Fast Versus Slow Infusion of 20% Albumin: A Randomized Controlled Cross-over Trial in Volunteers

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Abstract

Background

We studied whether plasma volume expansion of 20% albumin is greater when the fluid is administered rapidly compared with a slow infusion.

Methods

In this open-labelled interventional controlled trial, 12 volunteers (mean age, 28 years) received 3 mL/kg of 20% albumin (approximately 225 mL) over 30 min (fast) and 120 min (slow) in a cross-over fashion. Blood and urine were collected at 15 occasions during a period of 6 h. Mass balance and volume kinetics were used to study the plasma volume expansion and the capillary leakage of albumin and fluid based on measurements of hemoglobin and plasma albumin.

Results

The largest plasma volume expansion was 16.1% ± 6.5% (mean ± SD) during fast infusion and 12.8% ± 4.0% for slow infusion ($p = 0.52$).

The median intravascular half-life of albumin was 8.0 h for fast infusion and 6.3 h for slow infusion ($p < 0.03$) whereas the half-life of the plasma volume expansion did not differ significantly (4.6 *versus* 5.4 h, $p = 0.50$).

The urinary excretion was almost three times larger than the infused volume. The plasma concentration of atrial natriuretic peptide (MR-proANP) increased by 25% in both groups, and the absolute MR-proANP concentration was found to accelerateboth the capillary leakage of albumin and the urine flow.

Conclusions: The intravascular persistence of albumin was longer, but the fluid kinetics was the same when 20% albumin was infused over 30 min compared with 120 min. We found no disadvantages of administering the albumin at the higher rate.

Trial registration:

EU Clinical Trials Register, EudraCT2017-003687-12, registered September 22, 2017, https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003687-12/SE

Background

Albumin has become the colloid fluid of choice in the intensive-care setting. Albumin has a larger and longer-lasting plasma-volume expansion effect than is observed with crystalloid fluid [1–4]. This characteristic is determined by the osmolality and colloid osmotic pressure of the fluid, as well as by the elimination mechanisms.

The rate of infusion may also be important for clinical efficacy. Statkevicius et al recently compared 5% albumin administered over 30 min and 180 min during surgery and found that the rapid infusion was more effective [5]. The situation is still unclear for 20% albumin, which exerts a pronounced volume effect [6, 7]. As 20% has a high oncotic pressure, there is concern that oncotic-driven recruitment of extravascular fluid makes the plasma volume expansion greatly dependent on the rate of infusion. On the other hand, hormonal adjustment might counteract such fluid overload. For example, a fast infusion might stimulate release of atrial natriuretic peptide (ANP) from the heart, which increases capillary permeability and urinary excretion [8].

The primary objective of the present study was to compare the plasma dilution, which mirrors the plasma volume expansion, when 20% albumin is infused at different rates in volunteers. The secondary objective was to investigate the strength of the oncotic-driven recruitment of extravascular fluid that prolongs the intravascular persistence of the infused fluid volume.

Our hypothesis was that a fast infusion expands the plasma volume more effectively. We also hypothesized that recruitment of fluid from the extravascular space markedly prolongs the intravascular half-life of the fluid. The study methods consisted of mass balance calculations and volume kinetic analysis of the albumin and fluid components of 20% albumin. We measured the mid-regional pro-atrial natriuretic peptide (MR-proANP) to control for the role of ANP in this setting. The results should have clinical applicability, as the kinetics of 20% albumin is quite similar in volunteers as in clinical patients with and without trauma-induced inflammation [7, 9].

Materials And Methods

This study is an open-labeled interventional controlled trial with a cross-over design where 12 healthy participants (six male and six female) underwent two infusion experiments, 3–20 weeks apart, where they received 3 mL/kg of 20% albumin by intravenous infusion during either 30 min (“fast infusion”) or 120 min (“slow infusion”).

All participants gave informed consent orally and in writing. Inclusion criteria were an age between 18 and 60 years, and absence of medical disease and medication. Exclusion criteria were pregnancy, difficulties with placement of venous cannulas, and severe allergy.

