

High Medical College of Professional Studies, Belgrade

Professional article

Stručni članak

UDK 616-005.1:615.38

DOI: 10.2298/MPNS1602037S

## CHEMOTHERAPY ANALYSIS IN MASSIVE TRANSFUSION SYNDROME

### ANALIZA HEMOTERAPIJE U SINDROMU MASIVNE TRANSFUZIJE

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#### Summary

**Introduction.** Massive transfusion is defined as blood transfusion in quantities equal to or greater than the estimated patients' blood volume over a relatively short period of time (3-4 hours). The study was aimed at analyzing the application of chemotherapy in treatment of patients with acute massive bleeding and evaluating the results of hemostasis and platelet counts screening tests in the patients receiving massive transfusions. **Material and Methods.** Attempts were made to fully compensate hemostatic factors in 24 patients (14 male and 10 female, aged 23 to 76 years) with acute massive and uncontrolled surgical bleeding (polytrauma, abdominal aortic aneurysm, digestive tract bleeding as a result of a farina overdose, mortus fetus) over the five-year period, wherein a circulating patients' blood volume was compensated over a relatively short period of time. First the surgical bleeding was stopped. The objective of chemotherapy was the combined use of resuspended red blood cells, fresh frozen plasma, cryoprecipitates and the platelet concentrate in order to maintain the patients' normal circulating blood volume and blood pressure (systolic blood pressure  $\geq 100$  mmHg) with hemoglobin value higher than 100 g/l and the hematocrit above 0.30 l/l. **Results.** Transfusion treatment of 24 patients with acute bleeding consisted of an average of 16 to 18 units of resuspended red blood cells (ranging from 4,880 ml to 5,220 ml); fresh frozen plasma (980 ml to 1,220 ml); cryoprecipitates (an average of 10 to 15 units i.e. 500-750 ml) and concentrated platelets (approximately an average of 8 to 12 units i.e. 240 to 360 ml). **Conclusion.** In our study we have confirmed the pathophysiological mechanism shown in the available medical literature that after transfusion of a large red blood cell concentrate volume, dilutional coagulopathy develops, caused by a sharp drop in platelet count and the significantly reduced activity of unstable coagulation factors in the patient's circulation.

**Key words:** Blood Transfusion; Blood Component Transfusion; Treatment Outcome; Blood Coagulation Tests; Hemostasis; Platelet Count; Hemorrhage; Disseminated Intravascular Coagulation

#### Introduction

Massive transfusion is defined as blood transfusion in quantities equal to or greater than the patient's estimated blood volume over a relatively short period of time (3-4 hours) or as a compensation of the total circulating patient's blood volume by transfusion of stored allergenic blood within 24

#### Sažetak

**Uvod.** Masivna transfuzija se definiše kao transfuzija krvi u količinama jednakim ili većim od procenjenog volumena krvi bolesnika, u relativno kratkom vremenskom periodu (3-4 sata). Cilj istraživanja je analiza primene hemoterapije u tretmanu bolesnika sa akutnim masivnim krvarenjem i procena vrednosti rezultata skринing testova hemostaze i broja trombocita kod bolesnika koji su primili masivne transfuzije. **Materijal i metode.** Pokušaji potpune nadoknade hemostaznih činilaca kod 24 pacijenata (14 muškaraca i 10 žena, starosti od 23 do 76 godine) u petogodišnjem periodu, kod akutnog masivnog i hirurški nekontrolisanog krvarenja (politrauma, aneurizme abdominalne aorte, krvarenje iz digestivnog trakta kao posledica predoziranja farinom, fetus mortuus), gde je nadoknađen jedan cirkulišući volumen krvi bolesnika, u relativno kratkom vremenskom periodu. Najpre je hirurški zaustavljeno krvarenje. Cilj hemoterapije bio je kombinovana primena resuspendovanih eritrocita, zamrznute sveže plazme, krioprecipitata i koncentrovanih trombocita, radi održavanja normalnog volumena cirkulišuće krvi i krvnog pritiska bolesnika (sistolni pritisak  $\geq 100$  mmHg) i koncentracije hemoglobina više od 100 g/l, vrednosti hematokrita više od 0,30 l/l. **Rezultati.** U transfuziološkom zbrinjavanju 24 pacijenta sa akutnim krvarenjem utrošeno je: 16 do 18 jedinica resuspendovanih eritrocita (prosečno 4 880 ml do 5 220 ml); zamrznute sveže plazme (prosečno 980 ml do 1 220 ml); krioprecipitata (prosečno 10 do 15 jedinica, tj. 500-750 ml) i koncentrovanih trombocita (prosečno 8 do 12 jedinica, tj. 240 do 360 ml). **Zaključak.** U našoj studiji potvrdili smo patofiziološki mehanizam, prikazan u dostupnoj medicinskoj literaturi, da se posle transfuzije velikog volumena deplazmatisane krvi, razvila diluciona koagulopatija, uslovljena velikim padom broja trombocita i znatno sniženom aktivnošću labilnih činilaca koagulacije u pacijentovoj cirkulaciji.

