Effect of Albumin in Combination With Mannitol on Whole-blood Coagulation In Vitro Assessed by Thromboelastometry

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Background: Albumin and mannitol may interfere with hemostasis, but their coinfluence is unclear. We aimed to determine the effects of albumin alone and in combination with mannitol or Ringer acetate (RAC) on hemostasis in crossover in vitro study.

Materials and Methods: From citrated fresh whole blood withdrawn from 10 volunteers, we prepared 2.5, 5, 10, 15, and 20 vol% dilutions of 4% albumin (Alb group). Each sample was thereafter diluted by 15% mannitol (Alb/Man group) or RAC (Alb/RAC group) at a ratio of 9:1. Using thromboelastometry, FibTEM (fibrinogen ROTEM) and ExTEM (extrinsic ROTEM) tests were performed.

Results: A 20 vol%, but not 2.5 to 15 vol% dilution of albumin caused a prolonged clot formation time, α-angle decrease, and maximum clot firmness (MCF) weakening compared with undiluted sample ($P < 0.05$). Clot formation time prolonged more in Alb5/Man than in Alb5 and Alb5/RAC dilution ($P < 0.05$). In Alb2.5/Man, Alb10/Man, and Alb15/Man, dilution α-angle was lower than in corresponding Alb/RAC and Alb-group dilutions ($P < 0.05$). In ExTEM, MCF decreased similarly in every dilution of Alb/Man and Alb/RAC compared with Alb group ($P < 0.05$). In FibTEM, MCF decreased more in Alb10/Man than in Alb10/RAC dilution ($P < 0.05$).

Conclusions: In up to 15 vol% dilutions, albumin alone did not impair hemostasis in vitro, but in combination with mannitol or RAC coagulation was disturbed similarly at most concentrations. There was some significant additional effect with mannitol at certain concentrations. Our results indicate that coadministration of mannitol and albumin needs further study in vivo.

Key Words: albumin, mannitol, Ringer acetate, RAC, thromboelastometry, TEG, neurosurgery, neuroanesthesiology, blood coagulation

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Even a slightest disturbance in hemostasis can lead to catastrophic consequences in patients undergoing neurosurgery. Although mannitol is a solution being infused daily to decrease intracranial pressure and improve surgical conditions during craniotomy, only few studies have evaluated the effect of mannitol on blood coagulation.[1–6] In vitro mannitol seems to interfere with blood coagulation by reducing clot strength at 10 and 20 vol% dilutions,[2] which is possibly a result from poor fibrin clot formation.[3] Data from animal studies have also shown that mannitol impairs coagulation in vitro in a dose-dependent manner.[5] Results from 1 in vivo study, however, indicated that the use of 5 mL/kg of 20% mannitol during elective craniotomy seems to be safe in terms of hemostasis.[6]

Although crystalloids remain the first-line choice of maintenance fluid, in severely hypovolemic patients colloids are still often preferred to achieve hemodynamic stabilization faster and in a more volume-efficient way.[7,8] Compared with other colloids, albumin has been thought to have little effect on hemostasis[9–15] and there are even some data about its hypercoagulational effects at lower hemodilution levels.[10,16–18] Therefore, albumin could be used as an alternative colloid for rapid intravascular volume replacement and thereby maintaining adequate tissue perfusion pressure in most neurosurgical patients. However, because of increased mortality it should be avoided in patients with traumatic brain injury.[19,20]

Both albumin and mannitol may interfere with blood coagulation, but their coinfluence on hemostatic parameters has so far not been demonstrated in controlled situations. As normal hemostasis is essential in neurosurgery, it is relevant to investigate the coeffects of these 2 solutions. Therefore, in this crossover in vitro study we aimed to determine whether albumin alone or in combination with

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mannitol impairs blood coagulation and if this coeffect is enhanced at higher hemodilution levels.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care in the Hospital District of Helsinki and Uusimaa (no. 57/130300/2014). Written informed consent was obtained from every participant. We included 10 volunteers, who first answered the recruitment email that was sent to mailing lists of medical students in the University of Helsinki. All apparently healthy, nonsmoking volunteers were included in the study. No medication was allowed for 5 days before blood sampling. Fasting of 6 hours was required before blood sampling. Blood sampling and analyzing was performed at the Department of Anesthesia in Helsinki University Hospital.

