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Adverse events associated with donor plateletpheresis: A 10-year experience from Vojvodina, Serbia

Neželjeni događaji povezani sa trombocitaferezom kod davaoca: 10-godišnje iskustvo iz Vojvodine, Srbija

Zorana Budakov Obradović, Nevenka Bujandrić, Jasmina Grujić

Blood Transfusion Institute Vojvodina, Novi Sad, Serbia; University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Abstract

Background/Aim. Plateletpheresis (PLTP) is a medical procedure used for collecting donor platelets with multiple benefits for patients who will receive apheresis platelets. The procedure takes one hour and is well tolerated by donors. Nevertheless, adverse events (AEs) may occur during and after the PLTP procedure. The aim of the study was to determine the incidence and type of AEs associated with PLTP in donors. **Methods.** A retrospective analysis of AEs associated with donor PLTP was conducted at the Blood Transfusion Institute of Vojvodina from January 1, 2010, to December 31, 2019. **Results.** Out of 2,073 platelet donors, 94.84% were multiple blood donors, predominantly male (98.55%). AEs were identified during 180 (8.68%) platelet donations with no statistical significance in occurrence in the first time donors (10.28%) and repeat donors (8.59%). Mild local reactions related to venous access (42.22%) were the most common AEs. Generalized symptoms were exhibited in 16.67% of donors, 26.11% exhibited symptoms related to apheresis (citrate reactions), and 15% exhibited those related to other complications. It was found that 95.55% of AEs occurred during PLTP and only 4.45% after it. **Conclusion.** Donor PLTP is a generally safe procedure, well tolerated by donors. Understanding risk factors for a possible occurrence of AEs provides support for adopting measures to prevent them.

Key words:
blood donors; drug-related side effects and adverse reactions; plateletpheresis; risk factors.

Apstrakt

Uvod/Cilj. Trombocitafereza je medicinski postupak prikupljanja trombocita davaoca od koje pacijenti primaoci imaju mnogo prednosti. Postupak traje oko jedan sat i davaoci ga dobro podnose. Ipak, neželjeni događaji (ND) se mogu javiti, kako tokom, tako i nakon postupka trombocitafereze. Cilj rada bio je da se utvrdi učestalost i vrsta ND povezanih sa trombocitaferezom kod davaoca. **Metode.** Retrospektivna analiza ND povezanih sa trombocitaferezom sprovedena je u Zavodu za transfuziju krvi Vojvodine u periodu od 1. januara 2010. do 31. decembra 2019. godine. **Rezultati.** Od 2 073 davaoca trombocita, 94,84% su bili višestruki davaoci krvi, uglavnom muškarci (98,55%). ND identifikovani su tokom 180 (8,68%) trombocitafereza, bez statistički značajne razlike u pojavi između novih davalaca (10,28%) i višestrukih davalaca (8,59%). Blage lokalne reakcije povezane sa venskim pristupom (42,22%) bile su najčešći ND. Generalizovane simptome pokazalo je 16,67% davalaca, simptome koji se odnose na aferezu (citratne reakcije) 26,11% davalaca, dok je 15% davalaca imalo druge komplikacije. ND su se desili uglavnom tokom izvođenja trombocitafereze (95,55%), a svega 4,45% nakon nje. **Zaključak.** Trombocitafereza je, generalno, siguran postupak koji davaoci dobro podnose. Razumevanje faktora rizika od moguće pojave ND omogućava donošenje mera za njihovo sprečavanje.

Ključne reči:
krv, davaoci; lekovi, neželjene reakcije; trombocitafereza; faktori rizika.

