Plasma volume expansion of 5% albumin, 4% gelatine, 6% HES 130/0.4 and normal saline under increased microvascular permeability in the rat

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Abstract

Objective: To compare the colloids 5% albumin, 4% gelatine, and 6% HES 130/0.4 with one another, and with saline, regarding their plasma expanding effects at increased permeability, and to compare the results with those from a previous study at normal permeability.

Design: Prospective controlled randomised laboratory study.

Setting: University research laboratory.

Subjects: 48 adult male Sprague-Dawly rats.

Interventions: Permeability was increased by an injection of 0.5 ml dextran 70 using the fact that dextran causes anaphylactic reaction in the rat. Plasma volume was determined (^{125}I albumin tracer technique) after anaesthesia, 1 h after the dextran injection (before infusion for 10-15 min of 20 ml/kg bw of each of the colloids or 80 ml/kg of saline), and 3 h later. Blood pressure, haematocrit, blood gases and electrolytes were measured. CVP was measured in 4 rats.

Measurements and results: Plasma volume was 41.1±1.9 ml/kg at baseline (n=9), and 29.1±4.1 ml/kg (n=35) 1 h after the dextran injection ($p<0.05$). Three hours after infusion of the plasma expander, plasma volume had increased by 17.1±3.4 ml/kg in the albumin group, by 7.9±3.6 ml/kg in the gelatine group, by 7.4±4.4 ml/kg in the HES group, and by 12.2±3.1 ml/kg in the saline group. It was unchanged in a control group given no solution (n=7 for all groups) (Means ± SD).

Conclusion: Albumin was a more effective plasma volume expander than gelatine or HES or saline ($p<0.05$), which were equally effective. All solutions showed a smaller plasma expanding effect than observed in a previous study with normal permeability.

Introduction

Increased microvascular permeability is an important pathophysiological alteration in diseases such as sepsis/SIRS and following trauma, and results in increased transcapillary leakage of plasma fluid, hypovolaemia and interstitial oedema [1-3]. Hypovolaemia will decrease cardiac output resulting in reduced systemic oxygen delivery, and trigger generalized vasoconstriction by activation of the baroreceptor reflex through unloading of the high- and low-pressure receptors, which may lead to compromised perfusion in more vulnerable regions such as the gut [4-7]. Correction of low plasma volume therefore may be essential to maintain adequate organ perfusion and oxygen delivery [8, 9].

Crystalloids (all molecules of molecular weight (MW) less than 30 kDa) and colloids (also containing molecules > 30 kDa) are used as plasma volume expanders. For decades there has been a debate regarding whether one should use crystalloids or colloids [10-13], but there is also a debate regarding the efficacy of different colloids [14-16]. In contrast to colloids, crystalloids have small effects on coagulation, there is no risk of inducing allergic reactions, and they are inexpensive. Crystalloids are, however, relatively ineffective as plasma volume expanders as they pass freely across the capillary membrane, with fast distribution to the whole extracellular space, and only a minor proportion remaining in the bloodstream [11, 17, 18]. This means that relatively large volumes must be infused to maintain normovolaemia with risk of adverse tissue oedema [16]. Because of the larger MW, the transcapillary passage of colloid solutions is markedly restricted and they will therefore remain in the bloodstream for longer. The oncotic effect of the colloid may also reinforce their plasma expanding capacity [19, 20]. However, the plasma expanding effect of colloids is transient due to a continuous clearance from the circulation related to the rate of degradation, renal and gastrointestinal losses, and due to a continuous leakage of macromolecules into the interstitial

space [16]. According to the modern 2-pore theory of transvascular exchange [21], transcapillary leakage of macromolecules occurs through the large pores of the capillary/venular membrane and is compatible with the view that it is greater at increased permeability than at normal permeability. Except size and number of the large pores, transcapillary leakage may also be influenced by charge of the molecules and their interaction with glycocalyx and other endothelial structures [22, 23].

