Effects of Intraoperative Gelatin on Blood Viscosity and Oxygenation Balance

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Purpose: *We aim to investigate whether hemortheology and oxygenation balance are affected by intraoperative gelatin infusion, whether it poses a threat to the perioperative well-being of the patients, and thus creates difficult conditions for postanesthesia care.*
Design: *A randomized controlled clinical trial.*
Methods: *After anesthesia induction, 10 ml/kg succinylated gelatin was infused. Arterial blood gas analysis was performed, and whole blood viscosity and vital signs were recoded both before and after the infusion.*
Findings: *High shear and medium shear viscosities decreased (*$P = .003$ *and* $P = .04$*, respectively) after the infusion of both gelatin and Ringer's lactate. The peripheral vascular resistance was not significantly changed by the infusion of either fluid (*$P = .31$*). Ringer's lactate reduces the body's oxygen delivery index (*$P = .01$*).*
Conclusions: *Gelatin better maintains blood viscosity and stabilizes the body's oxygenation balance.*

Keywords: *hemortheology, blood viscosity, oxygenation balance, vascular resistance, perioperative care.*

GELATIN IS A 4% w/v solution used as an intravenous colloid and behaves much like blood filled with albumins. It is a clear colorless or slightly yellowish sterile solution and composed of polypeptides that are derived from animal collagen (eg, skin, tendons, bones), which are highly hydrolyzed. It is used to replace blood and body fluid and is widely used in the perioperative period as a substitute for plasma expansion in replacing volume deficits. Unlike crystalloid solution, gelatin is considered to be more stable within the vasculature because it has a high molecular weight and creates a higher colloid osmotic pressure to prevent itself from easily permeating through

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Conflict of interest: None to report.

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perivascular spaces, slowing down the development of tissue edema in the perioperative period, lowering the chances of pulmonary edema in postoperative care, and providing better physical condition for the management of postanesthesia nursing.[1-3]

Plasma expanders such as gelatin are commonly used to manage critically ill patients, who may exhibit altered hemorheology due to changes in blood viscosity.[4] However, during surgeries, blood viscosity is typically not monitored because no existing technology can provide simple, continuous, noninvasive analysis.[5] One preconception of potential benefit in the use of colloid solution is that it decreases blood viscosity and improves microcirculation and hemorheology.[6]

Hemorheology is the study of blood flow in a vessel with an emphasis on the behavior of the erythrocytes as they interact and as quantifiable biophysical patterns emerge from the interactions of erythrocytes in the vascular system.[7] Blood flow in large arteries is dominated by inertial forces exhibited at high flow velocities. In micro vessels, the blood flow is dominated by viscous shear forces as the inertial forces are negligible because of low flow velocities. As a result, blood viscosity is a crucial hemorheological factor in modulating microcirculation and organ perfusion.[8] High blood viscosity causes blood flow stagnation and, subsequently, leads to pathological thrombotic events, increasing the incidence of intraoperative ischemic stroke,[9] delayed postanesthesia recovery, and postoperative cognitive dysfunction, especially in the elderly. In the resuscitation of burn shock, the clinical effect of Gelatin treatment is similar to that of plasma treatment. Gelatin appears to be a fairly good plasma substitute for extensive application on the management of burn shock during the early stage.[10] This idea is promoted by colloid manufacturers and wildly shared by many convinced clinicians. However, we failed to find any data to verify this conception. No study in this regard has yet been published. So the question remains whether the infusion of colloid solution such as gelatin will indeed alter the normal rheological state. Will the alteration of blood viscosity affect the perfusion of vital organs such as the heart and lung, which will pose a threat to the circulatory hemodynamics and affect the lung's oxygenation condition, result in the altered state of oxygen delivery, and compromise the oxygenation balance.

Objective

The aim was to investigate how a colloid solution alters the rheology of circulation. We used a viscometer to test blood viscosity and its derivative indices both before and after the infusion of gelatin. In addition, we also calculated and compared the corresponding oxygen delivery and consumption indices to evaluate gelatin's effect on the body's oxygenation balance.