Introduction

Plateletpheresis (PLTP) is a procedure used for collecting donor platelets. The procedure involves removing whole blood from a donor, centrifugation to separate the blood into individual components, removing platelets in the separated – standardized platelet bags, and reinfusing the remaining blood components into the donor's bloodstream. PLTP is

Correspondence to: Nevenka Bujandrić, Blood Transfusion Institute Vojvodina, Hajduk Veljkova 9A, 21 000 Novi Sad, Serbia.
E-mail: nevenka.bujandric@mf.uns.ac.rs

performed by the apheresis machine and takes between one and two hours [1]. The platelets can also be separated from the whole blood unit collected from the donor by way of the traditional mode. Apheresis platelets are collected from a single donor and are equivalent to 4–8 pooled units obtained from whole blood. An apheresis platelet concentrate contains 200–400 mL of plasma and a minimum of 3.0×10^{11} platelets [2–4]. The benefits of PLTP are decreased risk of transfusion-transmitted infections, allergic transfusion reactions, bacterial contamination, as well as prevention of alloimmunization with platelets and leukocyte antigens due to the reduction of the number of donors a recipient is exposed to. Another significant benefit is providing leukocyte-reduced platelets by a modern generation of apheresis machines [5].

Donors can donate apheresis platelets more frequently than whole blood – a maximum of twice in 7 days or 24 times a year. A specially designed machine ensures the safety of the platelet donor during the procedure so that the procedure is well tolerated by the donor. Nevertheless, adverse events (AEs) of variable severity may occur not only during but also after the PLTP procedure [6, 7]. An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment or procedure that may or may not be considered related to the medical treatment or procedure [8, 9]. Local and systemic AEs during PLTP may be the result of a number of causes, but they almost always occur as mild reactions, very well tolerated [10, 11].

This study was performed at the Blood Transfusion Institute (BTI) of Vojvodina, Novi Sad, Serbia, one of the largest Serbian blood transfusion services and blood donation centers, which collects a total of 48,000 blood units and 200 platelet collections by PLTP annually. The BTI of Vojvodina meets the blood supply demand of secondary hospitals located in Vojvodina (north part of Serbia) and tertiary hospitals located in the city of Novi Sad.

The aim of the study was to present single-center experiences in order to determine the incidence and type of AEs associated with donor PLTP.

Methods

A retrospective analysis of AEs associated with donor PLTP in the BTI of Vojvodina, Serbia, was conducted from January 1, 2010, to December 31, 2019. Data from the register of AEs related to donation were used. During the observation period, 2,073 donors underwent PLTP. PLTP was done using two mobile cell separators: the Haemonetics MCS®+ cell separator (Braintree, MA, USA) and the Trima Accel® Automated Blood Collection System (Terumo BCT).

PLTP was performed on healthy non-remunerated first-time volunteers or repeat blood donors (BD), some of whom donated platelets for the first time. After the donors completed a questionnaire with standard questions relating to their general health, lifestyle, travel history, past medical history, and medication, they were physically examined, and the donated samples underwent serological and molecular tests for markers of four transfusion-transmitted pathogens (human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and *Treponema pallidum*).

Criteria for blood donor selection

In addition to the general criteria for the BD selection, platelet donors should be selected in accordance with the following criteria: the donor must have more than 60 kg of body weight; must be between 18 and 60 years old; the hemoglobin level of red cells must be greater than 125 g/L for a female and greater than 135 g/L for a male; the minimum pre-donation platelet count must be 150×10^9/L; an interval of 2 months between donations of whole blood must exist; an interval of 15 days between apheresis platelet donations must exist [12].

Classification of donor AEs

According to the time of occurrence, AEs are divided into AEs occurring during procedures and AEs occurring after the procedures.

All AEs were recorded and classified according to the International Haemovigilance Network categories of donor AEs in the following complications: complications mainly with local symptoms; complications mainly with generalized symptoms; complications related to apheresis such as citrate reaction, hemolysis, generalized allergic reaction, and air embolism; other complications related to blood donation [9].

Local reactions related to venous access are the following: hematomas (caused by incorrect placement of the needle during the venipuncture), pain, hyperemia, swelling; pain due to the subcutaneous nerve irritation/injury; local phlebitis and thrombophlebitis; delayed bleeding; local allergy.

Systemic reactions include vasovagal reactions (immediate/delayed), pallor, sweating, dizziness, gastrointestinal disorders, nausea, hypotension, and bradycardia.

