RESEARCH ARTICLE

Comparison of Plasma Viscosity Following Administration of Albumin 5% in Half-Normal Saline versus Normal Saline during Minor Surgeries

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Background: We aimed to compare the effect of albumin 5% in half normal saline (half NS) versus normal saline (NS) infusion on the plasma viscosity in the near-normal physiological condition. According to the high oncotic pressure of albumin along with prolonged half-life of its molecules in comparison to NS in the intra-vascular compartment, it has been proposed that a more significant reduction of the plasma viscosity might be expected after the infusion of albumin.

Methods: A total of 56 patients referring to the general operating room for their elective minor surgeries were evenly divided into two groups (V1, V2). It was calculated that 28 patients were needed to be enroll in each study group to detect a difference as big as 0.15 millipoise (mPa.s) with a statistical power of 80%. The V1 group received 1000 ml of NS but the V2 group received 1000 ml of recombinant albumin 5% in half NS within one hour, as fluid replacement therapy, during the intra-operative period. We have designed a simple measurement system according to Poiseuille's formula by which the viscosity value could be measured reliably since the system was calibrated frequently using distilled water as a reference.

Results: The mean value of the pre-operative plasma viscosity of the patients was 1.73 ± 0.25 mPa.s and 1.76 ± 0.21 mPa.s in V1 and V2 groups respectively. After the infusion of the fluids, the mean viscosity values decreased to 1.68 ± 0.30 mPa.s and 1.66 ± 0.17mPa.s in V1 and V2 groups respectively (p= 0.37).

Conclusion: The plasma viscosity reduction in patients of V2 group was not significantly different from that of V1 group.

Keywords: plasma viscosity; albumin; normal saline; Poiseuille's formula

It is not clear yet what type of fluid, colloid or crystalloid, is the best as to for intra-operative fluid replacement therapy [1]. Colloids are thought to be superior to crystalloids in terms of plasma viscosity reduction. It is known that hematocrit, erythrocyte deformability, plasma viscosity and temperature are the four principal contributors which have an effect on the value of blood viscosity [2-5]. Furthermore, it seems that plasma viscosity is tightly adjusted by regulatory centers in the brain. Plasma viscosity is influenced by some plasma constituents such as fibrinogen, immunoglobulin, albumin and lipoproteins [4-7].On the other hand, it has been found that whole blood viscosity is a very important clinical entity, because it is one of the main factors responsible in the pathogenesis of thrombotic events in humans [4-8]. There are many clinical studies that have investigated the significance of some blood constituent, other than albumin, on blood viscosity, while evaluating different means to diminish it and enhance the tissue perfusion in either normal or compromised hemodynamic states [9-17] Moreover, there are a few studies evaluating the effects of various types of fluids, such as albumin-contained ones on the viscosity [18-23]. Because the plasma viscosity itself is one of the principal contributors of the blood viscosity and there is rarity of facts in this field in the literature, we aimed to evaluate the effect of albumin 5% infusion versus normal saline (NS) on plasma viscosity, in near-normal physiologic condition.

Methods

This study is a single-blind randomized clinical trial to compare the viscosity of human plasma after administration of recombinant albumin 5% in half normal saline (half NS) versus normal saline (NS) in patients undergoing minor orthopedic or hernia repair surgery. The Ethics committee of Tehran University of Medical Sciences permitted the execution of the study. Having got that permission, the project was registered in the Iranian Randomized Clinical Trial (IRCT) website (IRCT2013022312573N1). All patients of both genders (ASA I) between 20-50 years old, who were the candidates of receiving either spinal or general anesthesia for minor surgeries, were eligible to be included in our study. The exclusion criteria considered very conservative to keep patients from probable risk of a rigid protocol for fluid

