ORIGINAL ARTICLE

Leukoreduced whole blood and platelet-sparing filter preserves its hemostatic function for 21 days: Could hemostatic resuscitation become a reality in Colombia?

Sangre total leucorreducida y filtro ahorrador de plaquetas preserva su función hemostática por 21 días: ¿La resucitación hemostática podría ser una realidad en Colombia?

Carlos Muñoz[1] ⓘ, Carmenza Macia[2] ⓘ, Edna Hernández[3] ⓘ, Mercedes Alcalá[4] ⓘ,
Mónica Guzmán-Rodríguez[5] ⓘ, Claudia Orlas[6] ⓘ, Yaset Caicedo[7] ⓘ, Alberto García[8] ⓘ,
Michael Parra[9] ⓘ, Carlos A. Ordoñez[10] ⓘ

1   MD, specialist in General Surgery, fellow of Trauma Surgery and Emergencies, Universidad del Valle, Cali, Colombia.
2   MD, specialist in Pathology, Blood Bank, Fundación Valle del Lili, Cali, Colombia.
3   Bacteriologist, Blood Bank, Fundación Valle del Lili, Cali, Colombia.
4   Bacteriologist, Clinical Laboratory, Fundación Valle del Lili, Cali, Colombia
5   MD, Master in Biomedical Sciences, PhD candidate, Instituto de Ciencias Biomédicas, School of Medicine, Universidad de Chile, Santiago de Chile, Chile.
6   MD, Research Fellow, Center for Surgery and Public Health, Department of Surgery, Brigham & Women's Hospital. Harvard Medical School & Harvard T.H. Chan School of Public Health, Boston, USA
7   MD, Centro de Investigaciones Clínicas (CIC), Fundación Valle del Lili, Cali, Colombia.
8   MD, specialist in General Surgery and Trauma Surgery and Emergencies, master in Epidemiology; Professor, General Surgery, Universidad del Valle y Universidad ICESI; Division of Trauma Surgery and Emergencies, Fundación Valle del Lili, Cali, Colombia.
9   MD, specialist in General Surgery and Trauma Surgery, Department of Trauma Critical Care, Broward General Level I Trauma Center, Fort Lauderdale, Florida, USA.
10 MD, FACS, specialist in General Surgery and Trauma Surgery and Emergencies; Professor, General Surgery, Universidad del Valle; Division of Trauma Surgery and Emergencies, Fundación Valle del Lili, Cali, Colombia.

Abstract

Background. Hemostatic resuscitation is a strategy to compensate for blood loss and reduce the impact of trauma-induced coagulopathy. However, balanced resuscitation presents challenges in its application in the clinical setting. Whole blood has re-emerged as a physiologic strategy with logistical advantages that offer the opportunity for early initiation of hemostatic resuscitation. The study aims to evaluate the cellular, coagulative, and viscoelastic properties of whole blood preserved for 21 days.

Methods. Whole blood units were donated by 20 healthy volunteers. These units were processed using a platelet-sparing leukoreduction filtration system. Units were stored under refrigeration (1-6°C), without agitation and were sampled on days 0, 6, 11, 16, and 21. The units were tested to assess their cellular properties and coagulation factors levels. In addition, viscoelastic features were tested using tromboelastography.

Results. Red blood cells count and hemoglobin levels remained stable. Platelet count had a 50% reduction by day 6, but remained stable until day 21. Coagulation factors II-V-VII-X, fibrinogen, and protein C remained within normal ranges. Tromboelastrography showed that the reaction time for clot formation was prolonged, but in the end, stable clot formation was not altered.

Conclusion. Leukoreduced whole blood with platelet sparing filter is able to retain its hemostatic properties for 21 days. This is the first step for Colombia in the clinical evaluation of this option, that will allow hemostatic resuscitation to become a universal reality in the patient with severe trauma.

Keywords: whole blood; blood preservation; hemostasis; resuscitation; hemorrhagic shock; blood transfusion.

Resumen

Introducción. La resucitación hemostática es una estrategia para compensar la pérdida sanguínea y disminuir el impacto de la coagulación inducida por trauma. Debido a que la disponibilidad de transfundir una razón equilibrada de hemocomponentes es difícil de lograr en el entorno clínico, la sangre total ha reaparecido como una estrategia fisiológica, con ventajas logísticas, que le permiten ser accesible para iniciar tempranamente la resucitación hemostática. El objetivo de este estudio fue evaluar las propiedades celulares, coagulantes y viscoelásticas de la sangre total almacenada por 21 días.