There are still no studies comparing the plasma expanding effect of contemporary colloid solutions, and of crystalloids using direct measurements of plasma volume specifically under a condition of increased permeability. The present study was designed to evaluate the plasma expanding effects of 5% albumin, 4% succinylated gelatine, 6% HES 130/0.4, and of saline on rats suffering a generalized increased permeability. The increased permeability was achieved from a bolus injection of dextran, based on the well-known phenomenon that dextran induces anaphylactic reaction with increased permeability in the rat [24, 25].

Methods

Materials and anaesthesia

The study was approved by the local ethics committee for animal research, and the animals were treated in accordance with the Guidelines of the National Institutes of Health for Care and Use of Laboratory Animals. Adult male Sprague-Dewley rats (n = 48), weighing 347 ± 11 g were used. Anaesthesia was induced by placing the animal in a covered glass container with a continuous supply of isoflurane (Forene; Abbot, Stockholm), and maintained, first by inhalation of 1.5-1.8% isoflurane, by means of facemask, and later by a tracheal cannula after tracheotomy. The animals were placed on a heating pad to maintain a body core temperature (measured rectally) of 37.0–37.3ºC via a feedback circuit. After tracheotomy, the animals

were connected to a ventilator (Ugo Basile; Biological Research Apparatus, Comerio, Italy). End-tidal PCO_2 was monitored continuously and kept between 4.7 and 5.4 kPa (Capstar-1000, CWE, Ardmore, PA). The left femoral artery was cannulated for continuous measurement of arterial pressure and to measure arterial blood gases (i-STAT; Hewlett Packard, Böblingen, Germany). The left femoral vein was cannulated and used for injections and infusions. At the end of the experiment the animals were euthanised by decapitation.

Experimental protocol.

The study was randomised but not blinded and involved four groups with seven rats in each, which were defined according to the volume expander given, and a control group given no solution. Central venous pressure was measured in 4 separate rats via the right internal jugular vein to evaluate if venous pressure effects on hydrostatic capillary pressure might have influenced the transcapillary leakage (see Discussion). The groups were the control group, the albumin group (5% albumin, Aventis Behring, Marburg, Germany), the gelatine group (4% gelofusine, Braun, Melsungen, Germany), the HES group (6% HES 130/0.4, Voluven, Fresenius, Halden, Norway), and the saline group (0.9% NaCl, Fresenius, Halden, Norway). Following a stabilisation period of 15 min after tracheotomy and vascular cannulations, the animals received an intravenous injection of 0.5 ml dextran 70 (Macrodex 6%; Pharmalink AB, Upplands Väsby, Sweden) for the purpose of increasing microvascular permeability.

The colloid solutions at a dose of 20 ml/kg body weight or normal saline at a dose of 80 ml/kg were given 1 h after the dextran injection (Fig. 1). Unpublished observation from previous experiments had shown that the decrease in plasma volume following a dextran injection reaches its maximum within 1 h, a result confirmed in the present study in the control group given no plasma expander (see Results). The time for infusion was 10 min for the colloids,

but 15 min for saline to minimize the risk for acute fluid overload. Arterial blood gases were measured just before the dextran injection (baseline values), 1 h after injection of dextran before infusion of the plasma expander, immediately after the infusion, and 3 h after the infusion (Fig. 1). Plasma baseline volume was measured after finishing the preparation, 1 h after the dextran injection before the infusion, and 3 h after the infusion (Fig.1).

The plasma volume (V) was calculated by measurement of the increase in radioactivity per ml of plasma (ΔC_2) after an intravenous injection of a known amount of activity of ^{125}I-albumin (C_1) (31)

$$V = C_1/\Delta C_2$$

Radioactivity was measured with gamma counter (Wizard 1480, LKB-Wallace, Turku, Finland). The increase in radioactivity of ^{125}I-albumin (ΔC_2) was determined by subtracting the activity in a blood sample taken before the injection from that taken 5 min after the injection, thereby taking into account the cumulative effects of radioactivity. The blood was centrifuged and the radioactivity in a fixed volume of plasma was determined. To determine the exact dose injected, the radioactivity of the emptied vial, the syringe and the needles used was subtracted from the total radioactivity in the prepared dose.