The test solutions were 4% albumin (Albuman, 40 g/L; Sanquin, Amsterdam, The Netherlands), 15% mannitol (Mannitol Braun, 150 mg/mL; Braun, Melsungen, Germany), and RAC (Ringer acetate Baxter Viaflo; Baxter Medical AB, Kista, Sweden) as a control solution. The main study groups were Alb, Alb/Man, and Alb/RAC, respectively.

Venous blood (40 mL) was drawn via a 20 G needle with a minimal stasis from the antecubital vein directly into vacuum polypropylene tubes (BD Vacutainer, Heidelberg, Germany) containing 3.2% buffered citrate. Immediately after sampling, blood was diluted first with albumin-only to make 2.5, 5, 10, 15, and 20 vol% end concentrations of the solution. Each dilution and the undiluted blood sample was then diluted by mannitol or RAC at a ratio of 9:1 (an additional 10 vol% dilution, Table 1), mimicking the clinical setting, where mannitol is normally infused 1 g/kg (500 mL of 15% mannitol for 75 kg person). Dilutions with similar end concentrations were:

(1) Alb10, Man, and RAC (10 vol%),
(2) Alb2.5/Man and Alb2.5/RAC (12.5 vol%),
(3) Alb15, Alb5/Man, and Alb5/RAC (15 vol%),
(4) Alb20, Alb10/Man, and Alb10/RAC (20 vol%),
(5) Alb15/Man and Alb15/RAC (25 vol%),
(6) Alb20/Man and Alb20/RAC (30 vol%).

An undiluted blood sample was used as a control.

The diluted blood and undiluted control samples were analyzed with 2 rotational thromboelastometry devices (ROTEM-Delta; TEM International GmbH, Munich, Germany) using tissue factor activator with (FibTEM; Tem Innovations GmBH, Munich Germany) or without cytochalasin D (ExTEM; Tem Innovations GmBH). Samples were analyzed within 4 hours after blood withdrawal. Coagulation was allowed to proceed for at least 30 minutes. Technical details and reference values[21,22] of ROTEM coagulation tests are shown in Figure 1. Automatically measured ROTEM parameters of blood coagulation were clotting time (CT), clot formation time (CFT), alpha-angle (α-angle) with ExTEM, and maximum clot firmness (MCF) with ExTEM and FibTEM. After initializing ROTEM, hemoglobin (Hb) concentration, hematocrit (Hct) value, and platelet count (Pc) were determined in all whole-blood samples using a Sysmex KX-21 Haematology Analyser (Sysmex Corporation, Japan).

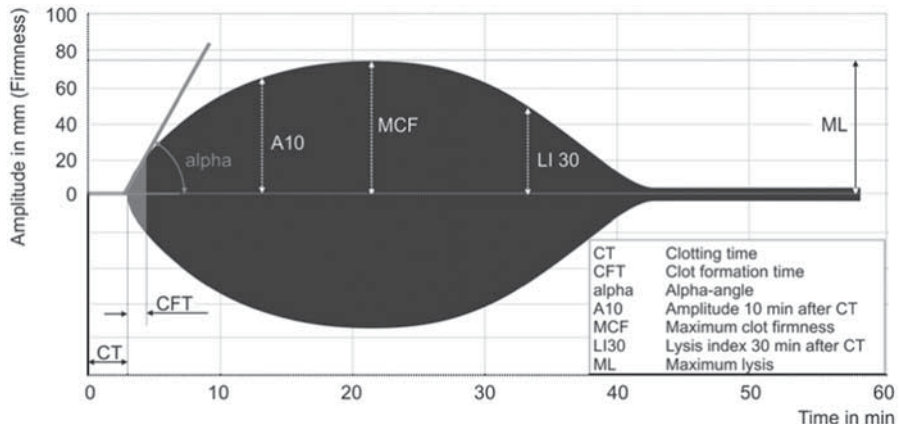
Statistics

The number of volunteers was based on earlier data regarding various in vitro colloid hemodilution studies.[2,3,10] Normality of data sets was assessed with Shapiro-Wilk tests and by examining graphically Q-Q plots. The differences between the study groups and dilutions were analyzed with the nonparametric repeated measures analysis of variance test (Friedman ANOVA). For paired comparisons and post hoc analysis, Wilcoxon signed-rank test was used with the Bonferroni correction applied whenever there were >2 comparisons within group. A $P < 0.05$ was considered statistically significant.