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replacement therapy. The exclusion criteria were existence of any type of co-morbid diseases, any history of anticoagulants and anti-platelet drugs consumption during the past 24 hrs, need to administer more than one liter of either fluid or blood product during surgery, pre-operative administration of any type of fluid in the past 24 hrs, occurrence of any unexpected disturbance in hemodynamic, respiratory or nervous system during operation, bleeding of more than 400 milliliter, preoperative hemoglobin of less than 12 g/dl and body mass index (BMI) of higher than 30 kg/m2. The study was performed from June to November 2012 in the general operating room of Sina Hospital. Fifty-six eligible patients were randomly divided into two equal groups using block randomization software. The informed consent was procured from the patients prior to surgery. All patients underwent either spinal or general anesthesia using a similar standard method, while the standard monitoring was established for all, throughout the operation. All patients received 5ml/kg of NS as compensated volume expansion (CVE), started ten minutes before the induction process, to lessen the hypotension due to vasodilatation. Intra-operative fluids were administered via a large-bore ante-cubital vein catheter during one hour; 1000 ml NS (group V1) versus 1000 ml recombinant albumin 5% in half NS (group V2) were given to the patients. In patients who underwent spinal anesthesia, every patient received 0.05 mg/kg of midazolam and 2µg/kg of fentanyl just after confirming the acceptable level of anesthesia using pinprick test. General anesthesia was performed using midazolam and fentanyl as premedication agents and propofol and artacurium as inducting agents. To maintain anesthesia, Isoflurane (0.5-1.5%) was used in an air/oxygen mixture. In each method, the performed anesthesia technique was the same for all patients. The operating room temperature was tightly kept at 23º C during the study. Two blood samples were taken from the patients; the baseline samples were drawn after IV establishment and before initiating the anesthesia and the second blood samples were taken one hour after the completion of fluid infusion. Considering the facts that albumin 5% in half NS is an iso-oncotic solution and its intra-vascular residence time is about 4 hours (intra-vascular residence time for NS is 30-60 minutes), it was assumed that the majority of infused albumin molecules may remain in intra-vascular space one hour after the termination of fluid infusion and may result in a lower viscosity value [24-26]. As blood is a non-homogenic and non-Newtonian fluid, its dynamic viscosity cannot be measured simply using Poiseuille's formula and it needs modern and pricy viscometers. Nonetheless, the plasma of human blood is a Newtonian fluid and its viscosity does not depend on flow characteristics. So, its viscosity can be measured using Poiseuille's formula [3-27]. Thus, we have set up a delicate measurement system using simple devices, capable of being calibrated with distilled water, with which we could perform the study according to Poiseuille's formula. The method of viscosity measurement was as follow: 10 ml of the patient's blood was drawn in a syringe, in which we have already poured 100 units of heparin for preventing clot formation. The syringe was centrifuged for three minutes and then was kept motionless for 10 minutes until the liquid phase separated from the cells. Accordingly, 5ml of the separated plasma was drawn into a low-friction syringe (20ml). Afterwards, we put a three way stopcock on the exit of the syringe. In one way of that stopcock, we put a 23-gauge hollow standard needle and in the other exit, an extension tube was fixed. Eventually the aforementioned syringe was located in its right position on the infusion pump and then the pump started infusing at the rate of 1 ml per minute. The plasma exited from the 23-gauge hollow needle and its back pressure made a column in the extension tube which stood at the point that the weight balances with the back- force generated by the pump infuser (Figure 1).All of the above-mentioned parts of this system have been exchanged with a new one for each patient. The height of the fluid column in the extension tube was recorded in millimeter and was used for loading the Poiseuille's formula (Figure 2):

$\eta = (\pi P R^4)/ (8 Q L)$

η: Viscosity that is calculated in millipoises (mPa.s)

π: Constant number (3.14)

P: Recorded pressure (water column height in millimeter)

Q: Constant flow of the plasma through the needle (1 ml/min)

R: Needle radius (0.165 millimeter)

L: Length of needle (32 millimeter)