Métodos. Las unidades de sangre total fueron obtenidas de 20 donantes voluntarios sanos. Se procesaron mediante un sistema de leucorreducción ahorrador de plaquetas y fueron almacenadas en refrigeración (1-6°C) sin agitación. Se analizaron los días 0, 6, 11 y 21. Las bolsas fueron testeadas para evaluar las líneas celulares, niveles de factores de coagulación y propiedades viscoelásticas mediante tromboelastografía.

Resultados. El conteo eritrocitario y la hemoglobina se mantuvieron estables. El conteo de plaquetas tuvo una reducción del 50 % al sexto día, pero se mantuvo estable el resto del seguimiento. Los factores de coagulación II-V-VII-X, fibrinógeno y proteína C se mantuvieron dentro del rango normal. La tromboelastografía mostro una prolongación en el tiempo del inicio de la formación del coagulo, pero sin alterar la formación final de un coagulo estable.

Conclusiones. La sangre total leucorreducida y con filtro ahorrador de plaquetas conserva sus propiedades hemostáticas por 21 días. Este es el primer paso en Colombia para la evaluación clínica de esta opción, que permita hacer una realidad universal la resucitación hemostática del paciente con trauma severo.

Palabras Clave: sangre total; conservación de sangre; hemostasis; resucitación; choque hemorrágico; transfusión sanguínea.

Introduction

Hemorrhagic shock caused by massive blood loss remains the leading cause of death in a patient with trauma [1,2]. Trauma-induced coagulopathy, acidosis, hypothermia, and hypocalcaemia have been defined as key points in the initial management of trauma to reduce the effect of tissue damage and massive blood loss [3,4]. The multidimensional molecular, physiological, and clinical imbalance of coagulopathy is directly responsible for the uncontrolled bleeding, organ failure, thromboembolic complications, and patient death [5].

Hemostatic resuscitation tries to compensate, in a timely manner, the loss of both volume and of cellular components in the trauma patient [6]. An ideal hemo-derived transfusion ratio has been sought to compensate the deleterious effects of trauma-induced coagulopathy, with results in favor of a 1:1:1 physiological ratio of red blood cells, fresh frozen plasma, and platelets [7]. Likewise, massive transfusion and transfusion protocols guided by viscoelastic tests, such as thromboelastography or rotational thromboelastometry, have been implemented to guide hemostatic resuscitation measures [8-10].

In recent years, the US military in the context of the wars in Iraq and Afghanistan, have started using whole blood as it was used during World War II and the Korean War. [11,12]. This practice was replaced in the Vietnam War by resuscitation with colloids and crystalloids, this, together with the separation of blood by components, made whole blood fall into disuse [13].

The advantages of whole blood are the reduction of transfusion volume, the lower technical demand, and compliance with a physiological transfusion ratio. One unit of whole blood provides higher hematocrit, platelets, and coagulation factors activity compared to reconstituted blood at a ratio of 1:1:1 [1,14,15]. A potential technical advantage of the use of whole blood is the possibility of applying hemostatic resuscitation in places where blood banks have limited resources or even in areas that lack them [3,16].

Advances in the treatment of whole blood, such as leukoreduction or platelet-sparing systems, have made it possible to control the risks of transfusion reactions. However, it is still not clear whether whole blood retains its hemostatic properties for periods longer than 14 days. This research group hypothesizes that the preservation of whole blood in civil blood banks for a period greater than 15 days, without compromising its hemostatic capacity, would be an ideal tool to be applied in trauma care services in Colombia, making hemostatic resuscitation a universal reality. The objective of this study was to evaluate the cellular, coagulant and viscoelastic properties of whole blood stored for 21 days in the blood bank of a Trauma reference center in Cali, Colombia.

Methods

Study design

Descriptive study on the cellular components, coagulation factors and viscoelasticity of whole blood. The blood donation was carried out following the standard for quality control of blood components and the manual of technical standards for blood banks of the Colombian National Institute of Health. The volume obtained per donation was approximately between 405 and 495 ml.