Differentiation based on the severity of the AEs

Based on the severity of the AEs, the following division was made: Grade 1 – mild (high blood pressure, vein collapse, poor vein flow, lip tingling, tongue tingling, facial tingling, weakness and fainting, urticaria at the injection site); Grade 2 – moderate (sweating, nausea); Grade 3 – severe (collapse).

Personal information concerning the donors' age, gender, address of residence, types of donations (first time/repeat), dates of all previous donations, previous and current deferrals, screening test results, and platelets donation history (yes/no) were obtained from the information system.

Statistical analysis

The Fisher's exact test and χ^2 test were used for assessing the occurrence of AEs in two donor groups (who donated blood/platelets for the first time or multiple times, men and women of different ages, relating to using different machine models). A *p*-value of 0.05 and less was considered statistically significant. Prism (GraphPad) statistics program was used for statistical analysis.

Results

During the study period, 2,073 persons donated platelets. Just 107/2,073 BDs donated platelets for the first time (5.16%). The majority of platelet BDs (1,966/2,073) were multiple BDs (94.84%).

The AEs were identified in 180/2,073 (8.68%) platelet BDs. Out of 107 first-time BDs, 11 (10.28%) suffered AEs. Out of 1,966 repeated BDs, 169 (8.59%) suffered AEs. The Fisher's exact test (p = 0.4845) showed no statistically significant difference in the incidence of AEs in BDs who donated blood for the first or multiple times.

The majority of donors who suffered AEs (93.89%) belonged to the repeat BDs (169/180). Out of 169 repeated BDs with AEs, 45 (26.63%) underwent PLTP for the first time, and 124 (73.37%) had already undergone PLTP. Ten BDs had already experienced AEs during the previous PLTP.

Out of the 2,073 donor PLTP, 1,151 (55.54%) were performed using Trima Accel® and 922 (44.46%) using Haemonetics MCS®+ cell separator. The analysis showed AEs in 112/1,151 (9.74%) platelet donors on the Trima Accel® and in 68/922 (7.42%) platelet donors on the Haemonetics MCS®+ cell separator. The Fisher's exact test (p = 0.06) showed no statistically significant differences between the groups and outcomes.

The most common cause of AEs associated with donor PLTP was venipuncture in 76 (42.22%) donors. Types of AEs during donor PLTP are shown in Table 1.

The largest number of AEs occurred due to local symptomatology in 76/2,073 (3.66%) donors.

Mild AEs occurred in 166 (92.22%), moderate in six (3.33%), and severe in eight (4.45%) donors. The most common AE was a collapsed vein that occurred in 41 (22.78%) BDs.

The demographic characteristics of platelet donors (gender, age) are shown in Table 2.

No statistically significant differences were observed in the occurrence of AEs between men and women (Fisher's exact test, p = 1).

AEs were statistically significantly more frequent in platelet donors aged 36-45 (the χ^2 statistic was 51.767, p < 0.00001).

The study showed that 172 (95.55%) AEs occurred during PLTP, while eight (4.45%) AEs occurred after PLTP.

Table 1

Types of adverse events (AEs) during donor plateletpheresis (PLTP)

Adverse events	Platelet donors with AEs		Total
	first time BDs	repeated BDs	n (%)
Local symptoms			
high blood pressure during returning blood		5	5 (2.78)
collapsed veins		41	41 (22.78)
poor blood flow	3	27	30 (16.66)
Total			76 (42.22)
Generalized symptoms			
weakness, fainting		16	16 (8.89)
nausea and sweating		6	6 (3.33)
vasovagal syncope	2	6	8 (4.45)
Total			30 (16.67)
AE related to apheresis – citrate reaction			
lip tingling	6	32	38 (21.11)
tongue tingling		3	3 (1.67)
facial tingling		6	6 (3.33)
Total			47 (26.11)
Other complications			
lipemic plasma		6	6 (3.33)
icteric plasma		3	3 (1.67)
injection site urticaria		3	3 (1.67)
instrument failure		15	15 (8.33)
Total			27 (15.00)

BDs – blood donors.