Figure 1- Picture of plasma viscosity measurement system

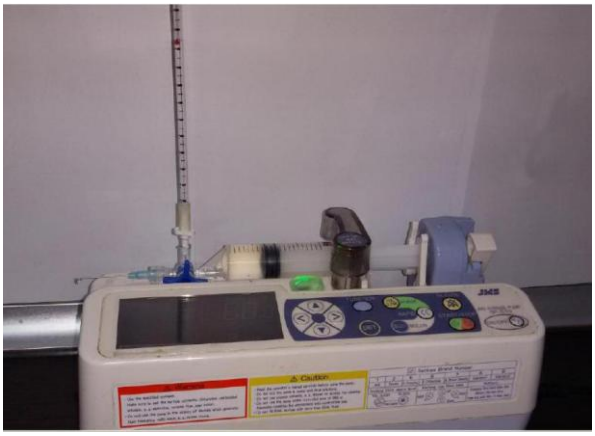
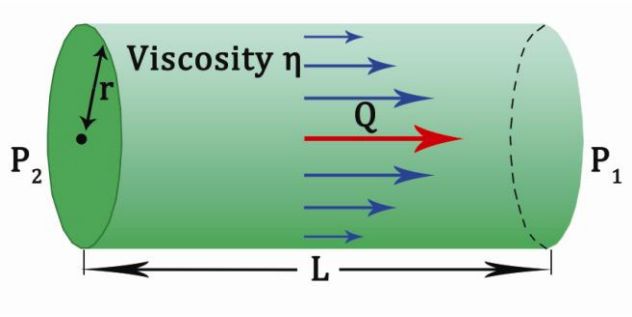


Figure 2- A scheme showing variables of Poiseuille's formula



After loading all known parameters in the above formula, we calculated the value of viscosity for each sample. Before every plasma viscosity measurement, we calibrated the system using distilled water (Temperature = 23º C) as a reference. With regard to the known viscosity of distilled water (1mPa.s), the height of distilled water column in the extension tube stopped at 92 millimeters. This height was regarded as a reference point for the study. Demographic parameters along with the laboratory variables (sodium, potassium, blood sugar, complete blood count, total protein, albumin, blood urea, and creatinine), amount of bleeding, and duration of surgery were recorded for all patients. In order to assess the primary outcome plasma viscosity between the two groups was compared one hour after completion of fluid infusion. Heart rate and mean arterial blood pressure were all

recorded every ten minutes during the study period as secondary outcomes.

Statistical Analysis

According to a pilot study and literature review, we chose a 0.15 mPa.s difference in the values of viscosity between the two groups of the study as a treatment effect size. By enrolling 28 patients in each group, we could detect that difference with a statistical power of 80% (we considered type I error equals 0.05). For description of qualitative and quantitative variables, we used frequency with percentile and mean ±SD, respectively. The comparison between the two groups was performed with T Test (CI = 95%). For elimination of the effect of baseline values, we used ANCOVA analysis. A p-value of less than 5% was considered significant. We used SPSS version 19.1 soft ware (Chicago, Il, USA) for analyzing the data.

Results

Among 62 patients who were candidate of enrolling into the study, 56 were eligible and were randomized evenly into two groups. Afterwards, none of the patients were excluded during the course of the study and the data of the selected 56 patients were entered into the final analysis. Flow-chart of the study progress is shown in (Figure 3). Comparison of the demographic variables, type of anesthesia, preoperative, and intra-operative variables of both groups are shown in (Table 1). The mean preoperative viscosity value in V2 group was 1.76± 0.21 mPa.s and decreased to 1.66± 0.17 mPa.s after infusion of albumin (p= 0.058).The mean preoperative viscosity value in V1 group was 1.73± 0.25 and decreased to 1.68± 0.30 after the infusion of NS (p= 0.836). The larger decrease in the mean viscosity value of the V2 group (albumin) was not statistically significant in comparison to another group (p= 0.37). In terms of hemodynamic variables, no significant difference was detected between the two groups ($p \geq 0.05$). Statistical comparisons of the primary outcome with their related p values are presented in (Table 2).

Discussion

The main concept conveyed from the current study is that in near-normal physiological condition, especially during minor surgeries, the impact of the type of the replacement fluid (albumin 5% in half NS versus NS) on plasma viscosity is negligible. Leonhardt through a study using capillary viscometer found that a high lipoprotein concentration in plasma is correlated with elevated viscosity values of plasma [28]. In addition, Blann found that acute phase reactants like von Willebrand factor and fibrinogen, and not the albumin, are major contributors to high plasma viscosity [29]. The results of the mentioned study were concurrent with our recent one. Moreover, Haidekker measured the viscosity of human plasma with a Brookfield viscometer and reported it as 1.60 mPa.s at 21° C. In that study, the mean baseline viscosity value and the temperature at which the measurements took place were the closest to the current study [30]. Using a capillary viscometer, Késmárky determined that normal plasma viscosity is in the range of 1.10-1.30 mPa.s at 37° C and that it is independent of age and gender. They proposed that plasma viscosity measurement could be used instead of erythrocyte sedimentation rate and C-reactive proteins in follow up of various inflammatory processes [31].

