Effects of saline or albumin resuscitation on standard coagulation tests

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ABSTRACT

Aims: To explore whether fluid resuscitation with normal saline or 4% albumin is associated with differential changes in routine clinical coagulation tests.

Design: Substudy from a large double-blind randomised controlled trial, the SAFE (Saline versus Albumin Fluid Evaluation) study.

Setting: Three general intensive care units.

Patients: Cohort of 687 critically ill patients.

Intervention: We randomly allocated patients to receive either 4% human albumin or normal saline for fluid resuscitation, and collected demographic and haematological data.

Methods and main results: Albumin was administered to 338 patients and saline to 349. At baseline, the two groups had similar mean activated partial thromboplastin time (APTT) of 37.2 s (albumin) v 39.1 s (saline); mean international normalised ratio (INR) of 1.38 v 1.34, and mean platelet count of 244 × 10^9/L v 249 × 10^9/L. After randomisation, during the first day of treatment, the APTT in the albumin group was prolonged by a mean of 2.7 s, but shortened slightly by a mean of –0.9 s in the saline group. The INR did not change in either group, while the platelet count decreased transiently in both groups. Using multivariate analysis of covariance to account for baseline coagulation status, albumin fluid resuscitation ($P = 0.01$) and a greater overall volume of resuscitation ($P = 0.03$) were independently associated with prolongation of APTT during the first day.

Conclusions: Administration of albumin or of larger fluid volumes is associated with a prolongation of APTT. In ICU patients, the choice and amount of resuscitation fluid may affect a routinely used coagulation test.

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Fluid resuscitation is common in critically ill patients.[1,2] However, there is uncertainty about which fluid should be preferentially administered. To examine the effects of choice of fluid resuscitation on clinical outcome, the SAFE (Saline versus Albumin Fluid Evaluation) study randomly allocated 6997 critically ill patients to receive either 4% albumin or normal saline.[3,4] No specific information was collected as part of this study to investigate the effect of choice of fluid resuscitation on routine measures of blood coagulation, such as international normalised ratio (INR), activated partial thromboplastin time (APTT) or platelet count. However, it has been suggested that fluid resuscitation may cause dilutional coagulopathy,[5-13] and that the effect may be greater with albumin than with saline.[3] Accordingly, in three of the trial hospitals, we conducted a pre-planned substudy of the coagulation results from SAFE study patients, to assess the differential effects of albumin and saline on routinely measured tests of coagulation. We hypothesised that patients resuscitated with albumin have higher INR, prolonged APTT, and lower platelet counts than patients resuscitated with saline.

Methods

This study was designed to extend knowledge derived from the 2004 SAFE study.[3] The SAFE study was a prospective, double-blind, randomised controlled trial in which 6997 patients requiring fluid resuscitation were randomly allocated to receive either saline or albumin for all fluid resuscitation in the ICU for up to 28 days.[3] As part of the original SAFE study, three of the 16 SAFE study hospitals collected additional coagulation data for the current analysis, with the approval of the ethics committee of each hospital and informed consent from patients or their next-of-kin. Data on coagulation variables were collected prospectively until the earlier of ICU discharge or the 5th study day. They included results of three daily tests performed as part of standard patient care — platelet count, APTT and INR. Baseline pre-randomisation values were taken as the coagulation results temporally closest to, but preceding, the time of randomisation in the SAFE study by not more than 6 hours.

Measurements of coagulation

APTT, INR and platelet counts were measured in the central laboratories of all three hospitals as part of standard care. APTT was measured at Hospital A using a Platelin LS reagent from BioMerieux, containing purified phospholipids

and micronised silica, buffer, stabiliser and preservative (BioMerieux, Marcy-líEtoile, France). At Hospital B, it was measured using the Dade Actin FSL assay from Dade Behring (Dade-Behring Diagnostics, Sydney, NSW), which contains purified soy and rabbit brain phosphatides with plasma activator, buffer, stabilisers and preservatives. Hospital C used the STA-PTT A 5 assay (Diagnostica Stago, Asnieres, France). This reagent involves the re-calcification of plasma in the presence of cephalin (a platelet substitute prepared from rabbit brain tissue) and a particulate activator (silica) in a lyophilised buffered medium.

INR was calculated from prothrombin time (PT), which was measured at Hospital A and Hospital B with the Hemosil RecombiPlasTin assay (Instrumentation Laboratory, Lexington, Mass) and, at Hospital C, with the STA-NEOPLASTINE CI PLUS assay (Diagnostica Stago, Asnieres, France).