Methods

The study was registered at clinicaltrials.gov (NCT02631356) and was approved by the ethics committee of the first hospital of the Sun Yat-Sen University (approval no.: [2015]22). Patients were recruited from the First Affiliated Hospital of the Sun Yat-Sen University. Ten patients were randomly placed into two groups (5 patients each), according to a randomized table. The inclusion and exclusion criteria for participants are listed in Table 1. Informed consent was obtained from all patients.

Testing

After the induction of general anesthesia, an arterial blood sample was drawn for blood gas analysis (GEM Premier 3000; Instrumentation Laboratory, New York) and for the testing of whole blood viscosity (Viscometer LB-2A; Tangyu, Tianjin, China). Then, 10 ml/kg of fluid (succinylated gelatin/Ringer's lactate) was infused through the central venous line within 15 minutes. After the infusion, the arterial blood sample was once again tested for viscosity and blood gas.

The primary and secondary outcomes are listed in Table 2. High and medium shear viscosities are commonly used to estimate the degree of red blood cell (RBC) aggregation in various blood products and RBC suspensions. A high shear viscosity is normally measured at 200s-1 shear rate and is mainly associated with RBC deformability. Medium shear and low shear viscosity are normally measured at 50s-1 and 1s-1-5 s-1 shear rates, and they are mainly associated with RBC aggregation. The systemic vascular resistance index (SVRI)

Table 1. Criteria for Participants

Inclusion Criteria	Exclusion Criteria
ASA I-II	Laparoscopic surgery
General anesthesia	Thoracic surgery
	Cardiovascular surgery
	Severe cardiovascular malfunction
	Unstable hemodynamic
	Moribund patient

ASA I-II, American Society of Anesthesiologists Physical Classification System.

and oxygen delivery and consumption indices were calculated using the following calculations: SVRI = 80 × (mean arterial pressure - central venous pressure)/cardiac index (CI); $DO_2I = CI \times CaO_2 \times 10$; $VO_2I = CI \times (CaO_2 - CvO_2) \approx CI \times 1.38 \times Hb \times (SaO_2 - SvO_2)$. Oxygen delivery and consumption index are functional assessments of the oxygenation balance in the microcirculatory system. The secondary outcomes listed are related to the mechanical properties of the erythrocytes.

Statistical Analysis

Data in each group were examined for normality using the Kolmogorov-Smirnov test. Unpaired Student *t* tests and Mann-Whitney U-tests were used to test for variables with and without normal distribution, respectively. Paired data were compared with paired sample *t* tests. A *P* value of < 0.05 was considered significant. IBM SPSS Statistics 19.0. was used as the statistical package for the study.

Table 2. Study Outcomes

Primary Outcomes	Secondary Outcomes
High shear viscosity	Erythrocyte aggregation index
Medium shear viscosity	Rigidity index
Low shear viscosity	Deformation index
SVRI	Electrophoresis index
Oxygen delivery index (DO_2I)	Blood yield stress
Oxygen consumption index (VO_2I)	Internal fluid viscosity of RBC

SVRI, Systemic Vascular Resistance Index; RBC, red blood cell.

Results

Patient Demographics

Preoperative demographic data presented no significant differences between the gelatin and Ringer's lactate groups (Table 3).

Whole Blood Viscosity

The high, medium, low shear whole blood viscosities were compared between the groups of succinylated gelatin and Ringer's lactate solution before and after the infusion. No significant differences were observed in whole blood viscosity between the two groups both before and after the infusion (Figure 1).

After the infusion, the high and medium shear viscosities decreased both in the succinylated gelatin and Ringer's lactate solution groups. Compared with the gelatin group, viscosity in the Ringer's lactate solution group decreased more dramatically (Figure 1).

Blood Viscosity Derivatives

The erythrocyte aggregation index, rigidity index, deformation index, electrophoresis index, blood yield stress, and internal fluid viscosity of RBCs were not significantly altered after the infusion of both succinylated gelatin and Ringer's lactate solution (Table 4).