Table 1- Comparison of demographic, type of anesthesia, preoperative, and intraoperative variables of the two groups

		Sex			P Value
		Male	Female	Total	
Fluid	N.S.	15	13	28	0.09
	Albumin	21	7	28	
Total		36	20	56	

		Anesthesia			P Value
		GA	SA	Total	
Fluid	N.S.	18	10	28	0.4
	Albumin	15	13	28	
Total		33	23	56	

	Fluid	Mean	Std. Deviation	P value
Age (year)	NS	33.7	11.28	0.99
	Albumin	33.6	9.54	
BMI	NS	24.8	3.75	0.82
	Albumin	24.6	3.37	
Duration (hour)	NS	1.3	0.16	0.31
	Albumin	1.2	0.28	
Bleeding (ml)	NS	170	135.04	0.75
	Albumin	180	111.43	
Na (mEq)	NS	140.5	2.13	0.93
	Albumin	140.4	2.33	
K (mEq)	NS	4.0	0.27	0.57
	Albumin	3.9	0.32	
Urea (mg/dl)	NS	29.3	8.90	0.06
	Albumin	33.8	8.25	
Creatinine (g/l)	NS	1.05	0.17	0.18
	Albumin	1.14	0.29	
Haemoglobin (g/dl)	NS	13.96	1.61	0.43
	Albumin	14.35	2.00	
Platelet (per ml)	NS	263000	66.41	0.99
	Albumin	252000	74.64	
WBC (per ml)	NS	7290	1.81	0.16
	Albumin	8120	2.50	
BS (mg/l)	NS	96.6	24.84	0.70
	Albumin	99.2	25.16	
Total Protein (g/dl)	NS	7.11	0.70	0.91
	Albumin	7.09	0.74	
Albumin (g/dl)	NS	4.35	0.59	0.83
	Albumin	4.38	0.51	