Leukoreduction, filtration and preservation

The donated blood was stored in IMUFLEX™ whole blood system bags (Ref. BB*LGQ456E6 from Terumo®). These quadruple bags are made up of an in-line filter for blood leukodepletion with platelet savings, to which 63 ml of citrate-phosphate-dextrose solution was added for a 21-day storage. Storage was done without stirring and under refrigeration between 1°C and 6°C. 4 ml of blood were drawn from each bag for each analysis performed.

Laboratory Measurement

Cell lines and coagulation factors were evaluated at the following times: day 0, 6, 11, 16, and 21. Viscoelastic tests were performed on day 1, 3, 7, 14, and 21.

Cell Lines

The red blood cell count was estimated using the direct current technique and hydrodynamic approach. Hemoglobin concentration was estimated using the sulfhemoglobin methodology. Properties such as hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and erythrocyte distribution width were estimated. Platelet count and corpuscular volume were also included.

Coagulation factors

Quantitative estimates of coagulation factors II, V, VII, VIII, IX, X and XI were made based on the prothrombin time assay according to IL Coagulation Systems (HemosIL®). Protein C was quantified

through an automated chromogenic assay (HemosIL®). Fibrinogen was estimated the Clauss method according to IL Coagulation Systems (HemosIL®).

Viscoelasticity

It was evaluated through thromboelastography (TEG), including variables such as the reaction time (R), which measures the time elapsed for the formation of the first fibrin bands, the coagulation time (K), which evaluates the time that elapses from the beginning of fibrin formation until the clot reaches its maximum strength, the α-angle, formed by the intercept between R and the slope of K, which reflects the speed of clot formation, the maximum amplitude (MA), that evaluates the moment in which the clot reaches its maximum strength due to the interaction between fibrin with the number and platelet function, and the strength of the clot globally (G) [17].

Statistical analysis

Continuous data were described as medians and ranges of minimum and maximum. The comparison of the distribution of continuous data between days was evaluated using the Kruskal-Wallis rank test and, if the difference between groups was statistically significant, a post-hoc analysis was performed using Bonferroni correction and Tukey's range test, to estimate which days were different from the initial value. Statistical analysis was performed using R-Language 4.1.0 [18].

Results

Whole blood units had a leukocyte count after leukoreduction of less than 1000 cells/dL. Regarding the properties of the red blood cells, the erythrocyte count, hemoglobin, hematocrit and mean corpuscular hemoglobin remained stable for 21 days. However, mean corpuscular volume (MCV) increased after day 11, an effect that was maintained until day 21. This increase in red blood cell volume was also observed in the standard deviation of red blood cell distribution width after day 11 (Table 1).

Regarding the platelet count (Figure 1), the median reduction in platelets between days 0 and 6 was 54.1% (range 13.3-87.3), but the rest of the days the platelet count remained stable, with a median for day 21 of 95,000 cells/dL (range 64,000-143,000 cells/dL). Platelet volume was not affected during the follow-up period.

The vitamin K-dependent coagulation factors had stable levels during the observed time. However, factor II values decreased significantly by day 21 compared to baseline, by 26.5% (range 0.9-37.9) (Figure 2). Factor IX values fell after day 16 by 33.8% (range 28-37.9). Regarding the other coagulation factors, factor V had a sustained decrease of 20.7% (range 4.6-37-5) after day 11 compared to the base value and factor VIII had a significant decrease at day 6 of 53.5% (range 44.6-67.2), but then the concentration remained stable throughout the observation window. Factor IX maintained stable concentrations during follow-up, as did fibrinogen and protein C concentrations.

Among the coagulation tests, the prothrombin and partial thromboplastin times had a persistent significant prolongation in the study period. The viscoelastic tests showed that, on the first day, the units of whole blood presented a prolongation in the R time of clot formation in 12/20 units of whole blood (Figure 3). The velocity (α-angle) and K time of maximum-force clot formation were also prolonged in all units of blood. However, the maximum clot strength due to the interaction of fibrin and platelets (Parameter MA) was only reduced in half of the bags. The overall clot strength (Parameter G) was reduced in 7/20 units of whole blood. All these parameters remained stable in the follow-up period, except for a prolongation of the K time and a reduction of the R time towards day 21, in 6/20 units of whole blood.