Hemodynamics and Systemic Vascular Resistance

There was no significant difference in the mean arterial pressure, central venous pressure, CI,

Table 3. Patient Demographics

	Ringer (n = 5)	Gelatin (n = 5)	*P*
Age (y)	51.00 ± 13.56	49.60 ± 9.63	.86
Height (m)	1.72 ± 0.09	1.68 ± 0.05	.42
Weight (kg)	68.40 ± 8.01	67.60 ± 8.85	.88
BMI	23.22 ± 2.66	24.04 ± 3.77	.70
BSA (m^2)	1.77 ± 0.14	1.74 ± 0.11	.68
Hematocrit (%)	36.8 ± 5.63	37.6 ± 3.65	.80
Hemoglobin (/L)	11.94 ± 2.17	11.74 ± 1.48	.80

BMI, body mass index; BSA, body surface area.

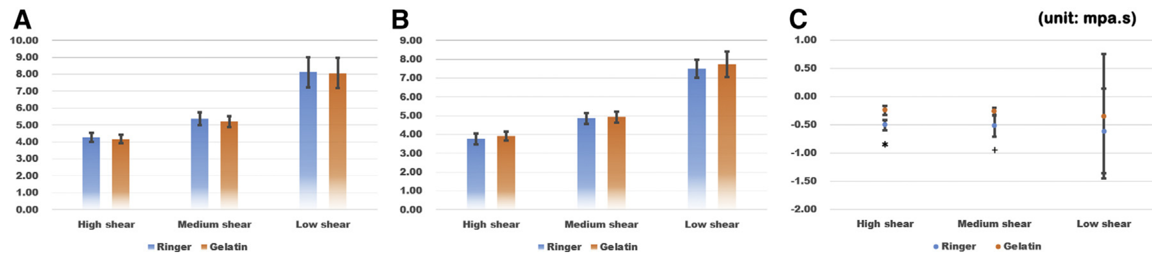

Figure 1. (A) Blood viscosity before the infusion. No significant difference was observed in the whole blood viscosity between the two groups before the infusion (all $P > 0.05$). High shear viscosity: Ringer 95% CI (4.02, 4.53) (mpa.s), gelatin 95% CI (3.92, 4.41) (mpa.s). Medium shear viscosity: Ringer 95% CI (4.99, 5.76) (mpa.s), gelatin 95% (4.87, 5.53) (mpa.s). Low shear viscosity: Ringer 95% CI (7.23, 9.00) (mpa.s), gelatin 95% (7.19, 8.95) (mpa.s). (B) Blood viscosity after the infusion. No significant difference was observed in the whole blood viscosity between the two groups after the infusion (all $P > 0.05$). High shear viscosity: Ringer 95% CI (3.48, 4.06) (mpa.s), gelatin 94% CI (3.67, 4.16) (mpa.s). Medium shear viscosity: Ringer 95% CI (4.56, 5.15) (mpa.s), gelatin 95% CI (4.64, 5.22) (mpa.s). Low shear viscosity: Ringer 95% CI (7.03, 7.97) (mpa.s), gelatin 95% CI (7.04, 8.40) (mpa.s). (C) Blood viscosity changes after the infusion. Comparison between the succinylated gelatin and Ringer's lactate solution groups (*$P < 0.01$, +$P < 0.05$). High shear viscosity: Ringer 95% CI (-0.60, -0.42) (mpa.s), gelatin 95% CI (-0.32, -0.17) (mpa.s). Medium shear viscosity: Ringer 95% CI (-0.71, -0.33) (mpa.s), gelatin 95% CI (-0.34, -0.20) (mpa.s). Low shear viscosity: Ringer 95% CI (-1.36, 0.13) (mpa.s), gelatin 95% CI (-1.45, 0.75) (mpa.s). CI, confidence interval. This figure is available in color online at www.jopan.org.

and SVRI both before and after the infusion of succinylated gelatin and Ringer's lactate solution (all $P > 0.05$) (Table 5).