TABLE 1. Composition of Dilutions

Group Name	Dilution Name	Blood (mL)	Alb (mL)	Man (mL)	RAC (mL)
	Control	1	—	—	—
Alb	Alb2.5	3.9	0.1	—	—
	Alb5	3.8	0.2	—	—
	Alb10	3.6	0.4	—	—
	Alb15	3.4	0.6	—	—
	Alb20	3.2	0.8	—	—
Alb/Man	Alb2.5/Man	0.9 of Alb2.5	—	0.1	—
	Alb5/Man	0.9 of Alb5	—	0.1	—
	Alb10/Man	0.9 of Alb10	—	0.1	—
	Alb15/Man	0.9 of Alb15	—	0.1	—
	Alb20/Man	0.9 of Alb20	—	0.1	—
	Man	0.9	—	0.1	—
Alb/RAC	Alb2.5/RAC	0.9 of Alb2.5	—	—	0.1
	Alb5/RAC	0.9 of Alb5	—	—	0.1
	Alb10/RAC	0.9 of Alb10	—	—	0.1
	Alb15/RAC	0.9 of Alb15	—	—	0.1
	Alb20//RAC	0.9 of Alb20	—	—	0.1
	RAC	0.9	—	—	0.1

Alb indicates albumin; Man, mannitol; RAC, Ringer acetate.



Normal values	MCF, mm	CT, sec	CFT, sec	α-angle, °
ExTEM®	49-71	42-74	46-148	63-81
FibTEM®	9-25			

FIGURE 1. ROTEM parameters and normal values. Clotting time reflects the time from the start of the measurement until the start of clot formation, describing the rate of fibrin formation at the beginning. Clot formation rate refers to the time from the beginning of clot formation until a clot firmness of 20 mm has been reached, indicating how fast the clot structure is forming. α-angle is the angle between the central-line and the tangent of the curve at the amplitude point of 2 mm, for example, clot formation rate, denoting the rate of the formation of a solid clot. Maximum clot firmness describes the strength of the clot and thus depends on platelet count, platelet function, and fibrinogen concentration.

Results are shown as medians with 25th/75th percentiles and percentage of undiluted value (for ROTEM parameters only). All statistical calculations were carried out using the Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL) and graphs were created with GraphPad Prism version 7.0b (GraphPad Software, La Jolla, CA).

With hemodilutional data (Hb, Hct, and Pc), we conducted comparisons between:
(1) Diluted and undiluted samples,
(2) Groups with similar dilutions.

With ROTEM parameters (CT, CFT, α-angle, and MCF) we conducted comparisons between:
(1) Diluted and undiluted samples,
(2) Alb10, Man, and RAC dilutions,
(3) Main study groups, that is, dilutions with the same level of albumin vol% dilution (eg, Alb2.5, Alb2.5/Man, and Alb2.5/RAC, etc.), all together 5 different comparison levels (2.5%, 5%, 10%, 15%, and 20%),
(4) The relative changes within Alb/Man group seen after adding mannitol to Alb group dilutions.

RESULTS

Four male and 6 female volunteers aged 22 to 29 years participated in the study. Six (1 in EXTEM and 5 in FIBTEM) of the ROTEM tracings (1.7% of all the tracings) were technically unsuccessful and excluded from the final analysis. The dilutional effect on Hb, Hct, and Pc is shown in Table 2. All study solutions at all levels of hemodilution induced a decrease in Hb, Hct, and Pc compared with the undiluted sample ($P < 0.05$). Hb, Hct, and Pc did not differ, on average, between various dilutions with similar end concentrations.

CT in ExTEM Analysis

CT was prolonged only in Alb15/Man dilution ($P < 0.05$), whereas remaining dilutions did not differ from control sample. On an average, CT showed difference neither between study groups nor within Alb/Man group. However, CT was longer in Man and Alb2.5/Man than in RAC and Alb2.5/RAC dilution ($P < 0.05$).