**Cljučne reči:** Transfuzija; Transfuzija derivata krvi; Ishod lečenja; Koagulacioni testovi; Hemostaza; Broj trombocita; Krvarenje; Diseminovana intravaskularna koagulacija

hours [1-4]. However, life saving of a patient with acute massive blood loss (30%-50% of total circulating blood volume) demands large blood quantities to be transfused over the shortest period of time. Such transfusions, though lesser than the total patient's blood volume, must be defined as massive ones because they can cause serious homeostatic disorders. Therefore, restricting the definition of

**Abbreviations**

2,3 DPG	– 2,3 diphosphoglycerate;
APTT	– activated partial thromboplastin time
VMA	– Military Medical Academy
PT	– prothrombin time
TT	– thrombin time
Hb	– hemoglobin
Hct	– hematocrit
CP	– concentrated platelets
FFP	– fresh frozen plasma
CRYO	– cryoprecipitate
RES. ER	– resuspended erythrocytes
GIT	– gastrointestinal tract
DIC	– disseminated intravascular coagulation

massive transfusion only to situations in which more than one (or more) volume of patient's circulating blood are compensated over 24 hours does not provide a complete definition of massive transfusion [1, 3, 4].

Massive transfusions are applied in the treatment of patients with hemorrhagic shock resulting from an injury, surgery or heavy bleeding (usually gastrointestinal or gynecological). It is well known that the storage of preserved blood at temperatures of  $4 \pm 2^\circ\text{C}$  does not stop metabolic and degradation processes, it just slows them down, causing the free hemoglobin, potassium, ammonia and lactic acid content increases in the blood, the disappearance of unstable coagulation factors activity, a decrease in the 2,3 diphosphoglycerate (DPG) or 2,3 DPG concentration and an increase in acidity, i.e. a decrease in the blood pH [1–5]. For these reasons, massive transfusion may be the cause of a number of disorders creating the massive transfusion syndrome: electrolytic and acid-based imbalance, impaired oxygen transport, hypothermia, disorders due to the presence of micro-aggregates and hemostatic disorder [6–14]. Another massive transfusion side effect worth mentioning is the post-transfusion depletion of coagulation factors, which may result in the unwanted development of hemorrhagic syndrome. After transfusion of a large volume of conserved (not fresh) blood or large amounts of red blood cells concentrate, a dilutional coagulopathy develops, caused by a sharp drop in the platelet count and the significantly reduced activity of unstable coagulation factors in the patient's circulation [14–17]. One of the most significant clinical manifestations of massive transfusion syndrome is bleeding, usually from the surgical wound, injury or puncture spot; it is rarely generalized with bleeding into the skin or mucous membrane [1, 4, 7].

According to some multidisciplinary studies [15–18], in hemorrhagic shock resulting from digestive tract bleeding, trauma or some other cause, the compensation of lost volumes typically begins with crystalloids and colloids, and then rapidly progresses through blood and chemo products transfusion (chemotherapy). The compensation of large volume blood loss can cause coagulopathy that can be difficult to manage in case of uncontrolled bleeding. Coagulopathy during massive transfusion is a multifactorial pathophysiological mech-

anism that occurs due to hemodilution, hypothermia, the use of fractionated blood products and disseminated intravascular coagulation (DIC). Maintaining body temperature within normal limits is the first line of an effective strategy to improve hemostasis during massive transfusion. Treatment includes maintaining adequate tissue perfusion, correction of anemia and the use of hemostatic blood products [18–23].