The platelet count was measured at Hospital A and Hospital B by a multiparameter automated haematology analyser — at Hospital A, a CELL-DYN Sapphire (Abbott Diagnostics, Abbott Park, Ill) and, at Hospital B, a Beckman Coulter LH750 (Beckman Coulter, Fullerton, Calif). At Hospital C, it was measured by an Advia 120 Hematology System automatic multicell analyser (Siemens Diagnostics, Bad Nauheim, Germany).

Single values measured as part of routine early morning tests were recorded. Information on any anticoagulation regimen at the time of measurements was also obtained, such as heparin infusion (including infusion for renal replacement therapy), subcutaneous heparin, subcutaneous low molecular weight heparin, or warfarin. The decision to administer anticoagulation and the dose used was at the discretion of attending physicians. Blood products administered on Day 1 (red blood cells, fresh frozen plasma or concentrated platelets) were also recorded.

Composition of study fluids

As described in detail in the SAFE study,[3] the 4% albumin solution (Albumex, CSL Bioplasma, Melbourne, Vic) contained 40 g/L of human albumin, 140 mmol/L of sodium, 128 mmol/L of chloride, and 6.4 mmol/L of octanoate. Normal saline contained 154 mmol/L of sodium and chloride.

Power calculations

We estimated that recruitment from the three hospitals would approximate 1000 patients, equally divided between the saline and albumin groups. Such a sample size would have about 89% power to detect a difference in platelet count of 10×10^9/L, assuming a standard deviation of 50×10^9/L and an α of 0.05.

Data analysis

Data are presented as means with 95% confidence intervals of the mean, or medians with quartiles and ranges, as appropriate. To compare the effect of the two types of fluid on coagulation, analyses of APTT, INR and platelet counts used each patient's change from baseline as the primary endpoint. This was defined as the difference between the pre-randomisation measurement and the first measurement during the period within 24 hours of randomisation, because most of the fluid resuscitation was given during the first day of treatment.

The relationships between change from baseline to Day 2 for each of the three coagulation results and the resuscitation fluid type, as well as selected patient characteristics, were assessed in a multivariable analysis of covariance (ANCOVA) model including each patient's relevant baseline coagulation result. Variables were included in the ANCOVA on the basis of a strong clinical rationale or suspected a priori association with the primary outcome. They included patient age, sex, APACHE II score on trial entry, volume of trial fluid administered in the first 24 hours and receipt of any fresh frozen plasma. Another four potentially influential binary variables were also included — patient postoperative status, receipt of any anticoagulation, and presence or absence of sepsis and of traumatic brain injury. All statistical comparisons were two-sided and a P value < 0.05 was considered to indicate statistical significance.

Results

Six hundred and eighty-seven patients were studied. Of these, 338 were assigned to receive albumin, and 349 to receive saline. Table 1 shows patient characteristics and diagnostic categories. There were no important differences between the two experimental groups in terms of age, sex distribution, severity of illness assessed by the APACHE II score, or broad diagnostic category. No patients received any "off protocol" albumin during the study.

Most of the study fluid was given on Day 1, with greater amounts of saline than albumin being administered ($P = 0.02$, Mann–Whitney test), accompanied by a somewhat greater overall median positive fluid balance in the saline group ($P = 0.16$, Mann–Whitney test) (Table 2). The median daily volumes of all fluids administered declined rapidly after Day 1, with the median daily volume of albumin remaining lower than the median daily volume of saline until Day 4. Over the first 4 days, the overall median total volume of study fluid delivered was 500 mL lower in the albumin than in the saline group ($P = 0.02$, Mann–Whitney test), although the overall fluid balance, taking into account other administered non-study fluid was only 152 mL lower ($P = 0.7$, Mann–Whitney test).