TABLE 2. Hemodilution Data

Dilution Name	Hb (g/L)	Hct (%)	Pc (×10 E9/L)
Control	130 (125-133)	38 (36-40)	169 (143-199)
Alb2.5	127 (122-131)*	37 (34-39)*	141 (131-199)
Alb5	124 (119-127)*	36 (34-37)*	131 (124-183)*
Alb10	118 (113-123)*	34 (32-37)*	126 (119-181)*X
Alb15	111 (107-115)*‘	32 (30-34)*	120 (112-162)*’
Alb20	104 (101-107)*	30 (29-32)*	119 (101-149)*
Alb2.5/Man	114 (111-119)*	33 (31-34)*§	96 (25-127)*
Alb5/Man	112 (109-115)*‘	32 (30-34)*”	90 (26-128)*’
Alb10/Man	106 (102-111)*”	31 (29-32)*	83 (18-104)*“
Alb15/Man	99 (96-104)*	28 (27-30)*~	76 (11-94)*
Alb20/Man	93 (91-99)*	27 (26-29)*#	68 (8-83)*
Man	118 (111-122)*	34 (31-36)*	95 (23-143)*
Alb2.5/RAC	115 (112-118)*	33 (32-34)*	78 (33-95)*
Alb5/RAC	112 (110-116)*	32 (31-34)*	64 (12-99)*
Alb10/RAC	104 (103-111)*	30 (29-32)*	42 (16-92)*“
Alb15/RAC	100 (98-105)*	29 (28-31)*	60 (21-71)*
Alb20/RAC	95 (91-99)*	28 (26-29)*	35 (19-63)*
RAC	117 (113-121)*	34 (32-36)*	92 (19-102)*

Medians (25th/75th percentiles) of Hb, Hct, and Pc are shown.
Alb indicates albumin; Hb, hemoglobin concentration; Hct, hematocrit value; Man, mannitol; Pc, platelet count; RAC, Ringer acetate.
*$P < 0.05$ compared with the undiluted sample.
‘$P < 0.05$ (Bonferroni correction applied) in comparison with Alb5/RAC.
$^{X}P < 0.05$ (Bonferroni correction applied) in comparison with RAC.
“$P < 0.05$ (Bonferroni correction applied) in comparison with Alb20.
§$P < 0.05$ in comparison with Alb2.5/RAC.
~$P < 0.05$ in comparison with Alb15/RAC.
#$P < 0.05$ in comparison with Alb20/RAC.

CFT in ExTEM Analysis

In Alb group, CFT was prolonged only at 20 vol% dilutions compared with undiluted sample ($P < 0.05$), but all values remained within normal range (Fig. 2). An albumin dilution of 2.5 vol% caused CFT shortening in comparison with undiluted sample ($P < 0.05$). A dilution of 10 vol% with mannitol caused greater CFT delay than RAC ($P < 0.05$), whereas albumin had no effect at this dilution level.

Comparing a combination of solutions, CFT was more prolonged in Alb5/Man dilution than in Alb5/RAC ($P < 0.05$). In the remaining dilutions of Alb/Man group (Alb2.5/Man, Alb10/Man, Alb15/Man, and Alb20/Man), CFT was also prolonged compared with undiluted sample and corresponding Alb group dilutions (Alb2.5, Alb10, Alb15, and Alb20, respectively; $P < 0.05$), but it was comparable with the changes seen in similar dilutions in Alb/RAC group ($P > 0.05$). Within Alb/Man group, the relative CFT prolonging compared with Alb group was similar between different dilution levels ($P > 0.05$).

α-Angle in ExTEM Analysis

Compared with undiluted sample, α-angle decreased significantly in all dilutions of Alb/Man and Alb/RAC