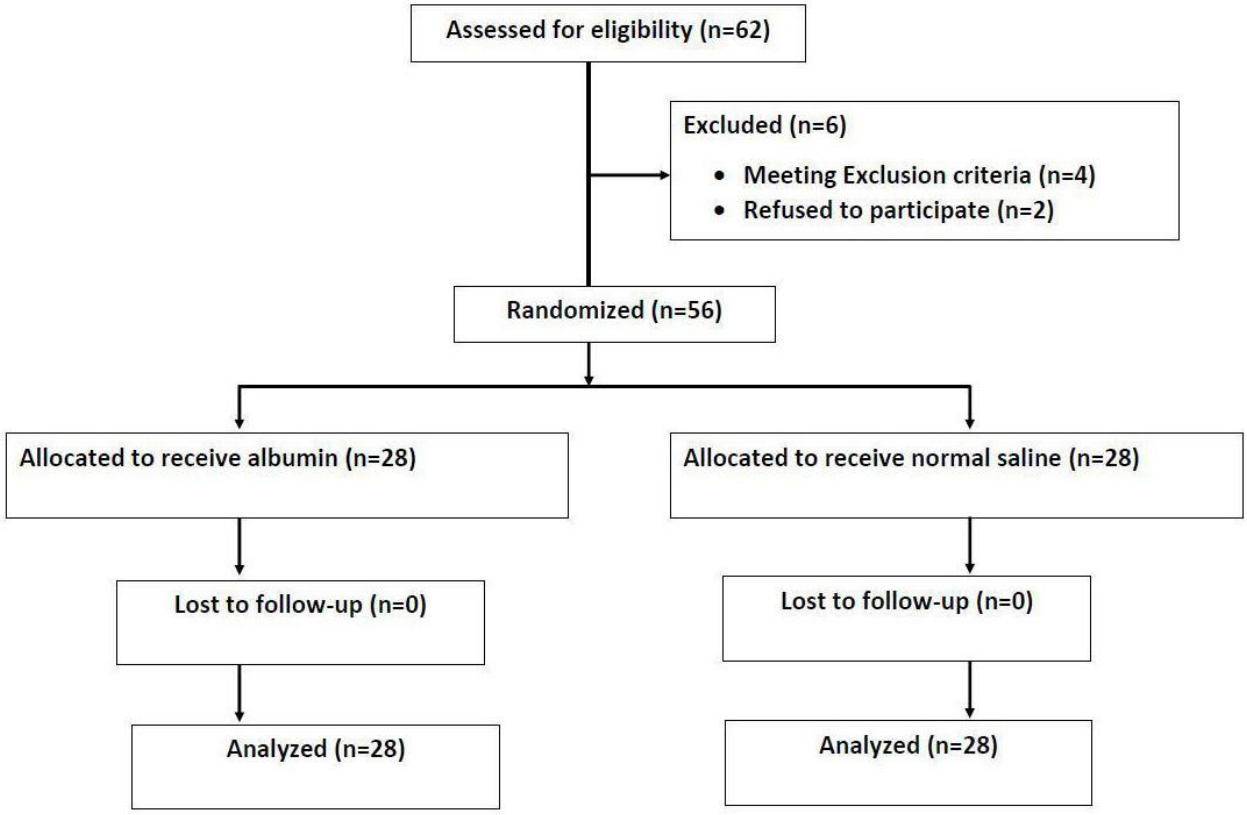
NS, normal saline; BMI, body mass index; BS, blood sugar; WBC, white blood cell; K, potassium; Na, sodium; SA, spinal anesthesia; GA, general anesthesia

Table 2- Comparison of the plasma viscosity levels between and in the groups

	NS(V1)	Albumin (n=28)	P value (between groups)
Before infusion millipoise (mean ± SD)	1.73± 0.25	1.76± 0.21	0. 37*
After infusion millipoise (mean ± SD)	1.68± 0.30	1.66± 0.17	
P-value (within group)	0.836	0.058	

SD, standard deviation; *, ANCOVA analysis; NS, normal saline

Figure 3- Flow diagram of subject progress through the phases of RCT



The baseline viscosity in the current study was in the range of 1.73- 1.76 mPa.s which was higher than Késmárky's study. The reasons are assumed to be as follow: one, all patients in the current study were fasting for a long time and were more dehydrated. Two, the temperature at which viscosity measurements were performed in the current study was 23º C that was 14 degrees lower than that of Késmárky's study. On the other hand, Vlastos GA and his colleagues, through a study on 17 healthy adults after 12-14 hours of fasting, reported that the mean baseline plasma viscosity at 37º C was 1.31±0.07 mPa.s [32]. The difference between the results of the current study and Vlastos's study is probably due to the temperature at which measurements were performed. It has been reported that temperature by itself, especially under 25º C, has a great impact on blood viscosity [33]. Bolts J thoroughly, reviewed the effects of albumin administration on different types of patient populations. He infused albumin 5% as a perioperative replacement fluid, and no more benefit in terms of hemodynamic variables was detected in comparison to crystalloids [26]. In the current study, we could not find a significant difference regarding the hemodynamic variables between the two groups, as well. This study had some limitations. The results of this study were limited to the ASA I patients who had undergone minor surgeries. Although we had no access to the state-of-the-art of the new viscometers to compare our viscosity measurement system with it, we designed an innovative system that undertook the calibration process using distilled water as a standard fluid with known viscosity value at a fixed temperature. Furthermore, if there was any deviation in measurement of viscosity in comparison to a modern viscometer, it would be applicable to all measurements. That is why the relative comparison between the groups is reliable.

In conclusion, although infusion of both albumin 5% in half NS and NS resulted in a lower plasma viscosity value, and the albumin 5% could decrease it further, none of them could reduce the viscosity value at a statistically significant

level. It seems that the albumin containing colloid solution is not as good as that has been thought at least in terms of viscosity reduction.

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