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The volume expanding effects of autologous liquid stored plasma following hemorrhage

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Short title: Plasma transfusion and volume effects

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Abstract

Background: Plasma use has increased since studies suggest that early treatment with blood components in trauma with severe hemorrhage may improve outcome. Plasma is also commonly used to correct coagulation disturbances in non-bleeding patients. Little is known about the effects of plasma transfusion on plasma volume, . We report a prospective interventional study in which the plasma volume expanding effect of autologous plasma was investigated after a controlled hemorrhage.

Methods: Plasma obtained by plasmapheresis from 9 healthy regular blood donors was stored at 2 - 6 degrees Celcius. Five weeks after donation the subjects were bled of 600 ml and then transfused with 600 ml of autologous plasma. Plasma volume was estimated using ^{125}I-albumin before and after bleeding, and immediately after plasma transfusion. Plasma volume changes were then estimated by measuring changes in hematocrit during the following 3 hour period.

Results: Estimated plasma volume after bleeding was 3170 ± 320 ml and 3690 ± 380 ml (mean+/-standard deviation) immediately following the transfusion of plasma ($p < 0.05$). This increase in plasma volume corresponds to 86 ± 13 % of the infused volume. Three hours after transfusion, plasma volume was still 3680 ± 410 ml.

Conclusions: Stored liquid plasma has a plasma volume expanding effect up to 86% of its infused volume with a duration of 3 hours.

Key words: Serum Albumin, Radio-Iodinated, plasma volume, plasma, hemorrhage, blood transfusion autologous,

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Background

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Studies indicate that early and aggressive resuscitation with blood components is associated with improved coagulation and decreased mortality following trauma with major hemorrhage [1, 2]. Plasma is also commonly used to correct coagulopathy in non-bleeding patients: a recent survey in the UK suggested that about 40% of plasma transfusions in the ICU are performed for this reason [3]. There is, however, also an extensive overuse of plasma in noncoagulopathic, normovolemic patients [4].

While the primary indication for plasma transfusion is coagulopathy, it is also used for its plasma volume expanding effect. Hedin and Hahn used hematocrit changes to estimate plasma volume expansion by autologous fresh frozen plasma (FFP) in healthy volunteers [5]. They found that FFP increased plasma volume by 75% of the infused volume immediately following transfusion and that the half-time for this effect was about 3 h. It can be argued that this method used to estimate changes in plasma volume and the fact that the patients were normovolemic at the time of the transfusion may have influenced the results. The plasma volume-expanding effect of liquid stored plasma (LSP) has only been studied using older plasma preparations, which differ from the currently used preparations with regard to volume and composition of the anticoagulant and degree of leucocyte and microaggregate reduction [6].

We report a study in which the plasma volume-expanding effects of LSP following a moderate hemorrhage was investigated. For this purpose human plasma donors were bled of 600 ml and subsequently transfused with 600 ml of autologous LSP. Plasma volume was estimated at baseline, after bleeding and for 3 h after transfusion using ^{125}I-albumin as a tracer and repeated hematocrit measurements

Methods

Volunteers

The ethical committee of Örebro County Hospital approved this prospective interventional experimental study (author US was at the time affiliated to that hospital). All procedures were in accordance and with the Helsinki Declaration of 1975, as revised in 1983. Nine healthy regular plasma donors (three women), gave informed and written consent to participate. The mean age ± standard deviation (SD) was 30 ± 4 years. Mean body weight ± SD was 70 ± 10 kg. The primary objective of the study was to investigate complement kinetics [7].

Autologous plasma components

Approximately 600 ml of plasma was collected from each donor by apheresis (centrifugation method, Haemonetics PCS, Braintree, Massachusetts) and the plasma was then divided into three 200 ml aliquots, each aliquot also containing 40 ml citrate-phosphate-dextrose (CPD) solution for anticoagulation (about 2.3 g/L of monobasic sodium phosphate, 27 g/L of dextrose, 21.2 g/L of total citrate, expressed as anhydrous citric acid and 6.9 g/L of sodium citrate). Osmolality in CPD was 430 ± 2 mOsm (n = 4) as estimated with a freeze-point method (Micro-Osmometer Model 210, Fiske Associates, Norwood, Massachusetts). The aliquots were stored at 2 – 6 degrees Celcius (°C) for 35 days in order to allow maximal complement activation for the study of anaphylatoxin kinetics [7].

