

# The role of Stromal Cell-Derived Factor 1 (SDF-1) and Transforming Growth-Factor-Beta 1 (TGF- $\beta$ 1) levels in Packed Red Cells (PRC) as the indicator of storage lesion at Sanglah Hospital-Blood Bank, Bali, Indonesia



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## ABSTRACT

**Background:** Packed Red Cells (PRC) is one of the blood component obtained from the whole blood through the removal of blood plasma. The storage of PRC aims to maintain the viability and function of erythrocytes by reducing cell metabolic activity. However, PRC's biochemistry changes could occur through storage lesion by releasing Stromal Cell-Derived Factor 1 (SDF-1) and Transforming Growth Factor-Beta 1 (TGF- $\beta$ 1) that affect the erythrocytes metabolism and viability prior to transfusion. This study aims to evaluate the increase of SDF-1 and TGF- $\beta$ 1 levels in PRC as the indicator of storage lesion at Sanglah Hospital-Blood Bank, Bali, Indonesia.

**Methods:** An observational cross-sectional study using randomized post-test only without control group design was conducted at Sanglah Hospital-Blood Bank, Bali. The consecutive random sampling technique was used in this study to the PRC, who met the inclusion criteria. Samples of the SDF-1 group (N=84) were divided into 3 such as Group 1 (1-7 days), Group 2 (8-14 days), and Group 3 (15-21 days). However, 53 PRC was divided into 2 groups as Group 1 (1-7 days) and Group 2 (8-14 days). The SDF-1 and TGF- $\beta$ 1 levels were evaluated for each group using Human SDF-1/CXCL12 and TGF- $\beta$ 1 Kit from Elabscience<sup>®</sup> by ELISA method. Data were analyzed using SPSS version 25 for Windows software.

**Results:** The median levels of SDF-1 in Group 1 group was 0.385 (0.050-1.020) ng/mL, followed by 0.455 (0.330-0.750) ng/ml in Group 2, and 0.490 (0.380-0.920) ng/ml in Group 3 ( $p < 0.05$ ). The mean of TGF- $\beta$ 1 levels was slightly higher in Group 1 (2,365.21 $\pm$ 715.96 pg/ml) compared with Group 2 (2,210.39 $\pm$ 994.68 pg/ml) ( $p = 0.523$ ). There was a significant difference in SDF-1 levels in Group 1-Group 2 ( $P = 0.041$ ) and Group 1-Group 3 ( $P = 0.000$ ) groups; however, no significant difference was found in Group 2-Group 3 ( $P = 0.133$ ) using the Mann-Whitney test. The Spearman's rho test found a moderate positive correlation between SDF-1 levels and storage time by day ( $r = 0.546$ ;  $P = 0.000$ ). In addition, based on the Pearson correlation test, there was a weak positive correlation between TGF- $\beta$ 1 levels and storage time by day ( $r = 0.461$ ;  $p = 0.001$ ).

**Conclusion:** The increase of SDF-1 and TGF- $\beta$ 1 levels in PRC by days of storage time could be used as the indicator for storage lesion at Sanglah General Hospital-Blood Bank, Bali, Indonesia.

**Keywords:** Blood Bank, PRC, SDF-1, Storage Lesion.

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## INTRODUCTION

Packed Red Cells (PRC) are one of the blood components obtained from whole blood (whole blood) through the removal of approximately 250 ml of blood plasma so that the components of red blood cells are obtained.<sup>1</sup> PRC is usually used as a blood component product to treat bleeding or increase oxygen delivery to peripheral tissues. Using one PRC unit should generally increase hemoglobin

levels by 1 g/dL (10 g/L) and hematocrit by up to 3%.<sup>1,2</sup>

Packed Red Cells (PRC) can be stored from donation until they are transfused to the recipient. PRC storage has a goal in maintaining the viability and function of erythrocytes by reducing the metabolic activity of cells. Proper storage is one way to preserve the quality of erythrocytes.<sup>3</sup> Storage of PRC at a temperature of 2-6°C can provide resistance for 21-42

days depending on the anticoagulant-preservative solution used. The increase in room temperature accompanied by storage time can change the biochemical composition of PRC, which can impact the quality of PRC.<sup>3</sup>

