Immature Platelet Count Levels as a Novel Quality Marker in Plateletpheresis

Ozlem Unay Demirel^{1,4} · Seyda Ignak² · Mustafa Cagatay Buyukuysal³

Received: 2 November 2017 / Accepted: 5 May 2018 / Published online: 14 May 2018
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Abstract The efficiency of plateletpheresis was improved owing to new developments in automated cell separators in the past decades. Nowadays multiple units of plateletpheresis products can be taken per collection from single donor and new parameters such as immature platelet fraction (IPF), immature platelet count (IPC) can be detected practically by automated hematology analyzers. Our aim is to find out a new quality parameter for evaluation of plateletpheresis by analyzing the platelet indices of donor and also to predict platelet recovery in recipients thereby preventing unnecessary platelet transfusion. In this study 104 platelet apheresis procedures were performed on the Trima Accel cell separator. Complete blood counts of donors and recipients were analyzed by Sysmex XN-1000 automated blood cell counter by means of quality parameters such as platelet count, IPF, IPC, mean platelet volume, platelet distribution width. We analyzed these parameters in the follow up after the transfusion of plateletpheresis and evaluated them as quality markers in the assessment of plateletpheresis effectiveness. For recipients of both single and double unit apheresis platelet

transfusions, the pre-apheresis donor IPC correlated significantly with 1st and 24th hour recipient IPC values (p values < 0.05 for all comparisons). A-IPC as well as % change in IPF can be used to determine the quality of plateletpheresis in conjunction with platelet number in terms of evaluation of donors and also in the follow up of recipients undergoing platelet transfusion.

Keywords Complete blood count · Reticulated platelets · Plateletpheresis · Platelet indices

Introduction

Blood component donation has become more common in the last few years thanks to technical developments, improvements in apheresis techniques, development of platelet additive solution and better storage conditions [1, 2]. Although some adverse effects of plateletpheresis are described [3], apheresis is a relatively safe procedure which is commonly used for donation and therapeutic purposes today. Some of the modern apheresis systems are equipped with a white blood cell (WBC) reduction device. Donor arm preparation is important so that use of diversion pouch reduces bacterial contamination in the transfusion recipient [2].

Nowadays there are a variety of apheresis instruments on the market, which allows collection of specific blood components purely in consistent volumes and use of multiple platelet units from a single donor for increasing the platelet yield [4, 5]. The ability to collect more than one apheresis platelet unit per collection event reduces cost per unit by at least 50% and also the incidence of immunological and infectious complications is reduced [6, 7].

✉ Ozlem Unay Demirel
ozlemunay@yahoo.com

¹ Department of Medical Biochemistry, Goztepe Medical Park Hospital, School of Medicine, Bahcesehir University, Istanbul, Turkey

² Department of Medical Biology, School of Medicine, Bahcesehir University, Istanbul, Turkey

³ Department of Biostatistics, School of Medicine, Bulent Ecevit University, Zonguldak, Turkey

⁴ Goztepe Medical Park Hospital Laboratory and Transfusion Center, School of Medicine, Bahcesehir University, 23. Nisan Sokak E-5 Uzeri Kadikoy, Istanbul, Turkey

On the other hand automated blood cell counters are becoming increasingly sophisticated and can analyze new platelet parameters such as immature platelet count (IPC), immature platelet fraction (IPF) and also routinely measured parameters like mean platelet volume (MPV), platelet size distribution width (PDW), plateletcrit (PCT), platelet large cell ratio (P-LCR) [8, 9].