Transfusion of the autologous plasma

The experiments were performed in the morning with all volunteers fasting from midnight and throughout the experiment. All volunteers lay supine for 30 minutes (min) before and

throughout the experiment. Non-invasive systolic and diastolic blood pressures were registered automatically and heart rates from continuous 5-lead electrocardiograms. Following placement of intravenous catheters in both antecubital fossae, each of the volunteers was bled 600 ml over 30 min. Directly after this hemorrhage, 600 ml of the predonated autologous CPD plasma (room temperature) was transfused in less than 15 min. There were at no stage in this experiment changes in systolic or diastolic blood pressure or heart rate. Fluids and tracers (see below) were given in the one intravenous cannula while blood and samples for analysis were taken from the other intravenous cannula.

Plasma and blood volume measurement

Five minutes prior to the controlled hemorrhage, ^{125}I-human serum albumin (HSA) was injected intravenously. To determine the exact dose injected, the radioactivity in the emptied vial, the syringe, and the needle was subtracted from the total radioactivity in the prepared dose. Venous blood sampling was performed immediately before and after the hemorrhage, then at 0, 5, 10, 20, 30, 45, 60, 120 and 180 min after the transfusion (Fig 1). Exact 5 ml of blood was collected in heparinized vials on each occasion. Following centrifugation, plasma was collected and the radioactivity in the blood samples was measured with a gamma counter (1282 CompuGamma CS; Wallac Pharmacia, Turku, Finland). Plasma volume can be reliably measured after a 5 min mixing period of tracer [8]. Plasma volume at baseline, following hemorrhage and immediately after transfusion was estimated by dividing the dose of HSA by the plasma concentration. The dose of HSA was corrected for the amount of tracer lost during hemorrhage. Plasma volume 5 min after transfusion and thereafter was calculated using a microhematocrit method [9]. The amount of unbound radioactivity in the bolus doses was determined by measuring the activity in the supernatant following precipitation with 10% trichloroacetic acid. Unbound activity was found to be less than 1 % in all cases.

Statistical analysis

Following tests for equal variance and normal distribution, a comparison of plasma volumes over time was performed with repeated ANOVA followed by a Student-Newman-Keuls posthoc test using a commercial software package (MATLAB 7.11.0, The MathWorks Inc., Natick, MA, 2000). Data are presented as mean ± SD unless stated otherwise.

Results

The infusion rate of plasma during the transfusion was 38-48 ml/min. The last plasma sample in one of the subjects was omitted due to technical sampling difficulties. No adverse reactions were observed.

Plasma volume

Plasma volume at baseline (t=5 min) was 3300 ± 280 ml (47 ± 4 ml/kg). The decrease in plasma volume caused by hemorrhage (t=35 min) was 130 ± 100 ml, while the increase in plasma volume between baseline and the end of plasma transfusion was 386 ± 90 ml ($P < 0.01$) (t=50 min compared to 5 min). The increase in plasma volume incurred by the plasma transfusion was thus 510 ± 80 ml ($P < 0.01$) (t=35 min compared to t=50 min), which corresponds to an increase in plasma volume of 86 ± 14 % of the infused volume. Maximum plasma volume was reached 45 min after transfusion: by this point the plasma volume had increased by 550 ± 87 ml compared to the estimated plasma volume directly after hemorrhage ($P < 0.01$). Changes in plasma volume in each of the study subjects are presented in Fig 2. Plasma volume in one study subject did not decrease following bleeding. The most likely explanation is an analytical error but since an extremely effective homeostatic response could not be excluded the patient was included in the analysis.

Hematocrit

Hematocrit was 39 ± 3 at t=0 min and dropped by 1.0 ± 0.8 ($P < 0.01$) immediately after the hemorrhage (t=35 min). After the plasma transfusion (t=50 min) the hematocrit was 3.5 ± 0.7 lower than at t=0 min and 2.5 ± 0.5 compared to directly after the bleeding (t=35 min) ($P < 0.01$). During the following 3 hours hematocrit did not change significantly and the decrease in hematocrit at the end of the study (t=230 min) compared to t=5 min was 4 ± 0.8 ($P < 0.01$). Individual changes in hematocrits are shown in Fig 3.