Table 1. Patient characteristics and diagnoses*

	Total (n=687)	Albumin (n=338)	Saline (n=349)
Age (years)	63.2 (61.9–64.6)	63.7 (61.8–65.6)	62.8 (60.9–64.6)
Sex (male) (%)	56.4% (52.6%–60.1%)	56.8% (51.4%–62.2%)	55.9% (50.5%–61.2%)
APACHE II score	18.9 (18.3–19.5)	19.0 (18.2–19.9)	18.8 (17.9–19.6)
Sepsis	152 (22.4%)	65 (19.5%)	87 (25.1%)
Acute respiratory distress syndrome	15 (2.2%)	5 (1.5%)	10 (2.9%)
Traumatic brain injury	16 (2.3%)	8 (2.4%)	8 (2.3%)
Diagnosis			
Medical	416 (60.6%)	191 (56.5%)	225 (64.5%)
Pneumonia	69 (10.0%)	26 (7.7%)	43 (12.3%)
Severe sepsis	53 (7.7%)	17 (5.0%)	36 (10.3%)
Cardiac arrest	27 (3.9%)	14 (4.1%)	13 (3.7%)
COPD	24 (3.5%)	12 (3.6%)	12 (3.4%)
Renal disease	20 (2.9%)	11 (3.3%)	9 (2.6%)
Other	223 (53.6%)	111 (58.1%)	112 (49.7%)
Surgical	271 (39.4%)	147 (43.5%)	124 (35.5%)
Gastrointestinal neoplasm	67 (9.8%)	34 (10.1%)	33 (9.5%)
Gastrointestinal perforation	28 (4.1%)	16 (4.7%)	12 (3.4%)
Gastrointestinal obstruction	20 (2.9%)	12 (3.6%)	8 (2.3%)
Lung neoplasm	13 (1.9%)	7 (2.1%)	6 (1.7%)
Hip fracture	11 (1.6%)	6 (1.8%)	5 (1.4%)
Other	132 (48.7%)	72 (48.9%)	60 (48.4%)
ICU stay (days)	7.3 (6.8–7.8)	7.1 (6.4–7.7)	7.5 (6.9–8.2)
Hospital stay (days)	16.4 (15.7–17.1)	16.3 (15.2–17.3)	16.6 (15.6–17.5)
28-day mortality (%)	20.4% (17.4%–23.5%)	20.5% (16.1%–24.8%)	20.4% (16.1%–24.7%)

COPD = chronic obstructive pulmonary disease. APACHE II = Acute Physiology and Chronic Health Evaluation II score.
* Values are expressed as number of patients (percentage) or mean (95% confidence interval of the mean).

Anticoagulation regimens in the two groups were similar throughout the study period (Table 3). Few patients received blood products, with the frequencies and amounts of blood product administered also being very similar in the two groups (Table 4).

At baseline, the two groups had similar mean APTT (albumin 37.2 s v saline, 39.1 s); mean INR (1.38 v 1.34), and mean platelet count (244×10^9/L v 249×10^9/L). Changes in coagulation test results from baseline were assessed on study Day 2 following administration of most study fluid. Mean APTT values on Day 2 for patients who received albumin resuscitation were observed to exceed values in patients resuscitated with saline (mean APTT change, 2.7 s for albumin v –0.9 s for saline), while both groups showed a slight reduction in mean circulating platelet number (Figure 1).

As expected, the observed change from baseline for each of APTT, INR and platelets was strongly associated with the baseline value. However, resuscitation with albumin remained independently associated with an increase in APTT, after adjustment for other potential influences (Table 5), notably the overall volume of study fluid administered. There was a trend but no strong evidence that resuscitation with albumin was independently associated with changes in INR (adjusted $P = 0.14$) and platelet count up to study Day 2 (adjusted $P = 0.08$) (data not shown).

Discussion

Within a large randomised double-blind study, we conducted a pre-planned substudy to assess the effect of albumin or saline fluid resuscitation on routinely measured coagulation tests (platelet count, APTT and INR) in ICU patients. We found that, during the first study day, when most of the study fluids were administered, resuscitation with albumin was not associated with a significant effect on INR or platelet count compared with saline, but it was associated with a significant increase in mean APTT. Furthermore, albumin resuscitation fluid was one of several identified independent influences on the change in APTT,

Table 2. Daily volumes of study fluid administered and overall fluid balance

	Day 1		Day 2		Day 3		Day 4	
Volume	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
Albumin								
Fluid volume (L)	0.75 (0.5 to 1.5)	0 to 6	0.1 (0 to 0.75)	0 to 5	0 (0 to 0)	0 to 3.5	0 (0 to 0)	0 to 2.3
Balance (L)*	1.2 (0.5 to 2.0)	–5.2 to 14.7	0.9 (0 to 1.9)	–3.9 to 9.7	0.3 (–0.5 to 1.1)	–4.3 to 7.6	0 (–0.5 to 0.9)	–4.1 to 5.6
Saline								
Fluid volume (L)	1.0 (0.5 to 1.5)	0 to 12	0.2 (0 to 1.0)	0 to 8	0 (0 to 0.2)	0 to 2.55	0 (0 to 0)	0 to 4
Balance (L)*	1.3 (0.6 to 2.4)	–1.7 to 12.7	0.9 (0.1 to 2.1)	–4.1 to 14.2	0.4 (–0.4 to 1.0)	–5.5 to 5.0	0 (–0.1 to 1.0)	–3.3 to 6.1

IQR = interquartile range. * For daily fluid balance, positive numbers represent fluid gain, and negative numbers represent fluid loss.