Circulating platelets vary in both size and functional activity. Larger platelets are usually relatively young and more recently released from the bone marrow, while smaller platelets may be older and have been in circulation for 7–10 days. Newly released platelets from the bone marrow (immature or reticulated platelet) are larger, more physiologically active, contain more RNA than mature platelets and produce more thrombogenic activity. Immature platelets, similar to reticulocytes, gradually lose their reticulation and assume a smaller size as they mature. These immature reticulated platelets have much shorter life span like less than 1 day. On the other hand immature platelets can be a marker of megakaryocytic activity in the bone marrow [10, 11]. The proportion of reticulated platelets to total platelets reflects the rate of thrombopoiesis, increasing where platelet production rises and decreasing when production falls [12]. Determination of reticulated platelets is useful in the differential diagnosis of thrombocytopenia due to bone marrow failure. It gives an idea whether thrombocytopenia originates from peripheral consumption or destruction. On the other hand IPC which is calculated from IPF multiplied by total platelet number in circulation, reflects the real time rate of thrombopoiesis [9]. Therefore IPF and IPC give an idea about the quantity of young and reticulated platelets in peripheral blood [10]. An IPF reference range in healthy individuals is established as 1.1–6.1%, with a mean of 3.4% [12].

In our study, we aimed to identify time dependant changes in platelet indices in both donors and recipients. We investigated whether these new platelet indices can be used in the screening of donors and also in the follow up of recipients after transfusion of either single or double units plateletpheresis and as a marker of quality to evaluate the effectiveness of plateletpheresis.

Materials and Methods

In this cross-sectional prospective study, 104 platelet apheresis procedures between June 2015 and December 2015 are investigated.

Donor Selection

All donors (98 male, 6 female) were informed about the apheresis procedure and informed consent from each

subject were obtained. Our study was approved by the Institutional Clinical Research Ethics Committee and was performed in accordance with the Protocol of Helsinki. Donors were monitored for general state of health and adverse effects during the whole procedure.

All the donors met the donor eligibility of Council of Europe guidelines and recommendations for apheresis and the Standard guidelines established by American Association of Blood Banks [13, 14]. The quality parameters were as follows: healthy men and women, with no known mental and physical disability, receiving no drug therapy no consumption of non-steroidal anti-inflammatory drugs and acetyl salicylic acid in the last 7 days; age 18–60 years; body weight ≥ 50 kg; collected maximum whole blood volume maximum of 10.5 mL/kg; at least 3 days after donation of plateletpheresis; hemoglobin (Hb) level > 12.5 g/dL for woman > 13.5 g/dL for man; preapheresis peripheral blood platelet count $\geq 1.5 \times 10^{11}/L$; free of major organ disease, abnormal bleeding tendency; 12 months after being of recipient for blood transfusion or tissue transplant; negative tests for hepatitis B antigen, anti HCV antibody, anti HIV-1 and 2 antibody and anti *Troponema pallidum* antibody and adequate venous accesses.

According to Turkish national transfusion guideline the quality parameters of collected plateletpheresis units are as follows: Volume of the product (> 40 mL), thrombocyte count ($2 \times 10^{11}/Units$), residual white blood cell ($< 1 \times 10^6/Units$), pH value after 5 days at 22 °C (> 6.4) [15].

Laboratory Tests

Whole blood samples of subjects were collected in EDTA vial and hematological parameters such as PLT count, IPF%, IPC, PDW, MPV, WBC, Hb, Hematocrit (Hct) of donors and recipients before and after apheresis process were determined by Sysmex XN-1000 automated blood cell counter (Sysmex Corporation, Kobe, Japan). The complete blood count parameters of the donor samples were collected before apheresis process collection and recipient samples were collected before apheresis collection at the time when plateletpheresis is decided, 1 and 24 h after the apheresis procedure.

Platelet Apheresis

Apheresis was performed by Trima Accel single needle system (Gambro BCT, Lakewood, CO) according to the manufacturer's instructions. Acid-citrate-dextrose formula A (ACD-A) was used as an anticoagulant during the apheresis procedures in 11:1 ratio. Whole blood flow was set to 60–100 mL/min. Apheresis time was limited to 80 min. The data such as donor weight, sex, height, Hb, Hct, pre-apheresis platelet count were entered into the cell

separator program of device. The processed blood volume required to reach target platelet yield for single unit was set to 2.5×10^{11} and double unit as 5×10^{11} in the device compatible with the European Guidelines [14]. WBC reduction process was performed by the leukoreduction system (LRS chamber) of the device in-line.