Procedure

A statistician prepared 12 envelopes for randomization of the participants to start with either the slow or the fast infusion. The envelopes were opened one day prior to the first infusion. All participants fasted from midnight before the study and throughout the study period. However, they were allowed to drink 2 dL of liquid and eat one sandwich 1.5 hours (h) prior to arriving at the research faculty at the hospital.

A venous cannula was placed in the right arm and another in the left for blood sampling and fluid infusion, respectively. The participants emptied their bladders 30 min before the study started and were

then placed in a supine position until the end of the experiment. Baseline samples were withdrawn, and the participants then received the infusion. Blood was sampled on 15 occasions over a period of 6 h.

When albumin was administered over 30 min, the excreted urine was measured and sampled just before the infusion started, at 30 min after the infusion ended, and at 6 h. When albumin was administered over 120 min, the excreted urine was measured and sampled just before and at the end of the infusion, and at 6 h.

Blood and urine analyses

Whole blood was analyzed for hemoglobin (Hgb) concentration and hematocrit with a coefficient of variation (CV) of 1.0%, as given by duplicate samples at baseline, using a Cell-Dyn Sapphire instrument (Abbott Diagnostics, Abbott Park, IL). Plasma was analyzed for albumin, creatinine, sodium, and potassium on a Cobas 8000 system (Roche Diagnostics, Basel, Switzerland) at the hospital's certified central laboratory (CVs were 2.3%, 1.9%, 0.7%, and 1%, respectively, as given by the laboratory).

The plasma colloid osmotic pressure (COP) was measured in our research laboratory on an Osmomat 050 device (Gonotec, Berlin, Germany) with a CV of 2%.

The plasma concentration of the mid-regional pro-atrial natriuretic peptide (MR-proANP) at baseline and 30 min after the infusion ended was analyzed by radioimmunoassay (Brahms MR-proANP Kryptor, Henningsdorf, Germany) with a CV of > 3.5%. The manufacturer reports a median value in healthy humans of 46 pmol/L.

Urine was analyzed for creatinine on the Cobas 8000 system with a CV of 1.9%.

Mass balance

The baseline plasma volume (PV_o) was estimated from the height and weight of the participants, as suggested by Nadler *et al* [10]. The PV change to a any later Time t of the experiment (PV_t) was calculated based on the hemodilution curve, with correction for sampled blood volume, as described previously [6].

The albumin mass was taken as the product of the plasma volume (PV) and the plasma albumin concentration (P-Alb). Multiplication with PV is necessary because P-Alb is diluted by the infused fluid volume and also by the oncotic-driven recruitment of extravascular fluid, which gives an unbalanced relationship between P-Alb and the intravascular albumin mass.

Capillary leakage. The capillary leakage of albumin was obtained as the change in albumin mass, with correction for the infused amount of albumin, between baseline (time 0) and a later time t [7]. The following equation was used:

Albumin leakage = Infused albumin + (PV_o x $P\text{-}Alb_o$) – (PV_t x $P\text{-}Alb_t$)

Half-life. The half-life of the infused albumin was obtained from the logarithm of the slope of the albumin mass, given as [(1 + PV_{dil}) P-Alb_t – P-Alb_o] *versus* time, when an apparent first-order elimination had been established post-infusion [7]. For each experiment, the half-life of the decay of the PV expansion was estimated in the same way for the albumin mass.

Albumin and fluid kinetics

A one-compartment model was used to study the kinetics of the infused albumin mass throughout the entire experiment. In this model, albumin mixed in fluid was infused at a rate R_o into a central body fluid space V_c, which was then expanded to v_c. The capillary leakage was given by the rate constant k_b. The dependent variable was the product of the increase in measured P-Alb and the plasma dilution; the latter was given by ((Hgb_o / Hgb_t) – 1) / (1 – $hematocrit_o$), where the subscript o denotes the baseline and *t* a later time. Minor correction of the plasma dilution for blood sampling was made [6].