Table 3. Anticoagulation during study period (% of patients)

	Day 1		Day 2		Day 3		Day 4	
Anticoagulation	Albumin	Saline	Albumin	Saline	Albumin	Saline	Albumin	Saline
No anticoagulation	55.8	56.2	31.6	33.3	25.5	24.0	20.9	19.0
Heparin infusion	4.8	4.4	6.6	7.6	8.0	10.1	12.8	9.8
Subcutaneous heparin	35.9	34.5	56.3	52.9	60.6	59.7	59.9	63.4
Subcutaneous LMWH	3.0	4.4	4.5	5.9	5.2	5.8	5.9	7.3
Warfarin	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
Others	0.3	0.3	0.6	0.3	0.8	0.4	0.5	0.5

LMWH = low molecular weight heparin.
Mantel–Haenszel estimated odds ratio for albumin versus saline for each 1 day increase in study duration, controlling for anticoagulation type, odds ratio (OR) = 0.99 (95% CI, 0.93–1.05). Approximate test of homogeneity of ORs: $\chi^2_5 = 2.74$, $P = 0.74$.

the others being volume of study fluid administered, medical versus surgical postoperative patient status and, as expected, baseline APTT.

Although the mean effect on APTT was relatively small, some clinicians might consider it clinically relevant. For example, some authors recently suggested that the worse outcome seen in the SAFE trial for patients with traumatic brain injury treated with albumin resuscitation[3,4] might result from a differential effect of fluids on coagulation.[5] Whether such concerns are justified cannot be answered by our study.

It has been suggested that fluid resuscitation-related coagulopathy is caused by dilution of coagulation factors.[6,7,10,11] Our findings provide some support for this attractive but likely over-simplistic notion. Adjusted for albumin use, greater volumes of study fluid were indeed independently related to increases in APTT from baseline to Day 2, supporting the concept that haemodilution played a part in our findings. Notably, however, the INR and platelet count changes observed in this study did not differ greatly between the trial fluid groups. Therefore, a dilution-related effect of fluid, although a significant independent factor, does not seem to fully explain the totality of findings. A

Table 4. Blood product administration on Day 1

	No. of	Volume (mL)	
Blood product	patients (%)	Median (IQR)	Range
Red cells			
Total	59 (9%)	500 (300–750)	47–2450
Albumin	29 (9%)	600 (300–750)	47–2450
Saline	30 (9%)	450 (250–600)	50–2400
P	1.0*	0.39†	
Fresh frozen plasma			
Total	33 (5%)	750 (300–1100)	150–2100
Albumin	17 (5%)	800 (450–1100)	300–1750
Saline	16 (5%)	660 (300–1050)	150–2100
P	0.86*	0.40†	
Platelets			
Total	8 (1%)	295 (175–600)	144–750
Albumin	5 (1%)	240 (150–350)	144–700
Saline	3 (1%)	500 (200–750)	200–750
P	0.50*	0.30†	

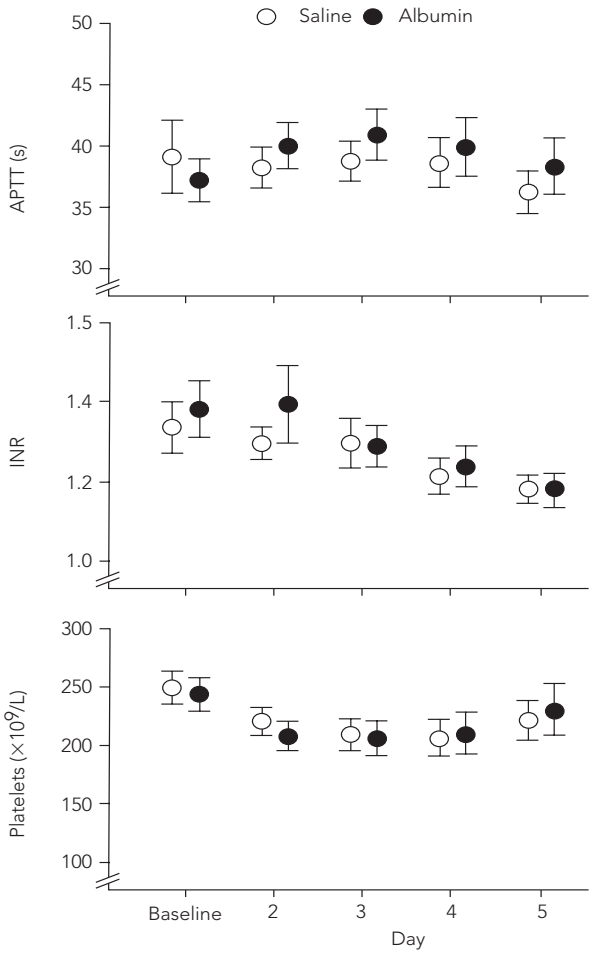
IQR = interquartile range. * Fisher exact test.
† Two-sample Wilcoxon rank-sum (Mann–Whitney) test.