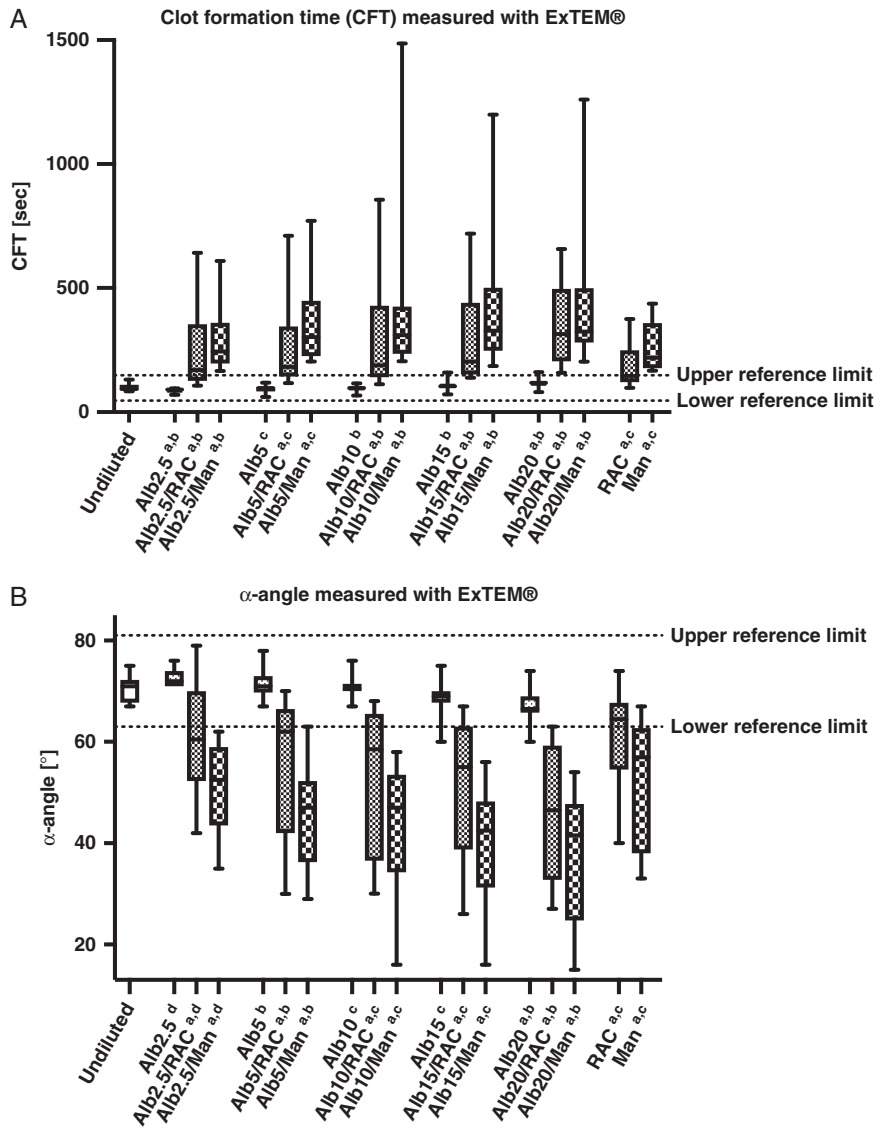


FIGURE 2. Box plot (minimum, 25th percentile; median, 75th percentile, maximum) values of clot formation time (A) and α-angle (B), measured with ExTEM. $P < 0.05$ compared with the undiluted sample (a); $P < 0.05$ (Bonferroni correction applied) between Alb and Alb/Man as well as Alb and Alb/RAC groups but not between Alb/Man and Alb/RAC groups within same level of albumin vol% dilution (b); $P < 0.05$ (Bonferroni correction applied) between all groups (Alb, Alb/Man and Alb/RAC) within same level of albumin vol% dilution or between Alb10, Man and RAC dilutions (c); $P < 0.05$ (Bonferroni correction applied) between Alb and Alb/Man as well as Alb/Man and Alb/RAC groups but not between Alb and Alb/RAC groups within same level of albumin vol% dilution (d).

groups, but in Alb-only group at 20 vol% dilution ($P < 0.05$, Fig. 2). At 10 vol% dilution there were similar differences in α-angle decrease (as the ones seen with CFT) between Alb10, Man, and RAC dilutions—mannitol decreased α-angle the most, RAC less ($P < 0.05$), and albumin had no effect.

α-angle was lower in Alb2.5/Man, Alb10/Man, and Alb15/Man dilution than in corresponding Alb/RAC and Alb group dilutions ($P < 0.05$; Fig. 2). In Alb/Man group, relative changes of α-angle caused by adding mannitol to each albumin dilution were not more enhanced at higher dilution levels ($P > 0.05$).