Discussion

The main finding in the present study was an immediate expansion of plasma volume by about 86 % of the infused volume of plasma. Plasma volume remained unchanged during the 3h after transfusion.

The ^{125}I-HSA method is regarded as the gold standard for measuring plasma volume and baseline volumes were similar to reported normal values [5]. In order to minimize radiation exposure to the subjects, plasma volumes before hemorrhage, after hemorrhage and immediately after transfusion were estimated by repeated measurements of plasma concentration of ^{125}I-human serum albumin (HSA) after one injection of the tracer. By not correcting for transcapillary escape of tracer this approach may lead to an overestimation of the volume expanding effects of plasma. Transcapillary escape of tracer is reported to be 4-7% per hour and this may lead to an overestimation of the immediate volume expansion effect of plasma by at most 1.8% [9]. Subsequent plasma volumes were estimated using changes in hematocrit, which are not affected by transcapillary leak of tracer. This calculation assumes a constant ratio of whole body- to large vessel hematocrit (F-cell ratio). While large changes in

plasma volume such as those induced by bleeding and transfusions are reported to change the F-cell ratio [10] it has been shown that F-cell ratio is constant during smaller changes in plasma volume such as those occurring after the initial distribution of the transfused plasma [11].

Bleeding initiates compensatory mechanisms, which rapidly mobilize extracellular fluid into the vascular compartment. Such a homeostatic response is the most likely explanation of our finding a decrease in plasma volume by on average only 130 ml following a hemorrhage that would be expected to decrease plasma volume by about 360 ml in the absence of compensatory mechanisms [12]. The observed decrease in hematocrit after the bleeding also supports the hypothesis that compensatory mechanisms may explain the small decrease in plasma volume after the hemorrhage.

Only one recent study has investigated the volume expanding properties of plasma. In that study changes in hematocrit were used to estimate plasma volume changes upon infusion of autologous FFP in normovolemic volunteer [5]. Infusion of 800 ml of FFP expanded plasma volume by 600 ml, which is 75 % of the infused volume – a value similar to the 86 % presented in our study. Three hours after transfusion, though, only 50 % of the initial plasma volume expansion remained compared to about 100 % in our study. Even though these two studies are not directly comparable due to differences in methodology, the results indicate that the immediate volume expanding properties of FFP and liquid stored plasma (LSP) are similar. This is supported by the study by Hutchison et al. (1960) reporting an immediate plasma volume expansion of autologous FFP by 83 % [13].The more persistent plasma volume expansion in our study compared to the study by Hedin and Hahn (2005) does not

necessarily reflect a difference in the duration of plasma volume expansion between FFP and LSP, but could be explained by differences in volume status relative to baseline after transfusion [5].

Our findings and the previously reported immediate plasma volume expansion by about 80 % of the infused volume is plausible considering that plasma preparations contain about 20 % citrate-phosphate-dextrose (CPD) anticoagulant. We are not aware of any study investigating the volume expanding properties of the hyperosmotic and hypernatremic CPD solution. However, considering that dextrose, which represents about 150 mOsm of the total osmotic pressure, distributes throughout both the intra- and extravascular fluid, the CPD solution has plasma volume expanding properties comparable to isotonic saline and expands plasma by about 20-25% of the infused volume.

To minimize volunteers' risk of contracting blood-borne diseases, autologous plasma was used rather than homologous plasma and it could be argued that this experimental design limits the study's clinical relevance. Two studies have compared plasma volume expanding effects of autologous- and homologous plasma. In these studies it was found that, in the absence of allergic reactions, the two types of plasma had similar volume expanding properties [6, 13]. Twenty-five % of the patients receiving homologous blood in these studies had allergic reactions with marked loss of plasma volume whereas allergic reactions are nowadays reported to occur at a rate of only 0.03-0.08%. A possible explanation for the decreased incidence of allergic reactions is the introduction of leucocyte-depleted plasma, but other mechanisms have been discussed [14].