The results of screening tests in massive transfusion syndrome show thrombocytopenia, with the extension of the activated partial thromboplastin time (APTT) and prothrombin time (PT) and thrombin time normal values (TT). It is necessary to monitor the hemostasis through laboratory testing during massive transfusion, and assess the frequency of further testing and the need for substitution transfusions therapy according to the results. It is often necessary to differentiate whether the hemorrhagic syndrome is a consequence of massive transfusion or DIC. In the massive transfusion syndrome, unlike the DIC, TT and fibrinogen concentrations are within the normal limits [4, 6–8].

In acute massive and surgically uncontrolled bleeding, where one patient's circulating blood volume has been compensated, the attempts to complete compensation of hemostatic factors in order to achieve adequate hemostasis are not useful. It is first necessary to stop the bleeding surgically. The combined application of stored whole blood, red cell preparations, colloid or crystalloid infusion solutions should maintain normal circulating blood volume and blood pressure of patients, as well as the hemoglobin concentration value (Hb) above 100 g/l or hematocrit (Hct) higher than 0.30 l/l. If the compensation of the lost blood is 0.2 l/hour or more, surgical bleeding is likely to be present, which would firstly require surgical care of patients. The application of hemostatic chemo products is indicated when the bleeding is caused by deficiency of hemostasis factors and not by surgical bleeding from an injured large blood vessel. Hemostasis deficit should be confirmed not only clinically, but also with laboratory findings. Thereby, DIC is the most complex therapy; out of hemostatic chemo products concentrated platelets (CP) (one unit/10 kg), fresh frozen plasma (FFP) (12 ml/kgbm) or cryoprecipitate (CRYO) (1-1.5 units/kgbm 10) should be applied, along with other medication therapy [1, 4, 7, 8]. It was previously thought that acute massive blood loss required compensation with the whole fresh blood exclusively (for the purpose of preventing or correcting hemostatic disorders, in addition to the erythrocytes compensation) [4, 14]. However, the introduction of targeted chemotherapy has changed this attitude in compliance with the concept that the use of only fresh whole blood ("uncooled" blood transfused immediately after taking it from a donor) is not only insufficiently effective in treatment of most patients, but also irrational. That is why the modern aimed chemotherapy recommends erythrocyte preparations, especially resuspended erythrocytes (RES. ER) [1, 4, 15–18].

According to some foreign studies [24], transfusion management of polytraumatised patients during peacetime should begin with the replacement

of lost blood volume with RES.ER until the patient is transported to a higher level of care (hospital in-patient facilities). Simultaneous infusion of FFP is proposed before surgical intervention. According to the recommendations of this study [24], the ratio of transfused RES. ER and FFP volume should be 1:1. Experience in the management of war injuries is similar, suggesting that RES. ER and FFP simultaneous compensation should be carried out in the ratio of 1:1 in supportive transfusion therapy [24]. Other studies [25] recommend transfusion trigger for the restoration of the lost circulatory volume with RES. ER transfusions at a dose of 40-60 ml/kgbm until reaching the concentration of Hb 100 g/l and Hct 0.30 l/l value [24, 25].

Further clinical trials are required for faster diagnosis and better definition of difference between the harmful effects caused by acute massive blood loss and massive blood transfusion, as well as rational and timely use of certain chemo products containing the necessary hemostatic factors [15–18].

Based on the experience gained in some foreign studies [24–26], an operative hypothesis was set up: “If in patients with acute massive blood loss immediate measures are applied as early as possible during transportation (surgical hemostasis, intravenous solutions infusion and oxygen dispensation), the intravascular volume will be preserved and will prevent the development of irreversible hypovolemic shock and DIC”.

This article was aimed at analysing the application of chemotherapy in the treatment of patients with acute massive bleeding and evaluating the hemostatic and platelet counts screening tests results in the patients receiving massive transfusion.

## Material and Methods

Transfusion management of 24 patients with acute massive and uncontrolled surgical bleeding (14 men and 10 women, aged 23 to 76 years) was followed through retrospective analysis at the “Bežanijska Kosa” Clinical Hospital Center in Belgrade during the five-year period. This study included 10 patients with polytrauma, 8 patients who

had undergone surgery for abdominal aortic aneurysm, 4 patients with gastrointestinal (GIT) tract bleeding as a result of a farina overdose and two women with uterus revision after a stillborn fetus (“fetus mortus”) (**Table 1**).