Statistical Analysis

R 3.2.1. software is used for statistical analysis. Descriptive statistics of categorical variables are given with frequency and percent where continuous variables are represented by median, minimum and maximum values. Shapiro–Wilk test used for test of normality. Wilcoxon test is used to test significant difference for dependent variables at different times. Spearman correlation used to test relationship among continuous variables. For all statistical analysis with a p value below 0.05 is assumed as statistically significant.

Results

General characteristics of pre- and postapheresis platelet and platelet derived parameters of donors are given in Table 1. There were 104 donors capable of giving single

($n = 74$) or double ($n = 30$) dose apheresis. Plateletpheresis parameters are also presented in Table 1.

Pre-transfusion values compared with 1st and 24th hour platelet count, IPF, IPC, MPV and PDW values in recipients receiving single and double dose apheresis. These are represented in Tables 2 and 3.

There is a statistically significant difference among pre-transfusion and 1st hour IPC values ($p = 0.001$) and 24th hour IPC values ($p = 0.015$) in recipients receiving transfusion from single dose apheresis unit donors. There is a statistically significance difference among pre-transfusion and 1st hour IPC values ($p < 0.001$) and 24th hour IPC values ($p < 0.001$) in recipients receiving transfusion from double dose apheresis unit donors. Although 1st hour post-transfusion IPF values are found to be statistically significant in recipients receiving transfusion from single dose apheresis donors when compared to pre-transfusion values ($p = 0.019$) whereas there is no significance between 24th hour post-transfusion and pre-transfusion values. On the other hand, pre-transfusion values of IPF when compared to 1st hour ($p < 0.001$) and 24th hour ($p = 0.002$) post-transfusion were found to be both statistically significant in recipients who received double dose apheresis.

Pretransfusion platelet counts and IPC values of recipients receiving transfusion from either single dose or double dose apheresis product donors were statistically significant in comparison to 1st and 24th hour posttransfusion values whereas PDW and MPV were not found to be statistically significant.

There is no statistically significant correlation between donors and recipients receiving transfusion either from single or double dose apheresis product donors by means of IPF, PDW and MPV parameters. There is no statistically significant difference among platelet count of donor and IPF, PDW and MPV values of recipients ($p > 0.05$). IPF, PDW and MPV values were not found to be appropriate for determining the quality of apheresis product by using logistic regression model (Table 4).

We found a statistically significant correlation between IPF, PDW, MPV and IPC levels of donor and percent change of pre-transfusion values when compared to 1st hour and 24th hour post-transfusion values of recipients (Table 5). Moreover there is a positive correlation between donor IPF values and percent change between pre-transfusion and 1st hour after transfusion of recipient (IPF-PC1), percent change between pre-transfusion and 24th hour after transfusion of recipient (IPF-PC2) values (p values are < 0.001 and < 0.001 ; r values are 0.536 and 0.411 respectively). This means with a high level of IPF value at donor increases the change rate at 1st and 24th hours of recipients' IPF values. Same comment is also possible for IPC values. There is a positive correlation between donor IPC values and IPC-PC1, IPC-PC2 values