Statistics

Results are presented as mean values ± SD. Statistical comparisons between groups were performed with the non-parametric Mann-Whitney rank sum test and ANOVA which, when necessary, was adjusted for multiple comparisons (Bonferroni). P-values less than 0.05 were considered significant. Sigma Stat 2.0 software was used.

Results

Physiological data

The data for haemoglobin (Hb), sodium (Na^+), potassium (K^+), pH, base excess (BE), P_aO_2, and P_aCO_2 for the different groups are summarized in Table 1. Hb increased from 135 ± 6 before the dextran infusion to 157 ± 13 g/l (n = 35) 1 h after the dextran infusion ($p<0.05$). Infusion of the plasma expander caused a decrease in Hb, followed by a successive increase. At the end of the experiment, Hb levels had increased in all groups, reaching significance compared with the baseline values in the gelatine and HES groups. Na^+ and K^+ did not differ between groups. Mean arterial blood pressure values at baseline, 1 hour after the dextran injection, after infusion of the plasma volume expander, and 3 h later at the end of the experiment are presented in Table 2. There was a lower arterial blood pressure 1 h after the dextran injection and 3 h after infusion of the plasma expander than at baseline. Arterial blood pressure was lower for all solutions at end of the experiment than shortly after the infusion. For pH, P_aO_2 and P_aCO_2, and BE there was no difference between the groups, except from a decrease in BE in the saline group after the saline infusion and at the end of the experiment. In the 4 experiments performed for measurement of central venous pressure, baseline central venous pressure was 3.0 ± 0.3 mmHg. It was 2.2 ± 0.7 mmHg 1 hour after the dextran injection, 3.3 ± 0.5 mmHg after the albumin infusion, and 3.0 ± 0.8 at end of the experiment.

Plasma volume

Baseline plasma volume determined in separate experiments (n=9) was 41.1 ± 1.9 ml/kg. Plasma volume directly before infusion of the plasma volume expander was 29.1 ± 4.1 ml/kg (n = 35) ($p<0.05$) with no difference between the five groups. The remaining increase in plasma volume 3 h after infusion of plasma expander (20 ml/kg for the colloids and 80 ml/kg for saline) (PV_3-PV_2 in Fig. 1) is shown in Fig. 2; it was 17.1 ± 3.4 ml/kg in the albumin

group, 7.9 ± 3.6 ml/kg in the gelatine group, 7.4±4.4 ml/kg in the HES group, and 12.2 ± 3.1 ml/kg in the saline group. The plasma expanding effect was larger in the albumin group than in the other groups ($p<0.05$). There were no significant differences between the HES, the gelatine and the saline groups. There was no change in plasma volume in the control group from 1 h after the dextran injection to the end of the experiment.

Discussion

The present study in rats was designed to compare clinically available plasma expanders regarding their capacity to restore reduced intravascular volume during a state of increased microvascular permeability. The permeability was increased in a standardized manner by inducing anaphylactic reaction with a small fixed bolus injection of dextran. Within one hour after the dextran injection, the anaphylactic reaction resulted in a reduction in plasma volume from baseline values of about 41 ml/kg to about 29 ml/kg. There was a simultaneous increase in Hb concentration and decrease in arterial blood pressure. The results show that, under the present experimental circumstances when the colloids are given in equal volumes and saline in a 4 times greater volume, 5% albumin is a more effective plasma volume expander than 4% gelatine or 6% HES130/0.4, and that gelatine, HES and saline were equally effective.

The finding of a better plasma expanding effect of albumin than that of HES and gelatine is compatible with the observations that haemoglobin concentration was lower in the albumin group than in the HES and gelatine groups at end of the experiments (Table 1).

The well-known fact that dextran induces an anaphylactic reaction in the rat [24] has been used in the present study to induce a standardized increase in permeability. Increased permeability with transcapillary leakage was confirmed by the visually observed marked

peripheral oedema that developed shortly after the dextran injection, by the equally large reduction in plasma volume for all groups, by the reduction in mean arterial pressure (Table 2), and by the increase in haemoglobin concentration (Table 1).