First, all these patients had adequate surgery and surgical hemostasis in order to prevent further uncontrolled bleeding. Due to the forthcoming hemorrhagic shock, a circulating blood volume of all the patients was compensated by certain chemo products in a relatively short period of time (3-4 hours). The chemotherapy goal was the combined use of RES. ER; FFP; CRYO and CP, thus maintaining the patients' normal circulating blood volume and blood pressure (systolic blood pressure of 100 mmHg) until they reached the value of Hb 100 g/l, i.e. value of Hct 0.30 l/l.

We performed a hemogram test [Hb (g/l) and Hct (l/l value)] and controlled the values of the hemostatic screening tests results in the patients who had received massive transfusions [PT which measures the plasma clotting time in the presence of tissue thromboplastin optimal concentrations, demonstrating the effectiveness of the extrinsic clotting pathways; activated partial thromboplastin time (APTT) which measures the clotting time after the contact factors activation, when tissue thromboplastin has not been added, so this test measures the activity of the intrinsic pathways of coagulation, while TT measures the clotting time after adding thrombin to plasma, influenced by the fibrinogen concentration and quality, fibrinogen, fibrin and heparin degradation products; the fibrinogen concentration was measured and protamine sulfate test done] [19]. In order to prevent the SEC, hemostasis test was repeated every 8 hours in the patients with massive transfusion syndrome.

Statistical parameters were used to calculate the mean values and percentage (%) ratio of the measured parameters, and the results were shown in tabular form and in the columnar graph.

## Results

During the transfusion management of 24 patients with acute bleeding, the following materials were used on average: 16 to 18 RES. ER. units (approx-

**Table 1.** Average consumption of certain chemo products in patients with massive transfusion  
**Tabela 1.** Prosečan utrošak pojedinih hemoprodukata kod pacijenata sa masivnim transfuzijama

Pathological condition <i>Patološko stanje</i>	Number of patients <i>Broj pacijenata</i>	Average chemo products consumption (ml) <i>Prosečan utrošak hemoprodukta (ml)</i>			
		RES.ER./RES.ER.	FFP/ZSP.	CRY/KRIO.	PC/KT.
Polytrauma/ <i>Politrauma</i>	10	2.050130	41090	210110	10050
Abdominal aortic aneurysm <i>Aneurizma abdo-minalne aorte</i>	8	1.650110	33080	17080	8040
GIT bleeding/ <i>Krvarenje iz GIT-a</i>	4	87050	17040	9040	4020
Fetus mortus/ <i>Fetus mortus</i>	2	41030	7030	3020	2010
Total/Average <i>Ukupno/Prosečno</i>	24	4.880320	980240	500250	240120

*Legenda:* RES.ER. – Resuspendovani eritrociti; ZSP. – Zamrznuta sveža plazma; KRIO. – Krioprecipitat; KT. – Koncentrovani trombociti; GIT – Gastrointestinalni trakt



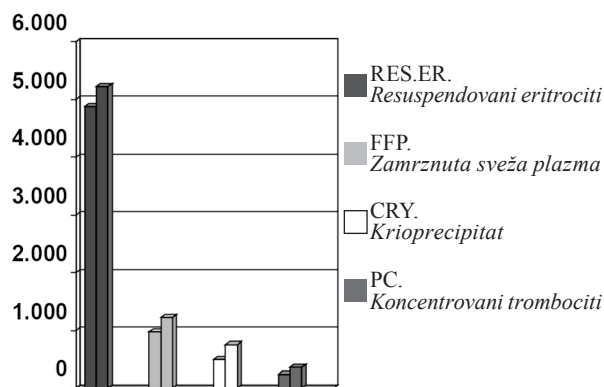
mately 4,880 ml to 5,220 ml); FFP on average 4 to 5 units, i.e. 980 ml to 1220 ml); CRYA (on average 10 to 15 units, i.e., 500 to 750 ml) and CT (on average 8 to 12 CT units or 240 to 360 ml). Transfusion management is shown in **Table 1** and the **Graph 1**.

According to the laboratory analyses, the number of platelets decreased in all patients who had received massive transfusions, being 3.2 to 12 times lower compared to the platelet number in the emergency room ( $70 \times 10^9/l$  up to  $550 \times 10^9/l$ ), and after massive transfusion, the platelet count ranged from  $10 \times 10^9/l$  to  $150 \times 10^9/l$ . Fifteen patients had lower platelet count of  $55 \times 10^9/l$  after receiving massive transfusions (**Table 2, Graph 2**).