The kinetics of the infused fluid volume was evaluated using a model with micro-constants that is developed for studies of 20% albumin [11]. This model has one infusion, one absorption route, and two elimination routes and was fitted to the plasma dilution and the urinary excretion, which served as the dependent variables.

Absorption occurred from an extravascular source, which is likely to be the interstitial fluid space, by (supposedly) oncotic forces and at a rate that was determined by a constant denoted k_{21}. The interstitial fluid volume at baseline (ICF_o) was assumed to contain fluid accounting for 15% of the body weight [12].

Fluid volume was eliminated by urinary excretion (k_{10}) and capillary leakage (k_b).

This “base model” was expressed by the following differential equations:

$$dv_c/dt = R_o - k_b\,(v_c - V_c) - k_{10}\,(v_c - V_c) + k_{21}\,ICF_o$$

$$dICF/dt = -\,k_{21}\,ICF_o;\ dU/dt = k_{10}\,(v_c - V_c)$$

where V_c is the baseline and v_c the expanded central volumes, and U the measured urinary excretion. The rate parameter k_{21} does not come into play before the infusion begins.

The fixed parameters in the albumin model (V_c and k_b for albumin) were estimated simultaneously for all 24 experiments using the First Order Conditional Estimation Extended Least-Squares (FOCE ELS) search routine in the Phoenix software for nonlinear mixed effects (NLME), version 8.2 (Pharsight, St. Louis, MO) and the additive model for the within-subject variability. The dependent variable was P-Alb corrected for plasma dilution.

The fixed parameters in the fluid model (V_c, k_{10}, k_b, and k_{21}) were estimated in the same way. Here, the dependent variables were the frequently measured plasma dilution and the urinary excretion measured at

1 h and 6 h.

Both base models were both refined by adding individual-specific covariates. Eleven potential covariates were examined. Age, body weight, gender, Hgb_0, and urine osmolality and urine creatinine at baseline were entered once for each patient. Plasma creatinine, and MR-proANP were measured twice per experiment and applied at the point in time when measured. Plasma albumin was entered as a time-varying covariate 15 times per experiment (at the same time points as Hgb was measured).

Outcome measures

The primary outcome measure was the plasma dilution, which is an index of plasma volume expansion, following the infusions of hyper-oncotic albumin. Secondary outcome measures were the colloid osmotic pressure and how much the intravascular persistence was prolonged by oncotic-driven recruitment of fluid from of extravascular tissues.

Statistics

Power analysis prior to the study was based on the previously obtained a mean and standard deviation (SD) for the plasma volume expansion of 15.8% ± 4.9% at end of infusing 3 mL/kg of 20% albumin [11]. We aimed at identifying a difference in plasma volume expansion of 20% at the $p < 0.05$ level and with a certainty of 80%. This calculation yielded 22 experiments.

The measured variables were reported as the mean (SD) and, when appropriate, as the median and interquartile range (IQR). Differences between the two infusions were studied, depending on the distribution of the data, by the paired *t* test or Wilcoxon's matched-pair test. $P < 0.05$ was deemed statistically significant.

Kinetic parameters were given as the best estimate and 95% confidence interval (CI). A new parameter (fixed or covariate) was accepted if its 95% CI did not include 0 and the inclusion decreased the − 2 log likelihood (-2 LL) for the model by > 3.8 points ($p < 0.05$).

Results

The participants were studied between February 2018 and November 2018. One participant was excluded due to difficulties with the placement of two venous cannulas before the infusion was administered. This subject was replaced by another volunteer. The finally included volunteers were 28 ± 10 years old, had a body weight of 75 ± 10 kg, and body mass index of 24.2 ± 2.8 kb/m^2. A CONSORT flow diagram is shown in Fig. 1.

The volume of infused 20% albumin amounted to 225 ± 31 mL. Characteristics of the participants and their fluid therapy are presented in Table 1.

Table 1
Demographic and clinical characteristics of the participants in the 20% albumin infusion study. Data are the mean ± SD.