MCF in ExTEM and FibTEM Analysis

In ExTEM analysis, albumin induced MCF weakening compared with control from 10 vol% hemodilution ($P < 0.05$), although all values remained within the normal range (Fig. 3). In FibTEM analysis, albumin caused significant MCF decrease only at 20 vol% dilution compared with undiluted sample ($P < 0.05$). At 10 vol%

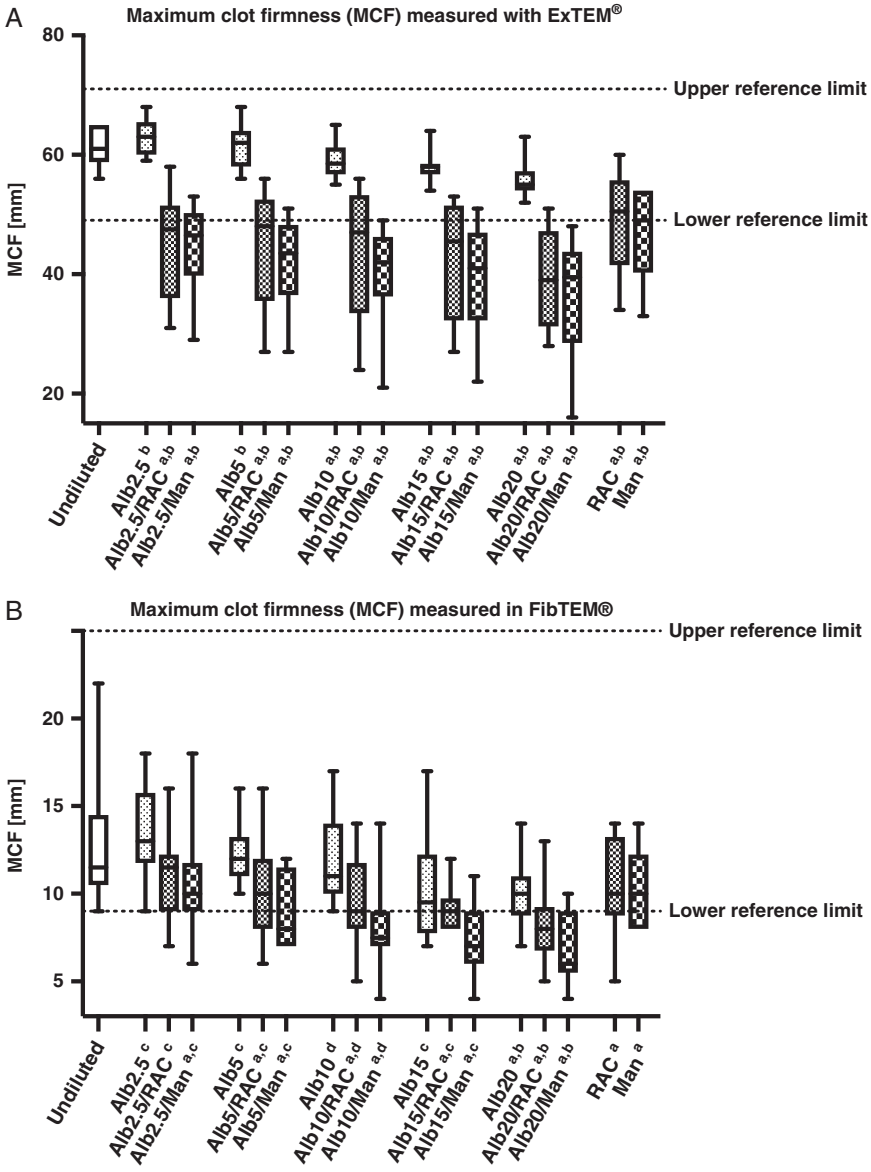


FIGURE 3. Box plot (minimum, 25th percentile; median, 75th percentile, maximum) values of maximum clot firmness (MCF), measured with ExTEM (A) and FibTEM (B) tests. $P < 0.05$ compared with the undiluted sample (a); $P < 0.05$ (Bonferroni correction applied) between Alb and Alb/Man as well as Alb and Alb/RAC groups but not between Alb/Man and Alb/RAC groups within same level of albumin vol% dilution or between Alb10 and Man as well as Alb10 and RAC dilution but not between Man and RAC dilution (b); $P < 0.05$ (Bonferroni correction applied) between Alb and Alb/Man groups but not between Alb and Alb/RAC nor Alb/Man and Alb/RAC groups within same level of albumin vol% dilution (c); $P < 0.05$ (Bonferroni correction applied) between all groups (Alb, Alb/Man and Alb/RAC) within same level of albumin vol% dilution (d).