Table 1 Donor characteristics and plateletpheresis parameters

Variables	Results
<i>Donor characteristics</i>	
Male/female	98/6
Height (cm) ^a	176 (159–190)
Weight (kg) ^b	81 $\pm$ 12.8
IPF (%) ^a	4.2 (1.5–12.8)
IPC ^a	10,500 (3375–26,752)
MPV (fL) ^a	10.7 (9–13)
PDW (fL) ^a	12.9 (10–19.8)
Preapheresis Hct (%) ^b	44.2 $\pm$ 2.6
Postapheresis Hct (%) ^b	41.5 $\pm$ 2.65
Preapheresis PLT ($\times 10^3 \mu\text{L}$) ^a	243 (171–385)
Postapheresis PLT ($\times 10^3 \mu\text{L}$) ^a	163 (123–303)
<i>Plateletpheresis parameters</i>	
Processed Blood volume (mL) ^a	3006 (1638–4279)
ACD-A (mL) ^a	302 (144–420)
Product volume (mL) ^a	392 (206–445)
PLT yield ($\times 10^{11}$) ^a	4.5 (2–6.8)
Separation time (min) ^a	60 (45–90)

^aMedian (range)

^bMean $\pm$ standard deviation

Table 2 Comparison of platelet parameters in single dose plateletpheresis in recipients

	Pre-transfusion median (min–max)	1st hour median (min–max)	<i>p</i> value (pretransfusion vs. 1st hour) ^a	24th hour median (min–max)	<i>p</i> value (pretransfusion vs. 24th hour) ^a
MPV (fL)	11.3 (8.5–15.1)	11.5 (10.2–13.4)	0.289	11.8 (10.1–13.7)	0.211
PDW (fL)	13.4 (8–21)	13.6 (7.7–20.6)	0.410	14.5 (9.2–21.4)	0.389
PLT ($\times 10^3 \mu\text{L}$)	10 (1–78)	27 (5–105)	< 0.001	23.5 (1–98)	0.004
IPC	0.48 (0–7.85)	1.34 (0–9.96)	< 0.001	1.13 (0–6.77)	0.015
IPF%	5 (0.9–18)	3.5 (0.6–19.2)	0.019	4.1 (1.1–19.9)	0.316

^aWilcoxon test**Table 3** Comparison of platelet parameters in double dose plateletpheresis in recipients

	Pre-transfusion median (min–max)	1 st hour median (min–max)	<i>p</i> value (pretransfusion vs. 1st hour) ^a	24 th hour median (min–max)	<i>p</i> value (pretransfusion vs. 24th hour) ^a
MPV (fL)	11.5 (8.2–15.4)	11.3 (9.8–13.7)	0.576	11.5 (8.1–13.8)	0.528
PDW (fL)	13.2 (8.3–24.6)	13.1 (8.5–19.5)	0.780	13.3 (9.5–24.5)	0.823
PLT ($\times 10^3 \mu\text{L}$)	14 (1–89)	46.5 (10–125)	< 0.001	31 (4–103)	< 0.001
IPC	0.71 (0–5.37)	1.5 (0–19.22)	< 0.001	0.93 (0–7.99)	< 0.001
IPF%	5 (0.5–37)	3.6 (0.4–24)	< 0.001	3.9 (0.5–22)	0.002

^aWilcoxon test

(*p* values are < 0.001 and < 0.001; *r* values are 0.416 and 0.313 respectively). Furthermore, percentage change of both IPC and IPF when compared to IPC-PC1 and IPF-PC1 have a moderately positive relation ($r = 0.481$; $p < 0.001$). Both parameters tend to increase together. On the other hand we found a weakly positive relation when compared to IPC-PC2 and IPF-PC2 ($r = 0.328$; $p = 0.001$). IPC-PC2 and IPF-PC2 have tendency to increase together but not as much as IPC-PC1 and IPF-PC1 do.