Table 2

The demographic characteristics of platelet donors with adverse effects (AEs)

Parameter	Platelet donors	Platelet donors with AEs
	n (%)	n (%)
Gender		
male	2,043 (98.55)	178 (8.71)
female	30 (1.45)	2 (6.67)
Age (years)		
18–24	427 (20.60)	14 (3.28)
26–35	777 (37.48)	63 (8.10)
36–45	629 (30.34)	93 (14.78)
46–60	240 (11.58)	10 (4.17)

The study did not analyze the most common causes of blood donor deferral, although 1,891 BDs were rejected. Out of them, 252/359 (70.19%) were first time BDs and 1,639/3,605 (45.47%) were repeated BDs; 189/219 (86.30%) were female BDs and 1,702/3,745 (45.45%) were male BDs. The total number of platelet donations compared to the number of donors who tried to donate platelets was 2,073/3,964 (52.29%).

Discussion

The study found that the AEs occurred in 8.68% of platelet donors as well as that most of them occurred during PLTP. Mild local reactions related to venous access were the most common AEs observed with apheresis procedures. The highest occurrence of AEs was recorded in platelet donors aged 36–45. During the observation period, the study found that repeat male BDs were mostly selected for platelet donors. Although no statistically significant difference was found in the incidence of AEs in platelet donors who donated blood/platelets for the first or multiple times, the majority of donors who suffered AEs (93.89%) were repeated donors (169/180). No statistical difference in the occurrence of AEs between men and women was found. However, AEs happened significantly more frequently in donors who experienced AEs during the previous PLTP. No significant difference was noted in AEs related to the two cell separators used for PLTP.

Platelet transfusions are used for prophylaxis and treatment of platelet-related bleeding. The indication for platelet transfusion depends on the platelet count and function, bleeding pathology, risk factors for bleeding, as well as the underlying disease [13]. Nowadays, the use of platelet concentrates as well as the use of apheresis platelet concentrate is increasing because collecting the platelets from a single donor improves the chance of a successful transfusion [2, 14]. Platelet supply management is not easy due to variable daily demand and short shelf life. Furthermore, a significant impact on the future platelet supply could have an increase in the demand for platelets as well as a reduction of the active donor base. British Society for Hematology Guideline pointed out that the majority of platelets in the UK are collected from approximately 14,000 registered platelet donors (apheresis platelets) while the whole BD base is steadily dropping by a 35% reduction in 15 years [15]. In Vojvodina, the entire blood collection dropped by 15% in two years, which reflects on the management of patients who require platelet transfusion. Minimizing platelet waste as well as minimizing AEs in order to achieve donor retention has become an essential requirement in guaranteeing optimal patient care.

PLTP is generally considered safe, although some AEs of varying severity may occur during or after the PLTP procedures. The incidence of AEs related to PLTP is usually low, which points to the fact that the procedure is well tolerated by donors. It is an important factor for donor recruitment and retention. PLTP has a lower incidence of AEs compared to whole blood donation, which can be explained by the longer-lasting donor preparation [14]. Additionally, platelet donors are selected not only based on general criteria for whole blood donation but also on specially defined criteria for PLTP. The results concerning the total number of platelet donors who had some type of AEs (8.68%) presented in the study are slightly more frequent than literature data (6.06%) which confirm that PLTP, although invasive, is relatively well tolerated [16]. The fact identified in the study indirectly indicates the possibility of donors' safety level improvement. At the same time, the study showcases that mild AEs were most common.

Understanding PLTP-related risk factors for AEs assists in the prevention of the occurrence of AEs. In the study, the majority of repeated BDs with AEs who had already undergone PLTP had their previous experiences on Haemonetics MCS®+ cell separator, as the first apheresis machine was used in the BTI of Vojvodina, Serbia. It took them a while to get used to a different style of machine, even if the machine had continuous blood flow with less procedure time, less volume processed, and less volume of used anticoagulant citrate dextrose (ACD). Ultimately, both donor recruitment and donor retention showed that the donors were comfortable using both separators.