Oxygen Delivery and Consumption

Both before and after the infusion, there was no significant difference in the oxygen delivery and consumption indices between the succinylated gelatin and Ringer's lactate groups (all $P > 0.05$) (Figure 2A; Figure 2B). But in the Ringer's lactate solution group, the oxygen delivery index (DO_2I) decreased significantly after the infusion (paired t test, $P = 0.01$); the oxygen consumption index (VO_2I) remained unchanged, without significant statistical difference (Figure 2C). Compared with the Ringer's lactate group, the oxygen delivery and consumption indices remained relatively

Table 4. Blood Viscosity Derivatives Before and After the Infusion

	Before Infusion			After Infusion			Change in Value		
Arterial Blood	**Ringer**	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***
Erythrocyte aggregation index	2.12 ± 0.29	2.22 ± 0.35	.63	2.05 ± 0.22	2.12 ± 0.30	.69	-0.07 ± 0.09	-0.10 ± 0.13	.67
Erythrocyte rigidity index	6.10 ± 2.04	6.47 ± 1.72	.76	6.04 ± 1.85	6.45 ± 1.43	.70	-0.06 ± 0.28	-0.02 ± 0.31	.84
Erythrocyte deformation index	0.89 ± 0.11	0.91 ± 0.10	.84	0.88 ± 0.10	0.89 ± 0.11	.93	-0.01 ± 0.04	-0.02 ± 0.03	.72
Erythrocyte electrophoresis index	4.96 ± 0.95	4.98 ± 1.20	.98	5.10 ± 0.79	5.12 ± 0.89	.98	0.14 ± 0.21	0.14 ± 0.35	.99
Blood yield stress (mpa)	15.14 ± 1.75	15.04 ± 2.51	.94	14.96 ± 1.27	14.93 ± 1.95	.97	-0.18 ± 0.58	-0.11 ± 0.86	.89
Internal fluid viscosity of red blood cell (mpa)	1.95 ± 0.95	2.15 ± 0.92	.74	1.92 ± 0.85	2.07 ± 0.71	.77	-0.02 ± 0.12	-0.08 ± 0.38	.76

Table 5. Comparison of MAP, CVP, CI, SVRI

	Before Infusion			After Infusion			Change in Value		
	Ringer	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***
MAP (mmHg)	76.20 ± 8.61	78.20 ± 6.42	.69	78.60 ± 8.79	80.80 ± 6.02	.66	2.40 ± 2.30	2.60 ± 1.95	.89
CVP (mmHg)	4.80 ± 2.59	3.80 ± 2.05	.52	6.40 ± 3.36	5.00 ± 2.00	.45	1.60 ± 1.14	1.20 ± 0.84	.54
CI (L/min/m^2)	2.84 ± 0.28	2.73 ± 0.60	.71	2.64 ± 0.33	3.08 ± 0.82	.30	-0.22 ± 0.37	0.35 ± 0.62	.12
SVRI (Dynes.sec/cm^5/m^2)	1776.15 ± 182.34	1944.17 ± 334.69	.35	1940.16 ± 163.78	1847.35 ± 663.30	.77	164.00 ± 212.93	-96.82 ± 497.52	.31

MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SVRI, Systemic Vascular Resistance Index.

stable in the gelatin group (the changes were relatively small in the gelatin group) (Figure 2C).

Blood Lactic Acid Level

In the gelatin group, the blood lactic acid level demonstrated little change (Table 6). But, the infusion of Ringer's lactate solution could increase blood lactate acid levels ($P < 0.01$).