Discussion

In our study, we investigated whether IPF and IPC can be used in the screening of donors and also in the follow up of recipients after transfusion of apheresis from either single or double units of plateletpheresis donors and as a marker of quality to evaluate the effectiveness of plateletpheresis. Moreover it is well known that evaluation of donors is an important part of therapeutic apheresis. In Turkey women donate whole blood less often than men. Among Turkish population women accounted for only 11% in a study [16]. Complete blood count is requested routinely in donors admitted to transfusion center. Platelet count which is a component of complete blood count is considered to be a

major parameter for determination of suitability of donor for plateletpheresis routinely [17]. However, we know that the level of platelet yield in apheresis influences the platelet recovery in the recipient so not only quantity of platelets but also other quality criteria must be taken into the consideration in donor selection. Therefore, nowadays the transfusion medicine specialists not only focus on collection of platelets but also pay attention to optimize platelet product in terms of platelet yield in apheresis [18, 19]. Platelet count is also used to determine whether single or multiple plateletpheresis units can be taken per collection from single donor. Minimum requirement for platelet yield in single unit apheresis product shows difference in countries (US, $\geq 3 \times 10^{11}$); (EU, $\geq 2 \times 10^{11}$), resulting in different collection targets for double unit apheresis product [$\geq 5 \times 10^{11}$ (EU) vs. $\geq 6.5 \times 10^{11}$ (US)] respectively [20]. A minimum dose of 2×10^{11} platelets per unit according to European and national guidelines [14, 15]. Furthermore, there is no consensus for a standardized platelet dose throughout the world [21]. Although there are safety concerns related to high dose platelet collection which are adverse events associated with circulation and anticoagulant use, post-apheresis platelet count of donor, a possible effect on thrombopoiesis, and white blood cell loss [5], there are also some advantages. Higher platelet doses

Table 4 Comparison of donor platelet count and platelet indices of recipients at different times

Platelet indices of recipients	Donor platelet count
Pre-transfusion IPF	$r = -0.072^a$ $p = 0.476$
1st hour IPF	$r = 0.048^a$ $p = 0.635$
24th hour IPF	$r = -0.042^a$ $p = 0.683$
Pre-transfusion PDW	$r = -0.058^a$ $p = 0.673$
1st hour PDW	$r = -0.002^a$ $p = 0.987$
24th hour PDW	$r = -0.149^a$ $p = 0.196$
Pre-transfusion MPV	$r = 0.124^a$ $p = 0.366$
1st hour MPV	$r = -0.007^a$ $p = 0.948$
24th hour MPV	$r = -0.109^a$ $p = 0.344$
Pre-transfusion IPC	$r = -0.042^a$ $p = 0.671$
1st hour IPC	$r = -0.031^a$ $p = 0.756$
24th hour IPC	$r = 0.023^a$ $p = 0.817$

^aSpearman correlation

are expected to increase platelet count in the recipient to a better extent and this leads to extension of time for next transfusion [21].

It is well known that single platelet apheresis unit, can lead to increase of platelet count of an adult by 20,000–40,000/ μL . In normal conditions it is assumed that approximately 1 h after transfusion, the blood platelet count usually increases by 8000–10,000/ μL per square meter of body surface area when 1×10^{11} platelets are transfused [22]. On the other hand corrected count increment (CCI) which is derived from the platelet count increment and body surface area divided by number of platelets transfused ($\times 10^{11}$) can be used as a parameter for evaluation of effectiveness of platelet transfusion. Practically a CCI value of > 7500 at 1 h or a CCI value of > 4500 at 24 h is excepted as successful transfusion but it does not show that a sufficient platelet number is accomplished. It indicates only the adequacy of platelet count increase when compared to the number of platelets transfused [17]. We found that platelet and IPC values are

Table 5 Comparison of donor and recipient platelet indices

Platelet indices of donor	Platelet indices of recipients	
	IPC (PC-1)	IPC (PC-2)
IPC	$r = 0.416$ $p < 0.001$	$r = 0.313$ $p < 0.001$
	IPF (PC-1)	IPF (PC-2)
IPF	$r = 0.536$ $p < 0.001$	$r = 0.411$ $p < 0.001$
	PLT (PC-1)	PLT (PC-2)
PLT	$r = -0.097$ $p = 0.337$	$r = -0.015$ $p = 0.888$
	PDW (PC-1)	PDW (PC-2)
PDW	$r = 0.393$ $p = 0.003$	$r = 0.256$ $p = 0.064$
	MPV (PC-1)	MPV (PC-2)
MPV	$r = 0.276$ $p = 0.044$	$r = 0.271$ $p = 0.049$