Discussion

It was shown that whole blood can be stored for a period of 21 days, maintaining its concentrations of hemoglobin and red blood cells, with a platelet count higher than that of reconstituted blood in a 1:1:1 ratio, and stable coagulation factors V, VIII

Table 1. Properties of leukoreduced whole blood units with platelet-sparing filter evaluated over a 21 day period.

	Day 0	Day 6	Day 11	Day 16	Day 21	p-value
Eritroides						
Red blood cell count (10^6 cell/uL)	4.24 (3.61-5.18)	4.16 (2.58-5.19)	4.18 (3.51-4.29)	4.24 (3.39-5.24)	4.28 (3.60-5.47)	0.7
Hemoglobin (g/dL)	12.05 (10.6-15)	12 (7.8-14.6)	12 (10.5)	11.85 (9.8-14.9)	12.35 (10.5-15.4)	0.6
Hematocrit %	37 (32-45.2)	36.4 (24.8-44.9)	37.8 (31.4-46.8)	38.1 (32.3-46.6)	39.7 (33.1-51.6)	0.09
Medium corpuscular volume fl	88.9 (82-96.4)	89 (83.2-96.5)	91.5 (83.7-97.4)	92.6 (84.4-97.5)	92.9 (85.3-98)	<0.001
MCH pg	28.9 (26.3-30.7)	28.55 (26.4-31.1)	29 (25.9-31.7)	29.15 (26.1-31.6)	29.05 (26.3-31.4)	0.9
RDWSD fl	43.0 (37.7-47.3)	43.4 (38.1-49.6)	47.1 (40-50.5)	46.4 (39.7-50.8)	47 (39.7-52.2)	<0.001
Platelets						
Platelet count (10^3 cel/uL)	187 (130-264)	82 (21-204)	79 (40-181)	71 (52-134)	95 (64-143)	<0.001
MPV fl	9.45 (8.2-11)	9.7 (8.6-11.1)	9.5 (8.7-10.8)	9.5 (8.1-10.7)	9.9 (8.2-11)	0.4
Coagulation Times, Fibrinogen and Protein C						
PT seg	12.4 (10.9-13.7)	14.3 (8.4-15.8)	15.2 (9.3-16.9)	15.3 (11.1-16.8)	16.5 (11.7-18.2)	<0.001
PTT seg	34 (30-39)	40 (31-65)	42 (32-63)	41 (32-54)	44 (32-59)	<0.001
INR	1.06 (0.93-1.17)	1.21 (0.73-1.35)	1.29 (0.80-1.43)	1.31 (0.96-1.43)	1.40 (1.01-1.55)	<0.001
Fibrinogen mg/dL	249 (161-368)	232 (194-378)	230 (194-339)	229 (184-381)	217 (178-360)	0.3
Protein C IU/dL	90 (70-126)	84 (72-168)	76 (62-147)	76 (65-148)	74 (56-142)	0.08
Coagulation factors						
II %	90 (72-120)	79 (35-170)	76 (62-120)	75 (60-123)	61 (53-106)	<0.001
V %	84 (49-110)	71 (45-100)	65 (36-83)	43 (26-63)	41 (23-58)	<0.001
VII %	80 (26-145)	58 (40-344)	59 (38-266)	55 (39-201)	52 (34-171)	0.365
VIII %	119 (58-203)	53 (26-97)	43 (18-83)	36 (17-83)	41 (20-86)	<0.001
IX %	101 (81-145)	94 (80-133)	93 (73-132)	87 (70-124)	89 (63-118)	<0.001
X %	80 (58-123)	80 (58-159)	79 (57-137)	74 (52-118)	72 (53-106)	0.3
XI %	100 (6-126)	102 (64-121)	98 (63-125)	100 (64-119)	101 (76-141)	0.8
Tromboelastogram						
	Day 1	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**p-value**
TEG-R (min)	0.9 (7.7-15.9)	11.05 (4.2-16)	10.2 (7.2-13.8)	9.75 (5.9-13.3)	9.35 (5.8-12.4)	0.03
TEG-K (min)	4.75 (2.6-9.5)	4.65 (1.3-9.2)	5.3 (3.7-9.1)	4.95 (2.2-9.8)	6.8 (4.2-10.6)	0.002
TEG-ángulo-a	36 (25-52)	39 (24-69)	37 (25-43)	36 (24-60)	32 (20-49)	0.2
TEG-MA (mm)	50.2 (37-60.1)	53 (37.8-69.5)	50.9 (39.1-58.9)	52.5 (40.5-60.3)	48.2 (41-57.7)	0.05
TEG-G (d/sc)	5.05 (2.9-7.5)	5.65 (3.0-8.1)	5.2 (3.2-7.2)	5.25 (1.4-7.6)	4.65 (3.5-6.8)	0.06

* Data are represented as median and minimum and maximum range.