Conclusions and Discussion

The results indicate that colloid solution such as gelatin can better maintain the blood viscosity levels at high and medium shear rates. The blood viscometer we used demonstrates great accuracy in the testing of whole blood viscosity at high, medium, and low shear rates. Whole blood viscosity is very much dependent on the shear rate. Viscosity usually increases when shear rate decreases. The "shear rate" in rheological term is similar to the velocity gradient. In human body, it can be determined by the diameter of blood vessel. The high shear rate presents fast blood flow in the small blood vessels diameter, and the low shear rate presents slow blood flow in larger vessels.[11] As a result, the selections of blood viscosities at high/medium/low rates in our study simulate a wider range of hemodynamic spectrum in the human body. The result in this study indicates that blood viscosities in small and medium vessels are better maintained by the use of gelatin, implicating that the blood viscosities are better maintained in the large and medium vessels such the pulmonary artery and aorta by the infusion of gelatin. This means that gelatin can better preserve the systemic volume but may be equally detrimental as crystalloid in creating tissue edema as a result of the low blood viscosity in the capillary systems. Extreme conditions can lead to pulmonary edema, resulting in desaturation, posing challenges for postanesthesia nursing care. In view of the importance of physiology and pathology of capillary circulation, blood viscosity and fluidity in the capillaries can be significantly affected in diseases such as cardiac and brain infarcts, diabetic gangrene, and many others.[12]

In addition to the measuring of whole blood viscosity at high, medium and low shear rates, derived indices such as the erythrocyte aggregation index, rigidity index, electrophoresis index, blood yield

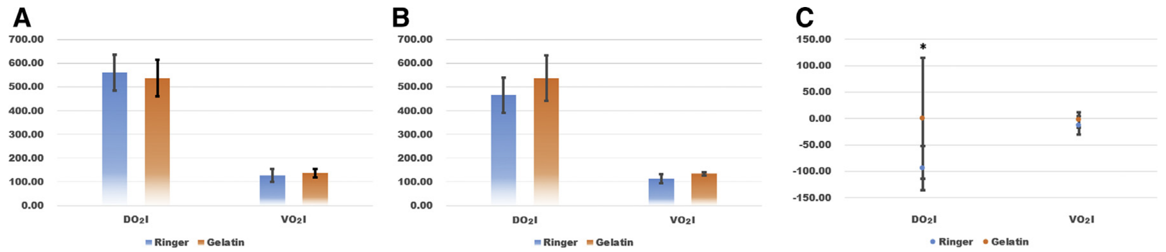

Figure 2. (A) DO_2I and VO_2I before the infusion. No significant difference was observed in the oxygen delivery (DO_2I) and consumption indices (VO_2I) between the succinylated gelatin and Ringer's lactate groups before the infusion ($P > 0.05$). DO_2I: Ringer 95% CI (484.50, 635.23), gelatin 95% CI (461.18, 613.49). VO_2I: Ringer 95% CI (100.48, 154.63), gelatin 95% CI (119.19, 154.13). (B) DO_2I and VO_2I after the infusion. No significant difference was observed in the oxygen delivery (DO_2I) and consumption indices (VO_2I) between the succinylated gelatin and Ringer's lactate groups after the infusion ($P > 0.05$). DO_2I: Ringer 95% CI (391.08, 539.61), gelatin 95% CI (441.80, 633.82). VO_2I: Ringer 95% CI (94.83, 133.54), gelatin 95% CI (127.01, 140.98). (C) DO_2I and VO_2I changes after the infusion. Analysis of the oxygen delivery index change in the Ringer's lactate solution group after the infusion (*paired *t* test, $P = 0.01$). DO_2I: Ringer 95% CI (-136.38, -52.66), gelatin 95% CI (-114.21, 115.15). VO_2I: Ringer 95% CI (-30.82, -4.07), gelatin 95% CI (-17.42, 12.09). CI, confidence interval. This figure is available in color online at www.jopan.org.