The results of hemostasis screening tests were abnormal in 68.6% patients, as follows: PT, PTT and TT were extended in 59.5%, in 23.1% and in 42.5% of the patients, respectively. Fibrinogen was reduced in 23.1%, and protamine sulfate test was positive in 38.3% of patients. Hemostasis test results indicated disseminated intravascular coagulation in 5 (20.83%) patients (**Table 3, Graph 3**).

## Discussion

Trauma is the major death cause in young adults from 1 to 44 years of age. According to the World Health Organization (WHO) data [25], it is estimated that 5 million people die from injuries worldwide each year and the mortality rate is 83.7 per 100,000 inhabitants (traffic accidents and war injuries are particularly on the increase); therefore, the dramatic increase in the number of polytraumatized patients is expected until 2020. Up to 40% of such patients die due to circulatory shock as a result of acute blood loss. In addition to the surgical control of bleeding and adequate volume of resuscitation with the restoration of circulatory volume, adequate volume of chemo products (blood and/or blood products) is crucial for the survival of polytraumatized patients [24–26].



**Graph 1.** Average consumption of certain chemo products in transfusion management of 24 patients with massive transfusion

**Grafikon 1.** Prosečan utrošak pojedinih hemoprodukata u transfuziološkom zbrinjavanju 24 pacijenata s masivnim transfuzijama

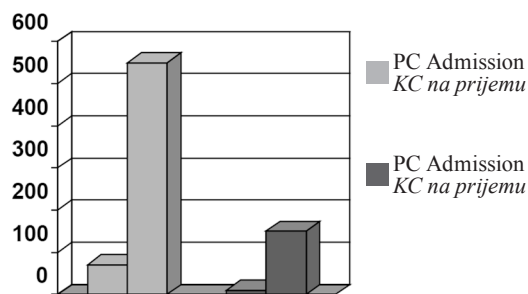
The most common causes of coagulation disorders in the patients with massive bleeding or massive transfusions are: coagulopathy due to loss of blood type, dilutional coagulopathy, consumptive coagulopathy, hyperfibrinolysis, acidosis, hypothermia, anemia and electrolyte imbalance [26].

According to recent studies [18, 21, 22], massive transfusion is defined as the entire volume of circulating blood restoration within 24 hours or 50% of blood volume compensation over 3 hours. In situations of acute bleeding, a definition based on the clinical practice experience is often used, which involves transfusion of 4 or more red cell units within one hour [23].

It is characteristic for massive transfusion that the total volume of transfused blood (required for adequate compensation) and the transfusion speed can potentially overcome the possibilities of compensatory mechanisms to maintain homeostatic balance in the patient's blood [1, 4, 16, 18].

In the patients with acute massive blood loss, it is necessary to take urgent measures during transport (surgical hemostasis, intravenous solutions infusion and oxygen administration) in order to maintain intravascular volume and prevent the development of irreversible hypovolemic shock [1, 4, 16].

The experiences of the first author of this study and a group of authors from the Military Medical Academy (VMA) in Belgrade [27, 28] have shown positive results in the survival and rescue of intraoperative autologous blood, as well as simultaneous intraoperative reinfusion of autologous blood recovered from uncontaminated hemothorax using "Pleur-evac system" in 25 wounded persons. They were classified into the fourth category of urgency ("moribund") after triage in a field hospital in war-affected areas in the former Yugoslavia (1991). During helicopter transport from a field hospital to the VMA, intraoperative autologous blood salvage was performed, as well as simultaneous reinfusion of autologous blood intraoperatively recovered from uncontaminated hemothorax using "Pleurevac system" [27]. These urgent measures increase the patients' survival rate. Acute loss of large amounts of blood always threatens patients' lives directly and is an indication for massive blood transfusion.

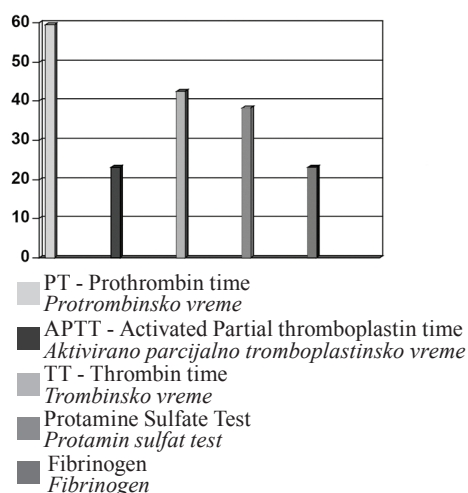


**Graph 2.** Patients' platelet count ( $10 \times 10^9/l$ ) on admission and after receiving massive transfusions  
**Grafikon 2.** Broj trombocita ( $10 \times 10^9/l$ ) kod pacijenata na prijemu i nakon primanja masivnih transfuzija