The tracer albumin technique is well established for measurement of plasma volume. Because of transcapillary escape of albumin during the 5-min period between tracer injection and blood sampling, the albumin-derived radioactivity measured in plasma may have been somewhat decreased, resulting in overestimation of the plasma volume. The overestimation, however, must be equally large for all groups and it must be small as the blood sample was taken very shortly (5 min) after the tracer injection. The fact that measured baseline plasma volume of about 41 ml/kg are in the same range as those presented in the literature for rats of 39-42 ml/kg [26] confirms the reliability of the plasma volume measuring technique used.

An increase in transcapillary leakage of macromolecules at increased permeability is compatible with the 2-pore theory of transcapillary fluid exchange [21]. According to this theory, fluid and smaller solutes pass the capillary membrane through all pores along the entire microvascular bed, whereas macromolecules pass the capillary membrane only through the 10–30 $\times 10^3$ times less common larger pores present in venules and at the venous side of the capillary network. The transcapillary/transvenular hydrostatic pressure is the only force responsible for fluid flow through the large pores, as the oncotic pressure across these pores is virtually zero [21]. This means that the macromolecules are lost to the interstitium mainly through convection by following the large-pore fluid flux, while the diffusion force is of less importance [21]. This hypothesis means that there is always a continuous leakage of macromolecules (normal transcapillary escape rate) and even a minute increase in total pore area via the large pores may cause a substantially greater loss of macromolecules. This means

that the plasma expansion of a colloid must be less effective at increased permeability than at normal permeability. Thus, the 2-pore theory is compatible with a less effective plasma expanding effect of colloids at raised than at normal permeability.

This hypothesis also means that the leakage of proteins through the large pores will increase with an increase in hydrostatic capillary pressure. If so, the leakage will be higher at a high systemic arterial pressure than at a low one. Transcapillary leakage of proteins can therefore be expected to increase after volume expansion, if the infusion is followed by an increase in arterial pressure. Our results that, there was no loss of plasma volume in the control group from 1 h after the dextran infusion up to end of the experiment, while there was a significant loss of plasma in the groups given a plasma expander, may be explained by the lower arterial pressure in the control group (Table 2). The hypothesis also means that avoidance of supranormal arterial pressure may help to preserve the plasma volume and to reduce the need for plasma expanders.

The plasma volume expanders analysed in the present study have been examined in the rat previously in our laboratory but under the condition of normal permeability [27]. In that study, blood volume was reduced before the infusion by a standardized haemorrhage of 16 ml/kg, a reduction in plasma volume of about the same magnitude as that obtained by the dextran infusion in the present study. While plasma volume increased by 21.1 ml/kg 3 h after the infusion of 20 ml/kg of 5% albumin in our previous study, it increased by 17.1 ml/kg in the present study. Corresponding values for gelatine were 13.1 versus 7.9 ml/kg, and 13.8 versus 7.4 ml/kg for HES 130/0.4. For saline, after the infusion of 80 ml/kg the values were 16.0 ml/kg in the previous study versus 12.2 ml/kg. This difference in plasma loss between the 2 studies may, if anything, even have been somewhat underestimated due to a larger

leakage of tracer albumin during the 5 min timespan between injection and blood sampling when permeability is increased.

In addition, arterial blood pressure was lower in the present study than in our previous study, most likely an effect of the dextran-induced anaphylactic reaction. Thus, the blood pressure in the present study was 5-10 mmHg lower after infusion of the plasma expander and 15-20 mmHg lower at end of the experiments (Table 2 and ref 27). If blood pressure is a factor influencing transcapillary fluid loss as discussed above, the lower blood pressure have saved plasma in the present study compared to the previous study [27]. Thus, also this factor means that the effect of permeability on plasma volume leakage, if anything, is underrated when making a direct comparison between the 2 studies.