specific, colloid-induced coagulopathy has also been suggested by some investigators,[6,8,13-17] and the current study may be seen to provide evidence of an albumin-induced change in APTT, independent of the effect of dilutional volume.

This study has both strengths and limitations. Strengths include the double-blind design, multicentre nature, relatively large number of patients, and the fact that it is by far the largest prospective controlled study of the effect of fluids on coagulation tests ever conducted. However, as with all substudies that use data from previous randomised trials, the findings may be caused by chance, even though the investigation was pre-specified. Nevertheless, this seems unlikely as the results were confirmed on multivariable analysis. Secondly, this investigation was not designed to have high power to detect changes in important clinical outcomes such as mortality. Accordingly, the clinical relevance of our findings is currently unresolved. However, the large SAFE trial of 6997 patients has already addressed this issue. Thirdly, we failed to recruit the planned number of randomised participants at our three substudy hospitals, reducing the power to identify statistically significant small changes in results, such as those observed with INR and platelet count. Nonetheless, an effect on APTT emerged, and the independent impact of fluid volume was also detected. Fourthly, we did not control the prescription of anticoagulation regimens or administration of blood products, providing another reason for caution in extrapolating our findings to a more general colloid effect on coagulation tests in resuscitation practice. However, after adjustment for anticoagulant therapy, the findings persisted. Finally, we did not measure the number of bleeding episodes, amount of blood loss, or need for surgery secondary to bleeding.

In conclusion, we conducted a pre-planned substudy within a large double-blind, randomised controlled trial

Figure 1. Coagulation results and platelet counts over time according to fluid type (mean and 95% confidence intervals)



APTT = activated partial thromboplastin time.
INR = international normalised ratio.

Table 5. Analysis of covariance for change in activated partial thromboplastin time from baseline to Day 2*

Variable	Reference	Coefficient	95% CI	*P*
Albumin	Saline	3.31	0.78 to 5.8	0.01
APTT baseline	Per second	–0.77	–0.03 to 0.12	< 0.001
Age (years)	Per year	0.05	–0.03 to 0.12	0.20
Male	Female	–0.12	–2.7 to 2.4	0.93
APACHE II score	Per unit	–0.05	–0.22 to 0.12	0.53
Study fluid volume Day 1	Per litre	1.4	0.16 to 2.6	0.03
FFP received	None	1.7	–4.2 to 7.6	0.57
Postoperative	No	–6.0	–8.8 to –3.4	< 0.001
Any anticoagulation	No	0.76	–1.8 to 3.3	0.56
Sepsis	No	0.66	–2.4 to 3.7	0.67
Traumatic brain injury	No	6.0	–4.1 to 16	0.24

APACHE II = Acute Physiology and Chronic Health Evaluation. FFP = fresh frozen plasma. * $n = 501$, model $R^2 = 0.589$.

Box 1. The Saline versus Albumin Fluid Evaluation Study Investigators

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comparing fluid resuscitation with albumin or saline. This found that albumin resuscitation was associated with prolongation of APTT during the period of greatest resuscitation, and that the volume of fluids was also an important determinant of changes in APTT. Although the observed difference in APTT was small and thus of questionable clinical importance, this investigation provides evidence of a differential effect of choice of fluid and an independent effect of the amount of fluid on at least one routine measure of blood coagulation. Appreciation of this possibility and its magnitude may help physicians assess changes in APTT in critically ill patients receiving fluid resuscitation.

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