PC-1, percent change between pre-transfusion and 1st hour after transfusion; PC-2, percent change between pre-transfusion and 24th hour after transfusion

statistically significant in recipients receiving single or double unit apheresis when pre-apheresis values are compared to post-apheresis 1st and 24th hour results. Platelet results are compatible with the literature. Up to our knowledge IPC levels are firstly shown as a quality marker for plateletpheresis in the follow-up of recipients.

Absolute platelet count (A-IPC) is calculated multiply by the IPF as percentage change and platelet count. It reflects absolute platelet count and the proportion of newly released young platelets which are immature and rich in mRNA. It is thought that A-IPC is a better parameter than IPF since it shows platelet production in the bone marrow when evaluating the etiology of thrombocytopenia [5, 12, 23].

In the literature, there are a few studies which draw attention to the relationship between IPF and thrombocytopenia due to viral etiology such as dengue and HIV positive patients [26, 27].

In our study, there is no viral etiology among our recipients. Hence our main purpose is to find out a new quality parameter for evaluating platelet indices of donor and recipients, we did not classify our recipients according to clinical diagnosis.

We did not find a statistically significant difference in recipients receiving single unit apheresis when pre-apheresis IPF values are compared with 24th hour IPF values in contrast to IPC. IPC is a better marker than IPF since IPC values at different times (pre-apheresis, 1 and 24-h post-apheresis) were statistically significant in

recipients receiving either single unit or double unit apheresis product.

The average life span of circulating platelets is 7–10 days, while reticulated platelets have much shorter life span (< 1 day) [10].

IPF has various reference interval studies and they are distributed in a wide range. Therefore, it is hard to determine cut off values for evaluating the product quality. IPF values in the healthy people are found as 3.3% (1.0–10.3) and upper limit of 95% confidence interval of IPF was obtained as 7.7% with Sysmex XE-2100 analyzer [24]. In another study IPF reference range was 0.5–3.2% in males and 0.4–3.0% in females with Sysmex XE-2100 analyzer [25]. We found that IPF has a range of 1.5–12.8% in healthy donors with a median of 4.2%.

Platelet indices such as MPV, PDW and IPF values are also searched but there are few articles related with IPC values in plateletpheresis [8, 9]. We could not find any article comparing single and double units in terms of platelet yield in the literature.

However in our study there is no statistically significant correlation between donors and recipients receiving apheresis from either single or double unit apheresis donors concerning IPF, IPC, PDW and MPV parameters so IPF, IPC, PDW and MPV alone can not determine the quality of apheresis product. On the other hand recipients' percentage change of IPF and A-IPC values at pre-transfusion, post-transfusion 1st and 24th hour values when compared to donors' IPF and A-IPC values is found to be statistically significant. This may show that both A-IPC and % change of IPF may be an outstanding parameter in transfusion of platelets.

We have some limitations in our study so that we evaluated the donors and recipient results but we did not classify the diseases of recipients etiologically. Future studies may focus on the effects of IPF and IPC according to etiology of diseases in recipients receiving plateletpheresis. Although we aimed to determine platelet parameters in recipients also on 3rd, 5th and 7th day post-apheresis, there were not a sufficient number of recipients who did not receive another plateletpheresis at that time for statistical analysis. Reference range and cutoff value of IPC can also be determined so that IPC can be used in combination with platelet number.

Conclusion

In conclusion A-IPC as well as % change in IPF can be used to determine the quality of plateletpheresis in conjunction with platelet number by means of evaluation of donors and also in the follow-up of recipients undergoing plateletpheresis.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent All human participants were informed about the research project and an informed consent from each subject were obtained.

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