** MCH: mean corpuscular hemoglobin; MPV: mean platelet volume; PT: prothrombin time; PTT: Partial thromboplastin time; RDWSD: red cell distribution width standard deviation; TEG: Tromboelastrogram.
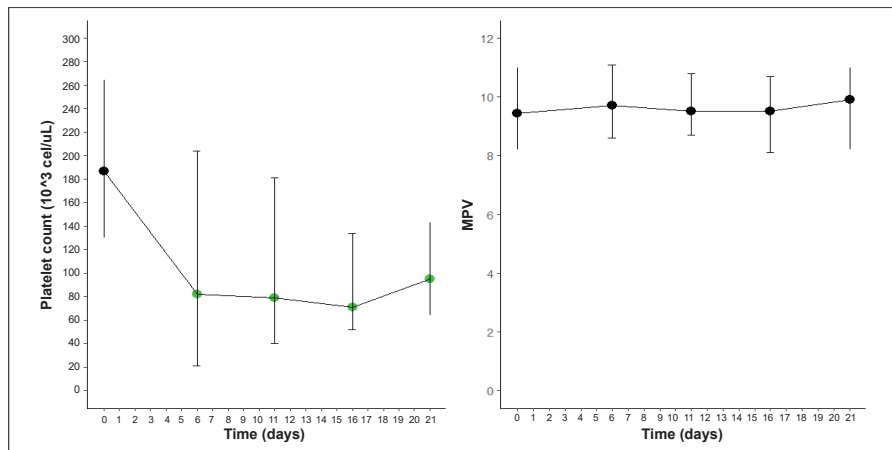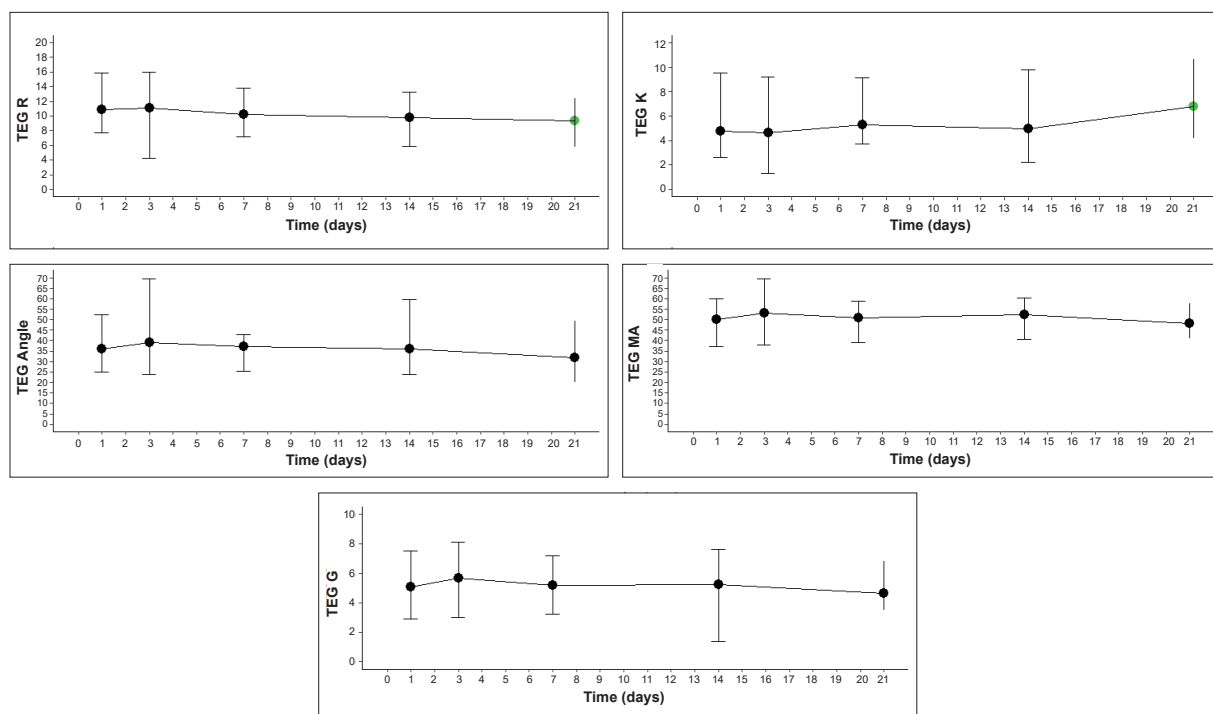