In the last few decades, many studies have discussed the quality and quantity of erythrocytes during the storage period and their various changes. Some of the changes that PRC can experience include

biochemical and structural changes that can affect the viability and function of erythrocytes after transfusion. These changes are known as erythrocyte storage injuries.<sup>4,5</sup>

Biochemical changes can occur in RBC even if the blood storage temperature of 4°C is considered capable of reducing RBC metabolism and the accumulation of various soluble factors that can affect the safety and quality of PRC.<sup>6</sup> Although classical storage lesions have been extensively studied, the inflammatory markers associated with storage time have not been fully investigated. During storage time, it is known that several biochemical changes take place, such as the appearance of aggregations and biochemical debris that accumulate in the supernatant from prolonged RBC storage.<sup>5</sup> Several factors involved were released and had a significant impact on the storage quality of PRC, including Stromal-Cell Derived Factor 1 (SDF-1) and Transforming Growth Factor-Beta 1 (TGF- $\beta$ 1).<sup>7</sup>

SDF-1, also known as CXC-motif chemokine 12 (CXCL12), is a chemokine protein encoded by the CXCL12 gene on chromosome 10, a proinflammatory cytokine that is immunomodulatory and can trigger allergic responses.<sup>8</sup> In addition, increased levels of microparticles (MPs) which are the result of damage to the integrity of red blood cells, can trigger the occurrence of reactive oxygen species (ROS) through a decrease in NO bioavailability due to the scavenging process.<sup>9</sup> Likewise, TGF- $\beta$ 1 is known as a proinflammatory cytokine secreted by many types of cells, including macrophages, which act as immunomodulators, cell proliferation, and cell differentiation and apoptosis.<sup>10</sup> As immunomodulatory factors, the accumulation of these proinflammatory cytokines in PRC has been implicated as a potential cause of transfusion reactions from the use of these products.<sup>11-13</sup>

Currently, the results of studies related to differences in SDF-1 and TGF- $\beta$ 1 on the storage time of PRC have not been widely studied. Previous research has been limited to platelet and whole blood products where the clinical application is less than the use of PRC in hospitals.<sup>14,15</sup> Therefore, this study aims to determine

and evaluate the role of PRC storage time on SDF-1 and TGF- $\beta$ 1 levels in the Hospital Blood Bank (BDRS) Sanglah General Hospital as a preventive indicator in minimizing post-transfusion reactions.

## METHODS

This research is a laboratory observational study using a cross-sectional design with a randomized post-test-only group design and a consecutive sampling technique. There were 84 PRC included in this study for SDF-1 analysis and 53 PRC for TGF- $\beta$ 1 assessment. This research will be conducted for 1 month at the Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Hospital Blood Bank Unit, Sanglah General Hospital, Bali, Indonesia. The independent variables were storage time based on days for SDF-1 (1-7 days, 8-14 days, and 15-21 days) and TGF- $\beta$ 1 (1-7 days and 8-14 days). The dependent variables were SDF-1 levels in ng/mL and TGF- $\beta$ 1 levels in pg/mL, assessed using the ELISA method using Human SDF-1/CXCL12 and TGF- $\beta$ 1 Kit from Elabscience®.