The study has several strengths related to the design: long-term study, detailed information about the study participants, and the link between routine practice and later outcomes. Our study also has one limitation. The limitation is the non-notation of the type of AE associated with each individual cell separator. As both cell separators are used worldwide, we have overlooked that those procedural problems related to the new separator can affect the appearance of AEs. However, the findings of this study offer new, potentially useful information for our future work. Finally, we could not control which separator would be associated with icteric or lipemic plasma type complications as well as local symptoms related to venous access.

The study found that the largest number of AEs was due to local symptomatology (42.22%). Vein collapse and poor vein flow during the apheresis procedure were the most common AEs associated with venipuncture. In a four-year study examining the occurrence of AEs, Diekamp et al. [17] reported that discontinued collections due to venous access problems, repeated venipuncture, and small hematomas were the most common AEs. In order to prevent such occurrences, the vein must be of a certain caliber, and the placement of the needle during the venipuncture must be correct as the same vein in the arm is used for the inflow and return of blood. Although the platelet donors with AEs who participated in this study did not attach special importance to these events, in order to prevent the risk of these AEs and to increase the return rate of platelet donors, the appropriate selection of donors according to the given criteria is necessary, as well as the evaluation of the quality of the cubital vein of both arms. Therefore, more rigorous selection criteria than those for whole BD are required [8, 18].

The study identified mild forms of AEs attributed to citrate in the form of tingling of lips, tongue, and face, which comprise one-quarter of all AEs identified in the study participants. The overall incidence of citrate reaction

during PLTP (47/2,073) remains low (2.27%), and these findings seem comparable to those found in the literature incidence rate reports, which range between 2.7% and 3.03% [18]. Citrate intoxication during PLTP was caused by the administration of the citrate anticoagulant ACD-A, which chelates calcium ions, leading to a decrease in their plasma concentration. Despite compensatory mechanisms that reduce the concentration of citrate in the extracellular fluid (intensive metabolism of citrate in the kidneys, liver, and muscles, as well as the return of blood to the circulation during apheresis), symptoms caused by a decrease in the concentration of calcium ions were realistically possible [19]. Routine determination of calcium ion concentration during the preparation of platelet donors was not performed. However, to prevent AEs of citrate etiology, donors were supplemented with calcium salts (calcium lactate gluconate and calcium carbonate) before and during the procedure. In a similar study performed in Southern India, similar citrate-related toxicity reactions (2.43%) were seen [20]. Citrate toxicity due to hypocalcemia may cause perioral paresthesia of the extremities, tremors, dizziness, chills, tetany, and seizure.

Most studies have shown that vasovagal reactions are usually of mild intensity, in the form of weakness and fainting, and, in most cases, allow the performance of platelet procedures in their entirety [21]. The study found that mild forms of syncopal reactions were the most common but that moderate and severe forms of syncopal reactions were also reported. It must be taken into account that these types of reactions arise as an effect of psychological factors prompted by the dynamics and the length of the procedure. For this reason, appropriate donor selection and proper psychophysical preparation for PLTP could be essential factors for preventing syncopal AEs. Although we are certain that vasovagal reactions occur more frequently among female donors because of the smaller circulatory volume [20], we were unable to show it in our study due to a relatively small sample size of female donors.

Technical aberrations due to machine malfunction in 15/2,073 (0.72%) donors were the least frequent causal factor of the AEs. In a study from Iraq by Bassi et al. [22], 0.94% technique-related AEs were found, while 1.40% AEs associated with defective kit/equipment were recorded. These types of errors should be minimized, but in reality, their occurrence cannot be ruled out.

Donor care is ensured by recognizing and diagnosing AEs, which occur during and after donor PLTP, as well as appropriately investigating and treating them. Systematic records, collation, and analysis of AEs, as well as continued monitoring and reporting, will establish a platform for evaluating the occurrence of AEs and ensure timely response as necessary. We have noted the need for professional and post-qualification staff training, as well as educating and helping donors prepare for platelet donation.

Conclusion

The low incidence of usually mild AEs related to PLTP indicates that the procedure is generally safe and well tolerated by donors. Understanding the PLTP-related risk factors for AEs provides support for the adoption of measures to prevent their occurrence.

Conflict of interest

None to declare.

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