Blood banks in Sweden supply two types of plasma: FFP and LSP, which is plasma stored at

2-6°C after component preparation. Thawed FFP can be used up to 2 weeks if stored at 2-6°C [15]. Previous regulations in Sweden allowed LSP to be stored for up to 42 days but current praxis is a maximum storage time of 7-14 days due to evidence that prolonged storage has detrimental effects on coagulation factor activity, overall coagulation function and the presence of some activation markers [7, 16-18]. The LSP used in the present study may therefore have different properties than the one currently available in clinical practice. There are also few studies comparing plasma's volume-expansion with its alternatives: the study by Hedin et al. (2005) compared the volume-expanding properties of a modern plasma preparation with another colloid: FFP and 5% albumin infusions resulted in similar plasma volume expansion [5]. A similar result was reported in the previously mentioned older study by Hutchison et al. (1960) in which autologous FFP and 6 % dextran 75 showed similar plasma volume expanding properties [13].

A limitation of the present study is the lack of a control group being bled but not transfused. While this omission does not influence our conclusions regarding LSP's immediate plasma volume expansion, it makes interpretation of the duration of the plasma volume expansion difficult. The present data cannot tell us how much plasma volume is influenced by factors such as homeostatic mechanisms. Our hemorrhage also differs from clinical practice in which a state of systemic inflammation with increased microvascular permeability, tissue damage and prolonged hypovolemia often exist. FFP may counteract glycocalyx sheeding and permeability increases following hemorrhage indicate that the volume expanding properties of FFP may depend on the prevailing pathophysiology [19, 20].

As mentioned in the methods section the data presented in the present manucript were collected as a part of a study with the main objective to study complement kinetics [7]. This

means that he present results could be considered to represent secondary end points and therefore should be veiwed with some caution.

Plasma's longstanding plasma volume expansion is relevant since it may contribute to TACO when plasma is administered in the absence of hypovolemia or in patients with marginal cardiac function, renal failure and liver disorders [3]. The critical limits for most coagulation factors are 30-50% of normal levels [21]. Treating slightly low plasma concentrations of coagulation factors will therefore unnecessarily increase the risk of circulatory overload [16]. In addition, since plasma transfusion leads to a prolonged decrease in hematocrit, the clinical result may be unnecessary red cell transfusion, possibly further increasing the risk for hypervolemia and TACO in susceptible patients as well as transfusion's other well known adverse effects. This line of reasoning may be supported by the results presented in the Saline versus Albumin Fluid Evaluation (SAFE) study in which patients receiving albumin were more likely to be transfused with packed red cells [22].

In conclusion, we have demonstrated a volume expanding effect of autologous LSP up to 86% of its infused volume lasting at least 3 hours in healthy, slightly hypovolemic regular plasma donors.

Author contributions: Ulf Schött designed the study and collected the data. All authors took part in literature search, writing the manuscript and data interpretation. Peter Bentzer and Johan Westborg made the figures and the statistical evaluation

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Conflict of interest: The authors have no conflicts of interest regarding this work.

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Legends

Figure 1. Schematic presentation of the experimental protocol. PV: plasma volume, HSA: 125I-Human serum albumin (HSA). Injection of HSA corresponds to time 0 in figure 2 and , 3. and

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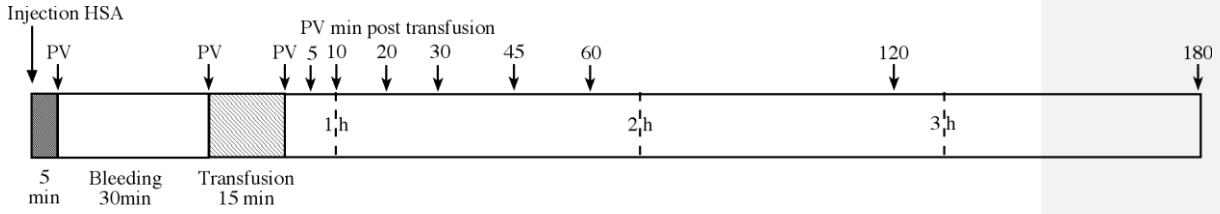
Figure 2. Plasma volume in the different subjects at baseline, following bleeding and for 3 h after transfusion.

Figure 3. Hematocrit in the different subjects at baseline, following bleeding and for 3 h after transfusion.