There are several steps in the SDF-1 and TGF- $\beta$ 1 examination procedure: 1) all reagents and samples are placed at room temperature (18-25°C) before use; 2) reconstruction of standard human SDF-1 and TGF- $\beta$ 1 by adding distilled water. Mix well and make sure the solution is homogeneous so that the standard solution concentration is 20 ng/ml. Let stand for 10-30 minutes before diluting in S1, homogenize; 3) perform standard dilution by preparing 7 tubes labeled S1, S2, S3, S4, S5, S6, S7. Fill the seven tubes with a sample diluent of 225 L each. Put 225 L of standard solution in tube S1. Perform homogenization and put the mixture in the S1 tube into the S2 tube as much as 225 L. And so on until the tube S7. In tube S7, take 225 L of the solution and discard it to obtain 7 standard solutions with serial dilutions; 4) Remove the dilution plate from its packaging. Prepare microwell strips according to the number of tests to carry out, including blanks, standards, and controls. Controls should be checked in duplicate; 5) add 100  $\mu$ l and 80  $\mu$ l of sample diluent respectively into the blank wells and sample wells; 5) add 20  $\mu$ l of each sample to each sample wells; 6) prepare Horse

Radish Peroxidase (HRP) –Conjugate and add 100  $\mu$ l HRP-Conjugate to each well; 7) Remove the coated microwell strips from the aluminium pouch and wash them twice with wash buffer; 8) transfer 150  $\mu$ l of the reaction mixture from the dilution plate to the coated microwell strips and cover the microwell strips and incubate for 2 hours at room temperature (18-25°C) on a rotator at 400 rpm; 9) empty and wash the microwell strips 3 times with wash buffer followed by adding 100  $\mu$ l of Tetramethylbenzidine (TMB) substrate solution to all wells; 10) incubation of microwell strips for 10 minutes at room temperature (18-25°C); and 11) add 100  $\mu$ l of stop solution to all wells followed by reading the absorbance on an ELISA reader with a wavelength of 450 nm.

Steps to calculate the results of SDF-1 and TGF- $\beta$ 1 examinations are carried out by following the following steps: 1) calculate absorbance for each standard and specimen examination; 2) standard curves are made with the y-axis being the absorbance value of each standard dilution and the x-axis is the concentration of SDF-1 and TGF- $\beta$ 1 in ng/ml; 3) the concentration of SDF-1 and TGF- $\beta$ 1 is determined by first finding the absorbance value of the specimen on the y-axis, then from that point, a horizontal line is made to intersect the standard curve. A vertical line is then made at the point of intersection to intersect the x-axis so that the SDF-1 and TGF- $\beta$ 1 levels of the specimen can be determined; and 4) specimens with SDF-1 and TGF- $\beta$ 1 levels of more than 10,000 pg/ml or 10 ng/ml should be diluted. The reported specimens of SDF-1 and TGF- $\beta$ 1 levels were obtained by multiplying the SDF-1 or TGF- $\beta$ 1 levels on the standard curve by the dilution factor.

Data were analyzed using SPSS version 25 for Windows. Normality test was carried out by Kolmogorov-Smirnov test. The homogeneity test was assessed using Levene's test. Kruskal-Wallis test was conducted to evaluate the significant difference of SDF-1 levels and followed by Mann-Whitney test to evaluate each group different. The Spearman correlation test was also performed in the SDF-1 levels group. The mean difference of TGF- $\beta$ 1 levels was assessed by Independent T-Test and followed by the Pearson correlation test.

## RESULTS

The median levels of SDF-1 in Group 1 group was 0.385 (0.050-1.020) ng/mL, followed by 0.455 (0.330-0.750) ng/mL in Group 2, and 0.490 (0.380-0.920) ng/mL in Group 3 (Table 1). There was a significant difference in SDF-1 levels between groups by the Kruskal-Wallis test ( $p < 0.05$ ). In addition, there was a significant difference of SDF-1 levels in Group 1-Group 2 ( $P = 0.041$ ) and Group 1-Group 3 ( $P = 0.000$ ) groups; however, no significant difference was found in Group 2-Group 3 ( $P = 0.133$ ) using the Mann-Whitney test (Table 2).