Variable	30 min infusion	120 min infusion	P-value
Mean arterial pressure (mmHg)	92 ± 11	93 ± 10	0.71
0 min	90 ± 15	91 ± 8	0.73
60 min	90 ± 12	91 ± 11	0.71
150 min	94 ± 13	94 ± 10	0.96
360 min	25.0 ± 1.0	25.1 ± 1.4	0.85
Colloid osmotic pressure, 0 min (mmHg)			
AUC Δplasma volume 0-360 min (L min)	103 ± 66	69 ± 47	0.11
Half-life albumin (h)	10.6 ± 5.7	5.9 ± 2.7	0.02
Half-life plasma volume (h)	5.4 ± 2.5	3.3 ± 2.2	0.005
Recruitment of extravascular fluid (mL/mL)	3.1 ± 1.3	2.7 ± 1.3	0.25
Thrombocytes (10^9 /L)			
0 min	201 ± 50	190 ± 37	0.10
360 min	193 ± 46	182 ± 41	0.02
Plasma sodium (mmol/L)			
0 min	141.3 ± 2.0	141.0 ± 1.6	0.61
360 min	142.1 ± 1.7	141.6 ± 1.8	0.36
Potassium (mmol/L)			
0 min	3.9 ± 0.3	3.9 ± 0.2	0.68
360 min	3.9 ± 0.2	3.9 ± 0.2	0.55
Serum creatinine (μmol/L)			
0 min	85 ± 14	85 ± 14	0.94
360 min	78 ± 13	79 ± 14	0.54
Urinary creatinine (mmol/L)			
0 min	15.1 ± 6.3	14.0 ± 4.5	0.30
360 min	9.5 ± 5.9	9.9 ± 4.4	0.82

TABLE 2.

Population kinetic parameters for infused albumin mass in the final model. Shown are the typical values (tv) for the fixed parameters in the group, followed by individual-specific covariates.

Kinetic parameter	Covariate	Covariate model	Best estimate	95% CI	CV%	-2 LL
ALBUMIN KINETICS						
tv V_c (L)			5.89	5.16-6.62	6.3	
tv k_{10} (10^{-4}min^{-4})			8.65	5.86–11.4	16.4	1213
k_{10}	Hgb baseline	Power	-5.50	-6.96 to -4.04	-13.5	1203
V_c	Albumin baseline	Power	4.32	1.60–7.03	31.9	1193
k_{10}	120-min infusion	Exponential	0.40	0.02–0.78	47.8	1187
FLUID KINETICS						
tv Vc (L)			2.09	1.45–2.73	15.6	
tv k_{10} (10^{-3}min^{-1})	-		11.5	8.4–14.5	13.4	
tv k_{21} (10^{-4}min^{-1})	-		3.19	1.49–4.88	27.1	-528
tv k_b (10^{-3}min^{-1})			12.5	3.90–21.0	35.0	-582
k_{21}	Δ Albumin	Linear	0.083	0.057–0.108	16.0	-609
k_{10}	MR-proANP	Power	0.80	0.37–1.23	28.7	-624
k_{10}	U-creatinine, baseline	Exponential	-0.96	-1.80 to –0.11	-45.0	-632

tv = typical value for the group. CI = confidence interval. CV% = coefficient of variation (inter-individual).

Mean blood Hgb at baseline 137 g/L and mean plasma albumin 40.0 g/L.

LL = log likelihood for the model during development. Decrease by >3.8 points = P< 0.05.

Mean MR-proBNP = 49 pmol/L and urine creatinine 10.3 mmol/L.
The measured blood Hgb and plasma albumin concentrations are shown in Fig. 2.

The mean (SD) MR-proANP was 43 ± 12 and 44 ± 17 pmol/L, respectively, before the fast and slow infusions were started. Thirty minutes after they ended, these mean (SD) concentrations had increased to 54 ± 24 and 55 ± 24 pmol/L, respectively. The change was significant by $p < 0.01$.