stress, and internal fluid viscosity of RBC can be calculated based on the relative and reduced viscosity. These hemorheological indices are important for clinical diagnoses.[13] For example, the aggregation index of erythrocyte will increase under pathological conditions when the blood viscosity in low shear rate is high.[14] A higher rigidity index of the erythrocyte means the deformability of RBC is low, which means the erythrocytes are less unlikely to travel through small capillaries and the tissue perfusion will likely be impaired. Under such condition, tissue edema, lower oxygen delivery index, and a higher blood viscosity at high shear rate are normally observed. This increase of rigidity index typically happens when the fluid infused is causing a state of hypotonic or hypertonic stress, so much so that the deformability of RBC is impaired. An increased blood yield stress of RBC indicates pathological conditions such as hypertension, hyperglycemia, thrombosis, and thrombocytosis. Under these conditions, the RBCs are prone to aggregate, causing the aggregation index to rise and the erythrocyte electrophoresis index to decrease. A dramatic decrease of the electrophoresis index indicates rapid RBC sedimentation and is a sign for the risk of thrombosis.[13] Finally, the internal fluid viscosity of RBCs we included is related to the deformability of erythrocytes. A high internal fluid viscosity of RBCs means low deformability. Consequently, similar abnormalities of a high-rigidity situation will be observed. The blood viscometer we used in this study does not detect significant alterations in terms of these derivative indices, and we cannot exclude the possibility when overzealous administration of colloid or crystalloid fluid is performed during acute traumatic hemorrhage, these derivative indices may be affected.

The present data show that colloid fluid retains the oxygen supply and consumption indices better than crystalloid fluid. Although no significant difference in terms of the effect on the cardiac output

Table 6. Blood Lactate Level Before and After the Infusion

	Before Infusion			After Infusion			Change in Value		
	Ringer	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***	**Ringer**	**Gelatin**	***P***
Lactic acid (mmol/L)	0.76 ± 0.38	0.88 ± 0.41	.64	1.46 ± 0.34	0.86 ± 0.33	.02	0.70 ± 0.19	0.00 ± 0.1	< .01

and other hemodynamic indices are observed, it is likely that colloid fluid may better retain the cardiac uid as well as both the oxfluid as well as both the oxygen supply index (DO_2 = CI*$Ca0_2$*10) and the oxygen consumption index ($VO_2 = CI \times [CaO_2\text{-}CvO_2] \approx CI \times 1.38 \times Hb \times SaO_2\text{-}SvO_2$) are positively correlated with cardiac index. The results do indicate a slight increase of cardiac output in the colloid group to the contrary of that in crystalloid group. In addition, lactic acid levels were also assayed to evaluate tissue perfusion.[15] When systemic oxygen delivery does not meet tissue oxygen demands, tissue hypoperfusion begins. Tissue hypoperfusion leads to oxygen debt, cellular injury, organ dysfunction, and death. This is characterized by markers of tissue perfusion (central venous oxygen saturation and lactate), which reflect the interaction between systemic oxygen delivery and demands. For the last 2 decades, studies and quality initiatives incorporating the early detection and interruption of tissue hypoperfusion have been shown to improve mortality and altered sepsis care.[16] In the study, no significant alteration of acid level was observed after gelatin infusion. However, Ringer's lactate solution could increase the lactic acid level in the blood, and it could impair the ability to estimate a patient's liquid cycle and microcirculation reperfusion to some extent.

Conclusions

This is the first study to investigate intraoperative blood viscosities under the influences of colloid fluid. Many conventional cardiovascular risk factors have been independently linked to whole blood viscosity, such as hypertension, total cholesterol, and triglycerides. Changes in blood viscosity and vascular resistance can affect coronary perfusion as well as the microcirculation and coagulation function.[17] Thromboelastography (TEG) variables are also influenced by whole blood viscosity. TEG is a viscoelastic assessment of clot kinetics. It is well established that hematocrit influences whole blood TEG tracings. Hematocrit is the main determinant of whole blood viscosity.[18] When rapidly infusing a colloidal solution into the central vein, the local venous return will be diluted instantaneously, and this will quickly have an unfavorable influence on the oxygen-carrying capacity in pulmonary and coronary circulation. Furthermore, if patients have cardiopulmonary dysfunction, the use of a colloidal solution would be a potential risk factor.[19] As a result, during clinical rehydration of patients, blood viscosity monitoring should be considered as part of a cardiovascular risk assessment, whenever an increased cardiovascular risk is detected.

Our study will serve as a reference for clinical rehydration and promotes the idea of choosing an optimal fluid therapy solution. The results shed light on the physiological influences that the perioperative fluid management may incur, and ultimately the latent risks and challenges for postanesthesia nursing care.

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