If as discussed, the hydrostatic capillary pressure is of importance for transcapillary fluid loss, also a change in venous pressure may have influenced the hydrostatic pressure. Differences in venous pressure, however, cannot explain the difference in plasma expansion between the groups as the better the plasma expansion of the solution the higher the venous pressure. The fact that central venous pressures measured in 4 separate rats given the best plasma expander albumin did not increase to values above normal (see Results) also indicate that a difference in venous pressure cannot explain the difference between plasma expansion in the present and the previous study [27]. Nor can the difference in Hb explain the difference in plasma expansion between the 2 studies, as experimental studies have shown that plasma leakage is lower at a high than at a lowered Hb [28], and the Hb values were higher in the present study than in our previous study. Taking all these arguments together, a comparison between the 2 studies thus strongly indicates that the plasma expanding effect of all solutions analysed is lower at increased than at normal permeability.

It is well accepted, and also in line with the 2-pore theory [21], that crystalloids are distributed rather fast to the whole extracellular space, and the volumes infused must be much larger than those for colloids for the same plasma expanding effect. This hypothesis was confirmed in the present study where the plasma expanding effect of saline was worse than that with albumin and showed only a tendency (not significant) of better volume effect than with gelatine and HES when saline was given in a 4 times larger volume (Fig. 2).

The difference in plasma expanding effects of the colloids analysed may have several explanations. Factors of importance may be average MW, MW distribution, oncotic pressure of the solution, degradation rate, threshold for renal elimination, molecular shape and electrical charge, and interference with glycocalyx [17, 18, 20, 22, 23, 29, 30]. Gelatine and HES are neutral molecules whereas albumin is negatively charged, which may prevent its penetration. Albumin is a monodisperse solution with a molecular weight of 69 kDa for all molecules, with insignificant degradation rate. Both HES and gelatine are polydisperse solutions with molecules ranging from very small to very large, and the larger molecules will undergo enzymatic degradation to smaller molecules. The small molecules will disappear relatively quickly from the intravascular space to the interstitium and will be cleared through the kidneys. HES solutions, and especially HES 130/0.4 with its low degree of substitution, are degraded by amylase to smaller molecules. The degradation rate of HES may be faster in rats than in man, due to the higher amylase concentration in rats. The gelatine molecules, with a relatively small average molecular weight of 35 kDa, undergo degradation by proteases in the reticuloendothelial system. Thus, several factors may be responsible for the better plasma volume expanding effect with 5% albumin than with gelatine and HES in the present study, and why gelatine and HES were equally effective despite the difference in molecular weight.

In conclusion, the present study on rats with increased permeability shows that, in a 3-hour timespan, the treatment of hypovolaemia with 5% albumin preserves plasma volume better than with 4% gelatine and 6% HES 130/0.4, or with normal saline given in a 4 times larger volume, while gelatine, HES and saline were equally effective. Comparison of these results with those from a previous study on rats with normal permeability indicates that the plasma expanding effect of these solutions is less effective when permeability is increased.

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Legends

Fig. 1. The time-axis of the experiment. PV_1 – baseline plasma volume measured just before the dextran injection. PV_2 – plasma volume measured 1 hour after dextran injection. PV_3 – plasma volume measured 3 hours after the bolus infusion of plasma expander. BGA – blood gas analysis.

Fig. 2. Increase in plasma volume, ΔPV (PV_3-PV_2 in Fig. 1) 3 h after the bolus infusion of 20 ml/kg for colloids and 80 ml/kg for saline, compared to the plasma volume 1 h after dextran injection, for the 5 groups analysed. It can be seen that the albumin group had a better volume expanding effect than the other groups. There was no significant difference between the gelatine group, the HES group and the saline group. The plasma volume did not change in the control group. (*=$p<0.05$).

Table 1. Data for the physiological parameters haemoglobin concentration (Hb), sodium concentration (Na^+), potassium concentration (K^+), pH, Base excess (BE), arterial oxygen concentraion (P_aO_2) and carbon dioxide concentration (P_aCO_2) at baseline, 1 h after dextran injection, directly after infusion of plasma expander, and 3 h later (at the end of the experiment).