Mass balance

The largest mean (SD) plasma volume expansion during the fast infusion experiment was 16.1% ± 6.5% and occurred 10 min after the infusion ended. The corresponding maximum value for the slow infusion was 12.8% ± 4.0 ($p = 0.52$), recorded at the end of the infusion (Fig. 3A).

The mean (SD) plasma albumin concentration was 40.0 ± 2.2 g/L at baseline prior to the fast infusion and 40.0 ± 2.0 g/L prior to the slow infusion. These concentrations had increased by 6.6 ± 2.3 g/L and 7.1 ± 2.3 g/L, respectively, at the end of the infusions (p = 0.62; Fig. 3B).

The plasma COP was 25.0 ± 1.2 prior to the fast infusion and 25.1 ± 1.4 prior to the slow infusion. The increase in COP was 2.7 ± 1.5 mmHg at the end of the fast infusion and 3.0 ± 1.1 mmHg after the slow infusion (P = 0.65; Fig. 3C).

At the end of infusion, the fast infusion had increased the plasma volume by twice the administered fluid volume, while the slow infusion had expanded the plasma volume by 1.6 times the infused volume (p = 0.19; Fig. 3D).

At 6 h, the capillary leakage of albumin amounted to 41% ± 16% of the infused amount after the fast infusion and 46% ± 14% after the slow infusion ($p = 0.53$; Fig. 3E).

The intravascular half-life of albumin was longer when 20% albumin was infused fast compared to the slow infusion 8.0 (IQR 5.8 to 11.1) h *versus* 6.3 (IQR 4.5 to 8.3) h, ($p < 0.03$). However, the half-life of the plasma volume expansion did not differ significantly 4.6 (IQR 2.8 to 9.8) h *versus* 5.4 (IQR 2.5 to 9.5) h, (p = 0.50).

The cumulative urinary output at 6 h amounted to 631 ± 354 mL and 612 ± 242 after the fast and slow infusion experiments, respectively (p = 0.83), which represented 2.9 ± 1.6 and 2.8 ± 1.2 times the infused volume.

Kinetic analyses

Relevant graphic output of the analysis of the kinetics of the *infused albumin* is shown in Fig. 4 (for underlying data, **Table 2, top**).

Covariance analysis showed that the capillary leakage of albumin, as represented by the rate constant k_b, was accelerated by plasma MR-proANP in the high range (Fig. 4C) and low Hgb at baseline (Fig. 4F).

Graphic output from the analysis of *fluid kinetics* is given in Fig. 5 (for underlying data, **Table 2, bottom**). The rate constant for urinary excretion of intravascular fluid (k_{10}) indicated a half-life of 60 min, but covariance analysis showed that the recruitment of fluid volume from the extravascular space increased significantly with the elevation of plasma albumin from baseline ($p < 0.0012$), which explains the much longer 5-foldt longer apparent intravascular half-life that was calculated by mass balance. The urinary excretion was also accelerated by high plasma MR-proANP (Fig. 5C) and a low urinary creatinine concentration at baseline (Fig. 5F).

The influence of the covariates on the simulated plasma volume expansion is illustrated by simulations in Fig. 6.

Discussion

Key results

The results show that 20% albumin is an effective plasma volume expander regardless of infusion rate. We found no negative effects of fast administration. The intravascular persistence of the infused fluid volume was prolonged from 1 h to 5 h by gradual recruitment of extravascular fluid due to the rise in plasma albumin, which is an important characteristic of the clinical efficacy of 20% albumin. Capillary leakage of albumin occurred continuously throughout the study and more slowly when the infusion was given fast. The fluid kinetics did not differ between the two study arms, but the fluid kinetics involved more individual-specific factors than the capillary leakage of albumin.

Factors promoting diuresis

The volume of excreted urine was almost three times larger than the infused fluid volume and was affected with two individual-specific factors.

The first factor was the urinary creatinine concentration, which is high in the presence of renal water conservation (Fig. 6D). We have observed the same retarding effect of urinary creatinine on the excretion of crystalloid fluid [13]. High urinary creatinine is caused either by acute dehydration or a low habitual intake of water [14]. The second possibility should be at hand in the present study as the subjects were healthy volunteers. The marked reduction of urinary creatinine during the experiment (to 65% of baseline, Table 1) illustrates that 20% albumin is a diuretic.