**Table 2.** Changes of platelet count ( $10 \times 10^9/l$ ) on admission and after massive transfusions  
**Tabela 2.** Kretanje broja trombocita ( $10 \times 10^9/l$ ) na prijemu i nakon masivnih transfuzija

Pathological condition Patološko stanje	Number of patients Broj pacijenata	Platelet count ( $10 \times 10^9/l$ )/Broj trombocita	
		On admission Na prijemu	After massive transfusions Nakon masivnih transfuzija
Polytrauma/Politrauma	10	5 ( $50 - 53 \times 10^9/l$ )	5 ( $10 - 15 \times 10^9/l$ )
		3 ( $52 - 55 \times 10^9/l$ )	3 ( $60 - 130 \times 10^9/l$ )
		2 ( $450 - 550 \times 10^9/l$ )	2 ( $350 - 470 \times 10^9/l$ )
Abdominal aortic aneurysm Aneurizma abdominalne aorte	8	4 ( $53 - 54 \times 10^9/l$ )	4 ( $45 - 52 \times 10^9/l$ )
		3 ( $460 - 530 \times 10^9/l$ )	3 ( $360 - 510 \times 10^9/l$ )
		1 ( $330 - 440 \times 10^9/l$ )	1 ( $280 - 360 \times 10^9/l$ )
GIT bleeding/Krvarenje iz GIT-a	4	3 ( $380 - 450 \times 10^9/l$ )	3 ( $320 - 430 \times 10^9/l$ )
		1 ( $320 - 440 \times 10^9/l$ )	1 ( $280 - 410 \times 10^9/l$ )
Fetus mortus/Fetus mortuus	2	2 ( $51 - 54 \times 10^9/l$ )	2 ( $35 - 52 \times 10^9/l$ )

GIT - gastrointestinal test

**Graph 3.** Results of chemostatic screening tests expressed in percentage (%) relation with pathological findings of the PV, APTT, TT and fibrinogen concentration  
**Grafikon 3.** Rezultati skrining testova hemostaze izraženi u procentualnom (%) odnosu sa patološki nalazima PV, APTT, TT i koncentracije fibrinogena

sion. Impediment of surgical hemostasis reduces the survival rate of the bleeding patients' significantly. Prolonged uncontrolled bleeding causes death in 41% of traffic accident injuries. Heterogeneity of patients whose lives are saved by massive transfusion requires an individual approach with no room for rigid standard protocols [1].

All 24 patients in our study sample who have received massive transfusions showed the signs of thrombocytopenia (from mild to very severe), which was of a pathological or a dilutional-type. According to the laboratory analysis, all patients had decreased platelet count after massive transfusion, which was 3.2 to 12 times lower than the number of platelets in the emergency room ( $70 \times 10^9/l$  to  $550 \times 10^9/l$ ), while after massive transfusions, the platelet count ranged from  $10 \times 10^9/l$  to  $150 \times 10^9/l$ . Fifteen patients had lower platelet count of  $55 \times 10^9/l$  after having received massive transfusions. Drastic drop in the platelet count after massive transfusion was compensated to the patients with the available number of platelet units in the Clinical Hospital Center "Bežanijska Kosa" Transfusion Service.

**Table 3.** Number of patients with reduced chemostatic test values after massive transfusions**Tabela 3.** Broj pacijenata sa sniženim vrednostima testova hemostaze nakon masivnih transfuzija

Pathological condition Patološko stanje	Number of patients Broj pacijenata	Reduced chemostatic test values after massive transfusions Snižene vrednosti testova hemostaze nakon masivnih transfuzija				
		PT	APTT	TT	Fibrinogen	Positive protamine sulphate/Test pozitivan protamin sulfat test
Polytrauma/Politrauma	10	8 (33.3%)	3 (12.5%)	5 (20.1%)	3 (12.5%)	4 (16.7%)
Abdominal aortic aneurysm Aneurizma abdominalne aorte	8	6 (25%)	2 (8.3%)	3 (12.5%)	2 (8.3%)	2 (8.3%)
Git bleeding/Krvarenje iz git-a	4	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	2 (8.3%)
Fetus mortus/Fetus mortuus	2	1 (4.2%)	-	1 (4.2%)	-	1 (4.2%)
Total number/ratio in % Ukupan broj/% odnos	24 (100%)	14 (59.5%)	6 (23.1%)	10 (42.5%)	6 (23.1%)	9 (38.3%)