The mean of TGF- $\beta$ 1 levels was slightly higher in Group 1 ( $2,365.21 \pm 715.96$  pg/mL) compared with Group 2 ( $2,210.39 \pm 994.68$  pg/mL), although not statistically significant ( $p = 0.523$ ) (Table 1). The Spearman's rho test found a moderate positive correlation between SDF-1 levels and storage time by days ( $r = 0.546$ ;  $P = 0.000$ ) (Table 3). In addition, based on the Pearson correlation test, there was a weak positive correlation between TGF- $\beta$ 1 levels and storage time by days ( $r = 0.461$ ;  $p = 0.001$ ) (Table 3).

## DISCUSSION

Numerous metabolic changes occur during normal blood storage conditions. These modifications mostly refer to the formation of aggregates and biochemical debris in the supernatant of RBCs that have been stored for a long time. Membrane and cytoskeleton protein oxidation, membrane phospholipid loss, aberrant rearrangement of membrane phospholipids, and morphological alterations are all examples of biomechanical storage lesions in the cytoskeleton and cellular membranes.<sup>5,16-21</sup> Extended RBC storage has also been discovered, resulting in SDF-1 and TGF- $\beta$ 1 changes over time.

SDF-1, better known as C-X-C motif chemokine 12 (CXCL12), is a chemokine protein that in humans is encoded by the CXCL12 gene on chromosome 12.<sup>8</sup> CXCL12 is expressed by many tissues in mice, including brain, thymus, heart, lung, and bone marrow where it is strongly chemotactic against lymphocytes.<sup>22,23</sup> SDF-1 is a proinflammatory molecule that plays

**Table 1. The SDF-1 and TGF- $\beta$ 1 levels according to PRC groups**

Variables	Median (Min-Max)	Mean $\pm$ SD	p
SDF-1 (ng/mL) (N=84)			
Group 1	0.385 (0.050-1.020)		<0.05 <sup>a*</sup>
Group 2	0.455 (0.330-0.750)		
Group 3	0.490 (0.380-0.920)		
TGF- $\beta$ 1 (pg/mL) (N=53)			
Group 1		2,365.21 $\pm$ 715.96	0.523 <sup>b</sup>
Group 2		2,210.39 $\pm$ 994.68	

SDF-1: Stromal-Cell Derived Factor 1; TGF- $\beta$ 1 Transforming Growth Factor-Beta 1; Group 1: 1-7 days; Group 2: 8-14 days; Group 3: 15-21 days; SD: Standard Deviations; Min: Minimum; Max: Maximum; <sup>a</sup>Kruskal-Wallis; <sup>b</sup>Independent T-Test; \*Statistically significant if p-value less than 0.05.

**Table 2. The SDF-1 levels based on the Mann-Whitney test**

Variables	p
SDF-1 (ng/mL) (N=84)	
Group 1-Group 2	0.041 <sup>*</sup>
Group 1-Group 3	0.000 <sup>*</sup>
Group 2-Group 3	0.133

SDF-1: Stromal-Cell Derived Factor 1; Group 1: 1-7 days; Group 2: 8-14 days; Group 3: 15-21 days; \*Statistically significant if p-value less than 0.05.

**Table 3. The correlation of SDF-1 and TGF- $\beta$ 1 levels to the storage time by days**

Variables	r	p
SDF-1 (ng/mL)	0.546	0.000 <sup>a*</sup>
TGF- $\beta$ 1 (pg/mL)	0.461	0.001 <sup>b*</sup>

SDF-1: Stromal-Cell Derived Factor 1; TGF- $\beta$ 1 Transforming Growth Factor-Beta 1; r=coefficient correlation; <sup>a</sup>Spearman correlation test; <sup>b</sup>Pearson correlation test; \*Statistically significant if p-value less than 0.05

an important role in regulating primitive hematopoiesis by suppressing apoptosis.<sup>24</sup> Its role in mast cell migration through interaction with Interleukin-8 (IL-8) is important in initiating allergic responses by stimulating histamine release.<sup>25</sup> A previous study found that when PRC was held in an Alyx unit for 7 days, SDF-1 levels increased significantly.<sup>26</sup> Another study also found that SDF-1 levels increased significantly with the amount of time RBC storage time in the form of whole blood (WB), from  $765.8 \pm 213.7$  pg/ml on Day 1 to  $2,320.4 \pm 563.7$  pg/ml on Day 21 and  $2,997.6 \pm 735.2$  pg/ml on Day 42.<sup>27</sup> The findings of our study were similarly consistent with those of other earlier studies in which SDF-1 levels increased with the amount of time the PRC blood components were held, ranging from 0.385 (0.050-1.020) ng/ml at 1-7 days to 0.490 (0.380-0.920) ng/ml at 14-21 days. The correlation between the increase in SDF-