Figure 1. Monitoring of platelet count and mean platelet volume. Source: authors.
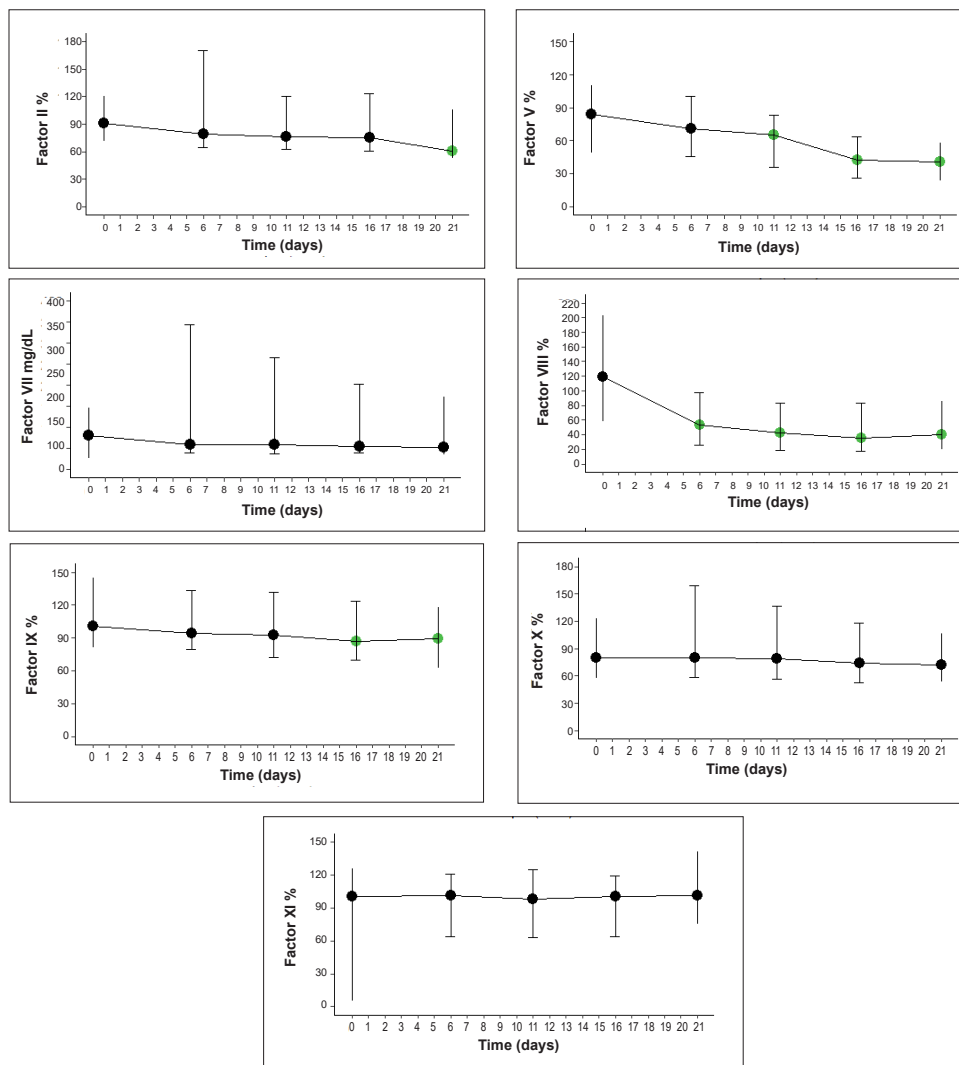
Figure 2. Monitoring of coagulation factors II-V-VII-VIII-IX-X-XI. Source: authors.