Injection HSA
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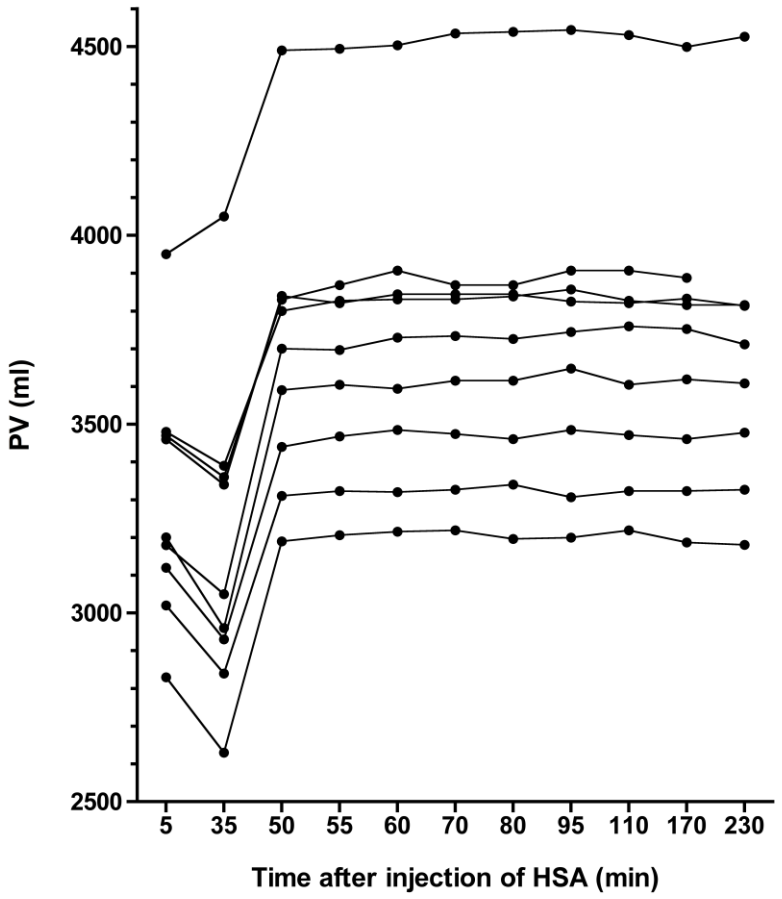
Transfusion 15 min

Figure 1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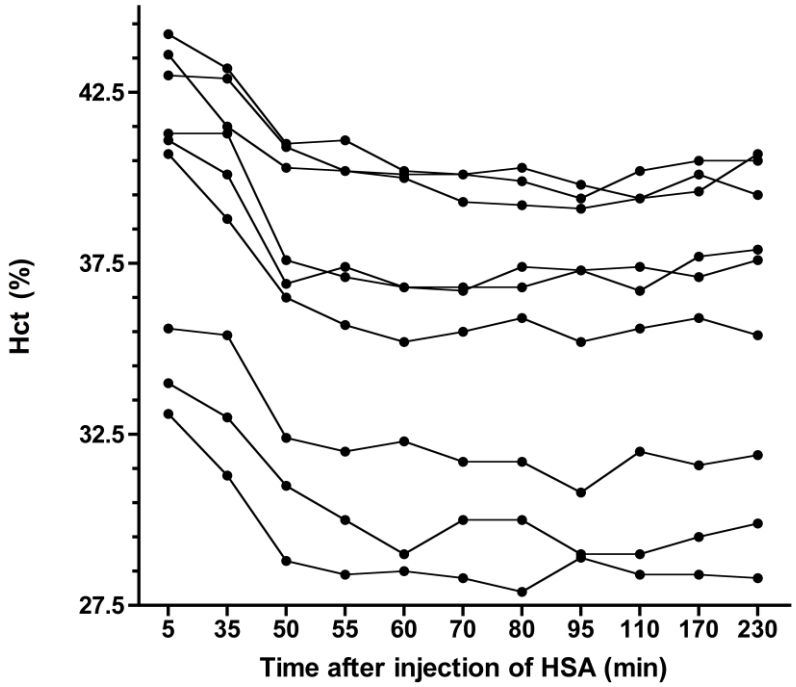
Time after injection of HSA (min)

Figure 2


42.5
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32.5
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230
Time after injection of HSA (min)

Figure 3