The second factor was the plasma MR-proANP concentration (Fig. 6C). Prior to this study, we had concerns that the rapid infusion of 20% albumin would increase the plasma volume sufficiently to markedly elevate MR-proANP, which is a precursor of ANP that is excreted from the atrium of the heart in response to distention. The increase reached only 25% in both groups, but the between-patient variation in MR-proANP was still large enough to still make this variable a statistically significant predictor of the urine flow.

The plasma concentration of ANP doubles in response to rapid infusion of a crystalloid fluid [15, 16] and that the urine flow increases also in response to modest elevations of brain natriuretic peptide, which is closely related to ANP [17].

Statkevicius *et al* recently compared slow and rapid infusions of 5% albumin after abdominal surgery and reported a greater increase in MR-proANP after a 30 min infusion than for a 180 min infusion. They found no difference in the transcapillary escape rate of albumin [5].

Half-life of albumin

Our finding that rapid infusion prolongs the intravascular half-life of albumin receives indirect support from other authors. Margarson and Soni infused 200 mL 20% albumin in volunteers over only 2 min [18]. After 4 h, as much as 79% of the infused albumin mass remained in the blood, which compares to the 60% measured in the present study (Fig. 3E). In septic patients, they reported that 69% of the administered albumin mass remained in the bloodstream after 4 h [18], which is still higher than in our volunteers. More recently, von Seth *et al* [16] studied the capillary leakage of albumin in septic pigs and found no difference between fast and slow infusions.

A possible explanation of why the intravascular half-life of albumin is longer when 20% albumin is administered rapidly is that the recruitment of extravascular fluid is quicker and more powerful. Transcapillary recruitment concentrates the interstitial albumin which, based on animal experiments [20, 21], would slow down the albumin leakage. Another possibility is that the recruited fluid consisted of lymph, which contains 40% as much albumin per volume as plasma [22]. The much lower k_b for albumin than for fluid implies that accelerated inflow of lymph would raise plasma albumin so as to artificially prolong the intravascular half-life.

Limitations

We included only volunteers who had a normal plasma albumin concentration (mean 40 g/L) before the infusions started. However, we have previously observed that the kinetics of 20% albumin is no different in healthy volunteers than in postoperative and post-burn patients, although these clinical groups had mean plasma albumin being 60% of the concentrations reported here [7, 9].

The measurements taken just after voiding during the study (at 75 and 165 min) were deleted because the efforts then made by the volunteers concentrated the blood.

Our kinetic models visualize changes in flow rates between body compartments, whereas the baseline flows are not included.

The kinetic model for albumin was relatively simple but was based on the entire concentration-time curve corrected for dilution. However, the first 60–90 min after the infusions ended could show fluctuating values, even to the extent that a “steady state” developed. The balance between body fluid compartments was apparently not yet in order, perhaps due to recruitment of lymph. We preferred to report the apparent

intravascular half-life of albumin based on mass balance applied to the terminal part of the experiment. This approach yielded values that better represented most elimination curves.

We believe that the generalizability of the present study is high as previous studies, using the same protocol, show that the kinetics of 20% albumin is quite stable between different clinical situations and similar to what is found in volunteers [7, 9, 11].

Conclusion

Infusion of 20% albumin over 30 and 120 min yielded stable plasma volume expansion curves. The intravascular persistence of albumin was longer for the 30-min infusion. There was no difference in MR-proANP response between the two infusions, but inter-individual differences in this hormone affected the capillary leakage of albumin and the urinary excretion.