dilution of mannitol or RAC, MCF decrease measured by ExTEM analysis was comparable between those solutions ($P > 0.05$), but both solutions caused greater MCF decrease than albumin did ($P < 0.05$). In FibTEM analysis, there was no difference between Alb10, Man, and RAC.

In ExTEM analysis, MCF decreased more in every dilution of Alb/Man and Alb/RAC compared with Alb group ($P < 0.05$), but mannitol did not decrease MCF more than RAC did at any dilution level ($P > 0.05$). However, in FibTEM analysis MCF decrease was more pronounced in Alb10/Man than in Alb10/RAC dilution ($P < 0.05$). In Alb/Man group, relative MCF weakening (measured by both, ExTEM and FibTEM) compared with Alb was similar between different dilution levels ($P > 0.05$).

DISCUSSION

The major findings of this in vitro study were: (i) the combination of albumin and mannitol impaired hemostasis slightly more than the combination of albumin and RAC solution; but (ii) this effect was not enhanced at a greater hemodilution level; (iii) hemodilution with 20 vol% of albumin, but not with 2.5 to 15 vol%, resulted in marginal disturbance of blood coagulation; and (iv) 10 vol% hemodilution with albumin had the least and mannitol the most negative effects on hemostasis.

Comparing 3 study solutions at 10 vol% dilution, mannitol had the most deleterious effect on hemostasis parameters—CFT prolonged > 2-fold compared with undiluted sample (unchanged and 1.5-fold with albumin and RAC, respectively). α-angle decreased also with mannitol and RAC, but the changes were not as pronounced as in CFT. The differences between mannitol and RAC after 10 vol% hemodilution were comparable with previous in vitro findings of mannitol and 0.9% saline.[3] However, 1 randomized prospective double blind clinical study on elective craniotomy patients concluded that neither mannitol nor hypertonic saline induced coagulation impairment measured by ROTEM and standard coagulation tests, although there was a slight increase in CFT measured in ExTEM and decrease in fibrinogen level (with values remaining in normal range). However, the authors concluded that, although the administration of hypertonic solutions reduced the levels of platelets and fibrinogen significantly, because of a dilutional effect, it was not enough to reduce MCF.[6] Another clinical study reported that CFT altered significantly from baseline after administration of mannitol alone as well as in combination with hydroxyethyl starch (HES) and MCF measured with FIBTEM did not change from baseline, but differed significantly between groups.[23] Nevertheless, as all ROTEM values remained within normal range, the authors also concluded that mannitol and HES can be safely administered in patients undergoing craniotomy for supratentorial tumors. These were both single-center studies, including 30 to 40 elective craniotomy patients without preexisting coagulopathies, who received 20% mannitol 1 g/kg intraoperatively, resulting in lower dilution than in any of the previous experimental studies. Further clinical studies are, therefore, needed to show whether the lower hemodilution using more concentrated mannitol might be the key to avoid its possible hypocoagulational effect or does mannitol in contrary to in vitro findings really have no impact on hemostasis in vivo.

In the current study, the combination of albumin with mannitol compromised coagulation more than the combination of albumin with RAC. This observation supports the idea that detrimental effects of mannitol on hemostasis in vitro seem to have other than pure dilutional mechanism.[2,3] This was particularly seen at some hemodilution levels, where albumin combined with mannitol caused greater coagulation abnormalities than combined with RAC, as seen by longer CFT and lower α-angle in ExTEM and weaker MCF in FibTEM. The dilutional effect of mannitol on coagulation has also been demonstrated in a previous study without a control group, where mannitol seemed to disturb clotting mainly by overall clot formation and strength but also by pure fibrin clot firmness at 20 vol% hemodilution.[3] Moreover, comparison of the 3 study solutions' effects in vitro also revealed that mannitol alone caused more impairment in hemostasis than other solutions.