Figure 3. Monitoring of viscoelastic properties measured by thromboelastography. Source: authors.

and vitamin K dependent. The viscoelasticity tests showed a prolongation of clot formation, without affecting its strength. These findings suggest that whole blood maintains adequate cell and coagulation factor levels, preserving its coagulating function.

These results are similar to those previously reported in the literature. Haddaway et al [19] performed an evaluation of the hemostatic properties of leukoreduced frozen whole blood with or without a platelet-sparing filter for 14 days and found that thromboelastographic parameters remained stable, coagulation times and coagulation factor activity were not affected by the platelet-sparing filter. Pidcoke et al [11] evaluated the impact of a storage temperature between 4°C and 22°C in units of whole blood with a pathogen reduction filter, observing that frozen units had a constant decline in coagulation times and the aggregation time was decreased; however, when comparing the units according to their storage temperature, it was reported that the frozen units preserved the thromboelastographic parameters.

Regarding the viscoelastic properties, Strandeness et al [20] carried out a detailed analysis through rotational thromboelastometry of leukoreduced frozen whole blood for 14 days, demonstrating a preservation of fibrinogen and platelet function, but a decrease in the firmness of the clot on day 10. This data differs from ours, where we report a constant preservation of the strength of the clot formation.

The leukoreduction and platelet-saving filtration method seems to be the best method in recent years for the preservation of whole blood, with conservation facilities and without short-term commitment if there is a delay between the donation and the filtration of the units [21,22].

The use of whole blood has already begun to be evaluated in the management of civilian trauma. Siletz et al [23] presented the results of a pilot study comparing patients treated with whole blood and blood component therapy versus patients treated with blood components alone, finding a higher red blood cell:plasma transfusion ratio in the whole blood group. The associated mortality in this

whole blood and blood component therapy group was 4.4% compared to the conventional therapy group, where it was 11.7%, but the difference was not statistically significant.

The main benefit of whole blood is that it would allow earlier hemostatic resuscitation. If the time between the injury and the start of the transfusion is shorter, the probability of survival in the trauma patient may increase [24,25]. This finding has begun to be observed in prehospital resuscitation measures with the use of whole blood with low O-positive blood titers, where, despite the fact that the patients had a worse physiological state, mortality was lower compared to the non-transfused patients [26].

The technical advantages in the storage of whole blood, the preservation of its hemostatic properties and the ease with which a single transfusion can meet the requirements of transfusion with blood components, give whole blood a promising role in hemostatic resuscitation.

Currently, according to the report of the PanAmerican Health Organization, in Latin America, and especially in Colombia, the donation rate for the year 2017 was 17.2 per 1,000 inhabitants, and only 18.2% were donors that have donated more than once. In addition, the supply of blood components is insufficient for the fulfillment of reconstituted whole blood, since 94% of donated blood is separated for red blood cells, 55% for plasma, and 35% for platelets [3,16]. For these reasons, a medium-term implementation is proposed, so that whole blood can be available in institutions that have blood banks with limited resources and low levels of transfusion for the care of trauma patients, or even start its implementation from pre-hospital settings in Colombia [27].

One of the limitations of this study is that the platelet aggregation capacity was not evaluated, despite the evaluation of the viscoelastic properties, which does not allow a clear understanding of the effect of whole blood on this process. On the other hand, the sample of donors was from healthy young people in a single hospital center following the institutional protocol, which may present biases when extrapolating these results to the conditions of conservation in blood banks in institutions with a lower level of care. The results and conditions of the study are favorable for starting a second investigation in which the applicability of the use of whole blood in massive transfusion protocols for traumatized patients, even in prehospital conditions, is evaluated.

Conclusions

Leukoreduced whole blood with a platelet-sparing filter preserves its cellular properties, coagulation factors and the quality of clot formation for 21 days. Whole blood has technical advantages in the requirements of hemostatic resuscitation. This is the first step for clinical evaluation in Colombia as a tool that allows hemostatic resuscitation of patients with severe trauma to become a universal reality.

Compliance with ethical standards

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