Abbreviations

ANP: atrial natriuretic pptide; CV: coefficient of variation;COP: coefficient of variation;dL: deciliter;FOCE ELS: First order conditional estimation extended least-squares; h: hours;Hgb: hemoglobin;ICF: extravascular (probably interstitial) fluid;IQR: interquartile range;k_{10}: rate constant for urinary excretion; k_{21}: rate constant for absorption of extravascular fluid to the plasma; min: minutes;MR-proANP: mid-regional pro-atrial natriuretic peptide; P-Alb: plasma albumin;PV_o: plasma volume at baseline; PV_t: plasma volume at time t of the experiment; R_o: infusion rate; k_b; rate constant for capillary leakage; V_c: conversion factor between mass and concentration (albumin) or between volume and plasma dilution (fluid kinetics); v_c: expanded volume of V_c; SD: standard deviation;

Declarations

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Author´s contributions

FS suggested the study topic. All authors designed the protocol. Experiments were carried out by MZ. Calculations and illustrations were made by MZ (mass balance) and RGH (kinetic analysis). The study was authored by MZ and RGH. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available as a Supplemental Excel file.xls

Ethics approval and consent to participate

The Regional Ethics Committee of Linköping (Dnr2017/478-31) approved this study. The Swedish Medical Products Agency also approved the protocol, which was registered prior to enrolment at EU Clinical Trials Register on September 22, 2017 (EudraCT2017-003687-12).The volunteers consented participate after having received oral and written information about the implications of the study.

Consent for publication

Not applicable.

Competing interests

R.G. Hahn holds a research grant from Grifols. Grifols played no role in the design, analysis, and interpretation of the data and in writing the manuscript. Remaining authors do not have any conflicts of interest.