Our observations on the coeffects of mannitol and albumin as a colloid are consistent with the results of a similar earlier in vitro study, which determined the effect of mannitol with HES or RAC on blood coagulation.[2] It was shown that 10 vol% and 20 vol% hemodilution in vitro with mannitol in combination with HES impaired whole-blood coagulation more than mannitol in combination with RAC. The impairment in coagulation was seen by delayed initiation of coagulation and fibrin formation and decreased MCF in FibTEM, similar to the findings of this study. The combination of mannitol and colloid (albumin or HES) decreased clot firmness measured with ExTEM compared with undiluted samples in both studies, but Lindroos and colleagues showed that MCF in 20 vol% dilution of mannitol with HES was lower than MCF in corresponding dilution with RAC, whereas in our study the decrease was comparable after mixing blood with albumin and mannitol or RAC (also at 20 vol% dilution). On the basis of the findings of these 2 studies, CT measured with ExTEM seemed to be unaffected by the combination of mannitol and albumin or HES.

Up to 15 vol% hemodilution in vitro, changes in blood clotting following albumin administration were minimal, as has been also previously shown.[10] The impairment in whole-blood coagulation was more clearly seen in hemodilution of 20 vol% with albumin. However, all median changes in thromboelastometric parameters (MCF, CFT, and α-angle) remained within normal reference range, that is, in standard clinical situations these slightly hypocoagulational effects might be of minor importance. In contrast, these minor changes may nevertheless play an important role in a patient predisposed to coagulopathy, for example, trauma patients with concomitant hemorrhagic shock. Previously it has been shown, that albumin may also cause hypercoagulation,

mainly by shortening CT in low to moderate hemodilutions.[10,16–18] In the present study, slight hemodilution (2.5 and 5 vol%) with albumin showed a minor trend of hypercoagulability (MCF strengthening in both ExTEM and FibTEM, increase in α-angle and shortening of CFT in ExTEM), but these findings were not all statistically significant.

Our study has some limitations, though. First, we did not assess platelet function, which might be decreased after administration of hypertonic solutions, as has been reported previously.[4] Second, we investigated only 10 vol% dilution with mannitol, but there is registered mannitol solutions with various concentration to be used in clinical practice, so, the desired effect could be achieved by different volumes and the dilutional effects of this solution might therefore vary greatly. At last, the most substantial limitation is that in vitro studies lack generalizability to clinical situations. The study was conducted under controlled conditions with whole blood withdrawn from healthy volunteers without preexisting coagulopathies. In vivo, the patient often does not receive albumin alone, but together with crystalloids. Also, as ROTEM measurements are classically performed in the absence of endothelial cells, our in vitro findings do not directly reflect the coagulational effects of investigated solutions in vivo, where endothelium counteracts hemostasis by providing tissue factor, thrombin inhibitors and receptors for protein C activation. Moreover, no fluid redistribution, buffering, or electrolyte homeostasis can happen in vitro. Therefore, the findings of this study cannot be extrapolated directly into clinical practice, but only aim to create a platform for further clinical studies to determine clear in vivo impact of combination of mannitol and albumin on coagulation.

Although current neurotrauma guidelines recommend mannitol for trauma patients with elevated intracranial pressure,[24] hypertonic saline has been shown to be at least as effective[25] or even better[26] than mannitol in reducing brain swelling, and from a hemostatic point of view hypertonic saline might be more suitable than mannitol in neurosurgery or neurointensive care.[3] So, whenever a possible coagulopathy is suspected during craniotomy, the coadministration of albumin and mannitol should be considered cautiously, especially because hypertonic saline seems to be safer alternative to mannitol.

CONCLUSIONS

Up to 15 vol% dilution, albumin caused in vitro marginal disturbances in ROTEM parameters. Mannitol in combination with albumin impaired clot propagation and firmness in vitro, but the effect was not enhanced at higher hemodilution levels. The detected detrimental effects of mannitol on coagulation seem to be mostly a dilutional consequence. Our observations may indicate that the simultaneous administration of mannitol and albumin might increase the risk of bleeding and should therefore be studied further in clinical settings.

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