Interpretation of results: AG, LG, JHM-M, DR, AO, NJ, SE, LB, JEM-B.

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