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Figures

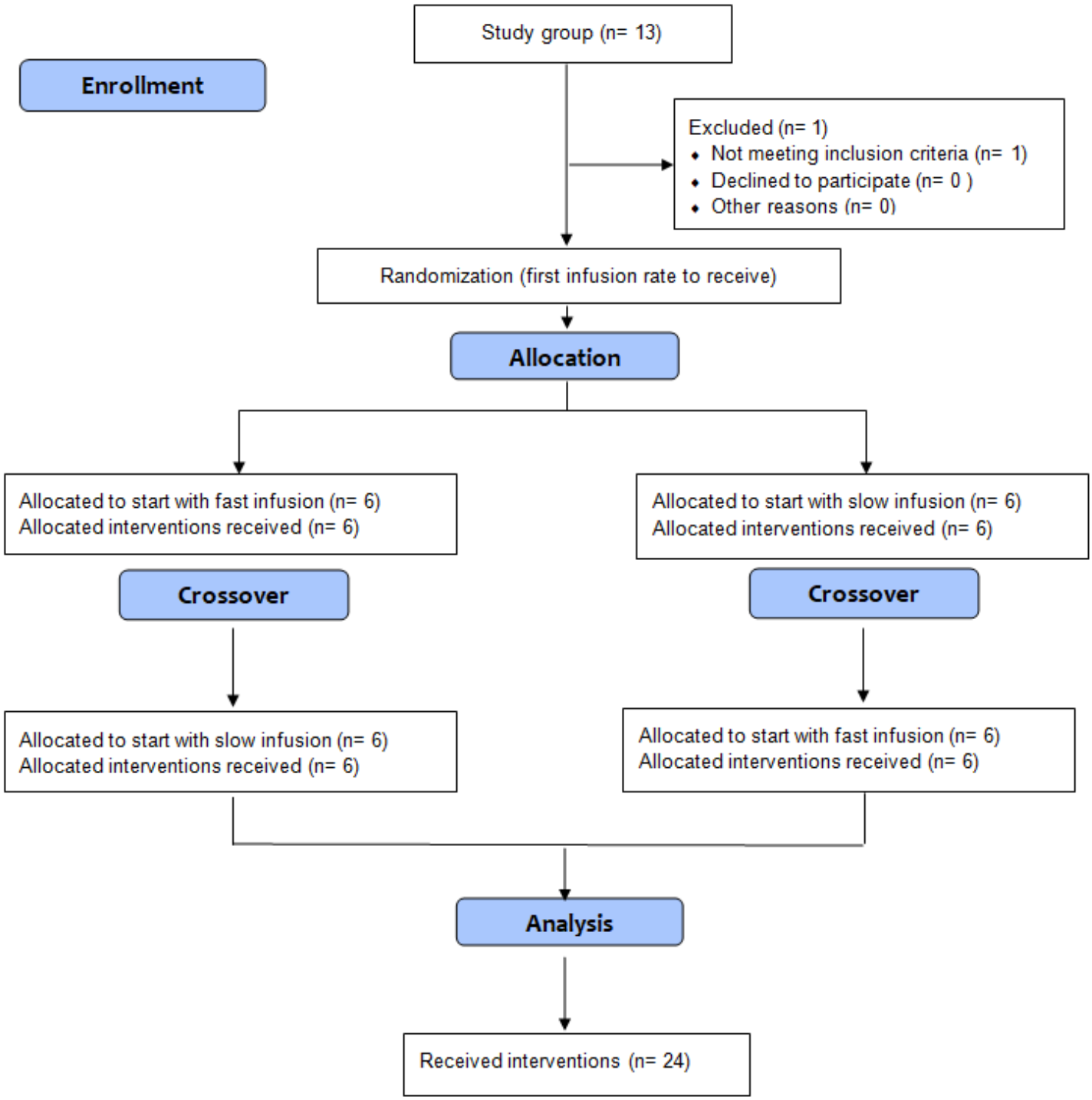

Figure 1

CONSORT flow diagram of the volunteer enrolment.

Figure 2

Raw data.

(**A**) The blood hemoglobin and (**B)** plasma albumin concentration during and after infusion of 3 ml/kg of 20% albumin over 30 min and 120 min in volunteers. Data are the mean (SD).

Figure 3

Mass balance.

(**A**) Plasma dilution (**B)** Changes in plasma albumin concentration (**C)** Changes in plasma colloid osmotic pressure (**D**) Plasma volume expansion divided by the infused volume of 20% albumin (**D**) Capillary leakage of albumin expressed as a percentage of the infused amount of albumin. All data are the mean (SD).

Figure 4

Albumin kinetics.

(A) Schematic drawing of the volume kinetic model.

(B) Curve-fit in the final model for the dilution-corrected change in plasma albumin concentration *versus* time

(C) Increase in the rate constant for capillary leakage of albumin for increasing plasma MR-proANP concentrations.

(D) Predicted *versus* measured dilution-corrected change in plasma albumin concentration in the final model.

(E) Original data (red points) with the associated5%, 50%, and 95% quantiles (black lines) and the corresponding quantiles obtained by predictive checkbased on 1,000 simulations using the model parameters in the final model (blue lines). A small difference between observed and predicted quantiles indicates good model performance.

(E) Inhibitory effect of high blood Hgb concentrations on the capillary leakage of albumin.

Figure 5

Fluid volume kinetics.

(A) Schematic drawing of the volume kinetic model.

(B) Curve-fit in the final model for the plasma dilution *versus* time.

(C) Correlation between the plasma MR-proANP concentration and the rate constant for urinary excretion (k_{10}).

(D) Predicted *versus* measured plasma dilution in the final model.

(E) Measured plasma dilution (red points) with the associated 5%, 50%, and 95% quantiles (black lines) and the corresponding quantiles obtained by a predictive check based on 1,000 simulations using the model parameters in the final model (blue lines).

(E) Inverse correlation between the urinary creatinine concentration at baseline and the rate constant for urinary excretion (k_{10}).

Figure 6

Factors of importance to the plasma volume expansion.

Computer simulations contrasting (**A**) rates of infusion (**B**) excessive (x 2) or reduced (x 0.5) increase in plasma albumin as compared to the measured concentrations (**C**) the plasma MR-proANP concentration was high or low (**D**) whether the baseline urinary concentration of creatinine was high or low. The data from Table 2 was used. Simulations were performed by setting all kinetic parameters to the mean value except for the parameter that was varied. Subplots B, C, and D were based on the kinetic data from all 24 experiments but the plasma albumin measured during the 30-min infusion only.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalExcelFile.xls