		Hb g/l	Na^+ mmol/l	K^+ mmol/l	pH	BE mmol/l	P_aO_2 kPa	P_aCO_2 kPa
Control	Baseline	133±7	134±2	5.0±0.5	7.47±0.11	4.6±1.0	9.4±1.2	5.4±0.3
	After dextran	163±13 *	137±2	5.7±0.4	7.37±0.12	1.0±2.1	9.8±0.8	5.1±0.5
	End	158±15 *	132±1	6.4±0.5	7.41±0.04	0.0±3.1	10.1±1.4	5.0±0.6
Alb	Baseline	136±4 #	135±2	4.7±0.4	7.46±0.03	6.0±0.9	9.7±0.9	5.4±0.5
	After dextran	157±16 *#	133±2	5.1±0.4	7.43±0.05	2.6±3.3	10.5±1.1	5.2±0.5
	After infusion	114±7 *	137±2	4.1±0.4	7.41±0.03	3.2±1.1	8.5±1.0	5.7±0.6
	End	125±8 ⊥	136±1	4.5±0.4	7.44±0.03	2.4±0.9	8.9±0.8	5.1±0.2
Gel	Baseline	135±4 #	134±1	4.7±0.5	7.42±0.12	5.3±2.5	10.4±1.9	5.3±0.5
	After dextran	160±14 *#	132±3	5.4±0.6	7.41±0.04	1.3±2.6	10.4±1.0	5.3±0.6
	After infusion	110±13 *	135±1	4.5±0.4	7.42±0.03	3.6±1.7	9.0±1.1	5.7±0.6
	End	144.0±8 *#	135±1	5.1±0.3	7.40±0.11	2.0±1.5	9.7±1.0	4.9±0.5
HES	Baseline	136±6 #	134±1	5.2±0.3	7.43±.0.06	5.0±1.8	9.1±1.0	5.7±0.7
	After dextran	153±6 *#	133±1	5.4±0.4	7.42±0.04	1.9±0.7	9.2±3.5	5.1±0.5
	After infusion	99±3 *	136±1	4.7±0.2	7.39±0.03	3.0±0.9	8.0±0.6	5.6±0.4
	End	142±9 *#	135±1	5.6±0.5	7.42±0.03	1.1±1.1	9.6±0.8	5.2±0.4
Saline	Baseline	134±10 #	135±6	4.5±0.2	7.45±0.03	4.7±1.4	9.2±1.3	5.7±0.5
	After dextran	149±13 *#	132±1	5.1±0.1	7.42±0.02	3.0±1.6	9.5±0.9	5.7±0.5
	After infusion	112±9 *	140±1	4.0±0.4	7.34±0.03	-2.6±0.8 +	8.7±1.0	5.7±0.5
	End	125±10 ⊥	137±1	4.9±0.4	7.37±0.03	-1.9±0.9 +	8.7±1.1	5.2±0.5

* Difference in Hb compared with baseline; # difference in Hb compared with values after infusion of plasma expander; ⊥ difference compared with corresponding values in control, gelatine and HES groups; + difference in BE compared with corresponding values in control, gelatine, albumin and HES groups, as well as compared with values at baseline and after dextran in the saline group ($p<0.05$). Data expressed as mean ± SD.

Table 2. Mean arterial pressure (mm Hg) at baseline, 1 h after dextran injection, directly after infusion of plasma expander, and 3 h later (at the end of the experiment). Corresponding values are given for the control group.

Group	Baseline mmHg	1h after dextran mmHg	After infusion mmHg	After 3 h mmHg
Control	101±10	70±14 *	60±10 *	53±7 *
Albumin	102±12	64±9 *	89±6 +	65±5 #*
Gelatine	104±12	68±17 *	94±9 +	63±9 #*
HES	100±11	62±7 *	90±7 +	60±7 #*
Saline	108±10	67±17 *	84±11 +	61±6 #*

* Difference compared with baseline values; # difference between values after the infusion and 3 h after the infusion; + difference compared with the control group ($p<0.001$). Data expressed as mean ± SD.