Legenda: PT - protrombinsko vreme, APTT - aktivirano parcijalno tromboplastinsko vreme, TT - trombinsko vreme

Our study as well as other larger clinical ones [21–26] have proved the main postulate that a drastic fall in the platelet count (apparent thrombocytopenia) occurs primarily as a result of consumptive coagulopathy after massive transfusions.

The deficit of coagulation factors was adequately compensated by providing sufficient volume of FFP and CRYA.

Screening test results reported in many foreign [1, 15, 17, 21–26] and national medical publications [4, 16, 18] showed that massive transfusion syndrome, in addition to the reduced number of platelets, leads to the extension of the APTT and PT and normal TT values. The results of our tests are in accordance with the above findings. For example, the hemostasis screening tests results were found to be pathological in more than two thirds (68.6%) of patients, and the most common disorder was prolonged PT in almost 60% of patients, and APTT and TT was prolonged in about a quarter of the studied patients (23.1%), and almost half of patients (42.5%), respectively. The fibrinogen concentration values were reduced in almost a quarter of the studied patients (23.1%), while a protamine sulfate test was positive in 38.3% of patients. Although screening tests for hemostasis were performed every eight hours after massive transfusion, one-fifth (20.83%) of patients developed DIC.

An attempt was made within this study during the five-year period to monitor and analyze chemotherapy with massive transfusion syndrome in a small group of patients. The opportunities in supportive therapy for massive hemorrhage were limited in our conditions. The aim of this study was to compare our experience in the analysis of chemotherapy in massive transfusion syndrome with international multicenter studies that included a much larger number of patients with massive transfusion syndrome, had access to a wide range of chemo products in supportive therapy, and had done more detailed laboratory tests in order to monitor hemostatic status and the clinical status of patients so as to prevent hemorrhagic shock and DIC [1, 15, 17]. Nevertheless, test parameters recorded in our patients were crucial and sufficient for the evaluation of hemostasis, the normalization of which is largely determinable for the chemotherapy effectiveness.

The shortcomings of our study are that in a retrospective analysis “limited” medical documentation was used and inadequately managed (without chemotherapy protocols at the wards and departments, without com-

plete lists of blood transfusion and/or chemo products and with an incomplete registration of adverse effects of chemotherapy, i.e. non-compliance with the fundamental legal principles of hemovigilance prescribed by the “Law on Transfusiology” [20]. One of the shortcomings of this study is that it followed a small group of patients with massive transfusion syndrome over a short period of time and at only one medical center in Belgrade, unlike foreign multidisciplinary studies which include several decades of research with a greater number of patients at several medical institutions.

For these reasons, further research should be undertaken over a longer period of time, which would involve several hospital centers in the Republic of Serbia and analyze chemotherapy outcome in a larger sample of patients with massive transfusion syndrome. A wider range of laboratory tests should be applied and all necessary quantities of chemo products should be used in transfusion management of patients in order to prevent hemorrhagic shock and DIC.

## Conclusion

This study has confirmed the pathophysiological mechanism found in available medical literature that dilutional coagulopathy, caused by a sharp drop in platelet count and the significantly reduced activity of unstable coagulation factors in the patient’s circulation, develops after large volumes of red blood cell concentrate transfusion. Due to the rapid decline in the number of platelets, the majority of patients developed uncontrolled bleeding from the surgical wound, injury or puncture spot, which is rarely of the generalized type with bleeding into the skin or mucous membranes.

The results of screening tests obtained in our study are consistent with the findings reported in international studies, and they have shown that massive transfusion syndrome includes extended activated partial thromboplastin time and prothrombin time and in most cases the normal value of the thrombin time in addition to a reduced number of platelets.

The aims of our study have been fully accomplished, and the administration of chemotherapy in treatment of the patients with acute massive bleeding over the five-year period has been completely analyzed. In addition, the values of the hemostatic and platelet counts screening test results obtained for the patients who received massive transfusion have been thoroughly assessed.

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Rad je primljen 17. X 2014.

Recenziran 26. II 2015.

Prihvaćen za štampu 3. III 2015.

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