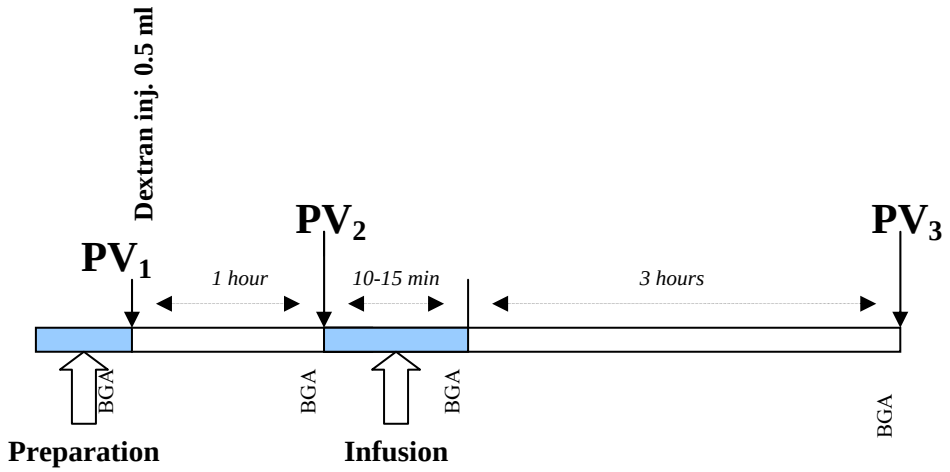
Dextran inj. 0.5 ml
PV1
PV2
PV3
1 hour
10-15 min
3 hours
BGA
BGA
BGA
BGA
Preparation
Infusion

Fig. 1.

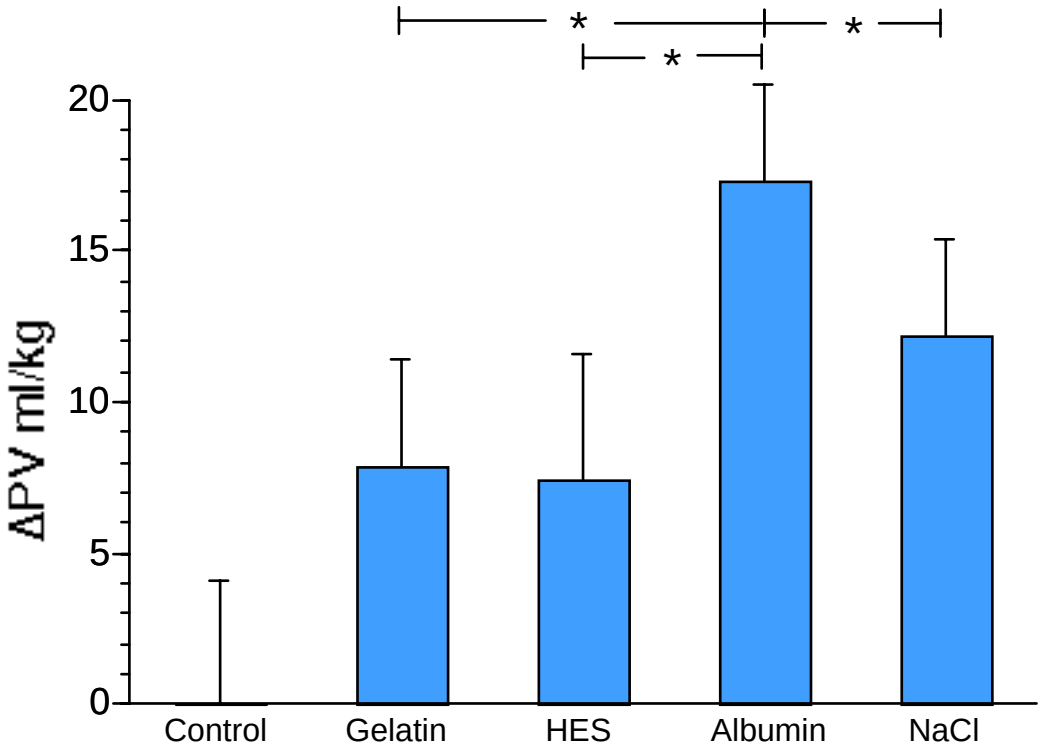
*
*
*
20
15
10
5
0
ΔPV ml/kg
Control
Gelatin
HES
Albumin
NaCl

Fig. 2