1 release and the storage duration of PRC suggests that the metabolic activity of red blood cells is involved in the development of storage lesions.<sup>28</sup> Metabolic deficiencies of stored RBCs result from extracting RBCs from a donor's circulation, isolating them from plasma, and keeping them in an acidic solution with a small solution volume at a hypothermic temperature. In component processing and storage, essential substrates (extracellular resources like glucose and intracellular purine derivatives like urate) are depleted, and metabolic waste products are dominated by lactic acid.<sup>28</sup> A unit of RBC contains a range of cell ages, from those that have just been put into circulation to those that have reached the end of their circulatory life. The majority of the in vitro characteristics given in this panel are averaged values from this heterogeneous RBC population, in which the rate of damage accumulation may not be linear

with storage time or consistent from one donor to the next. Thus, a preserved RBC unit contains some senescent cells with reduced antioxidant capacity (e.g., glucose 6-phosphate dehydrogenase activity decreases in older circulating RBCs).<sup>29</sup> All of them are known to contribute to the release of SDF-1 as senescent RBC increases by storage time.

TGF- $\beta$  is a multifunctional cytokine involved in various biological processes, including cell replication, differentiation, migration, apoptosis, healing, bone formation, angiogenesis, and immune system control.<sup>30,31</sup> TGF- $\beta$ 1 is the most common and widely expressed isoform of the three homologous isoforms found in mammals (TGF- $\beta$ 1, TGF- $\beta$ 2, and TGF- $\beta$ 3). TGF- $\beta$ 1 synthesis is regulated at several levels in cells, including transcription, translation, secretion, and activation in the extracellular environment, as shown in erythrocytes.<sup>31-33</sup> The TGF- $\beta$ 1 gene is found on chromosome 19q13.2 and comprises seven exons and six extremely long introns.<sup>34</sup> In addition, TGF- $\beta$ 1 is produced as a pre-pro-TGF- $\beta$ 1 monomer with 390 amino acid residues and a 29-amino-acid signal peptide at the N-terminus and released to the activating signaling molecule or a particular environment.<sup>34</sup> Previous studies have mentioned that the TGF- $\beta$ 1 is changed in PRC related to the storage time.<sup>7,34</sup> A study conducted by Sut C et al. found that TGF- $\beta$ 1 and TGF- $\beta$ 2 were decreased significantly over time in both RBCC groups during day-0 and day-42.<sup>7</sup> According to the Pearson correlation test, our findings suggest that there was a significant weak positive correlation of TGF- $\beta$ 1 based on the storage time by days. However, based on weeks as divided into Group 1 and Group 2, the TGF- $\beta$ 1 levels slightly tended to be higher in Group 1 (2,365.21 $\pm$ 715.96 pg/ml) compared with Group 2 (2,210.39 $\pm$ 994.68 pg/ml). This discrepancy could be caused by the data distribution of storage time by days was not homogenous due to the outliers.

However, this study still has some limitations, such as the evaluation of the storage lesion, the storage time was not measured until the PRC storage period ended, which was 30 days in accordance with the regulations at the Sanglah Central General Hospital, Bali. This is because most of the PRCs that have reached the

storage period of about 3 weeks and above have been given to patients who need them before they expire. Therefore, it is very difficult to evaluate PRC bags aged 3 weeks and over. In addition, the limited number of PRC samples studied and the inability to assess individual longitudinal blood bags led to the conclusion that the efficacy of giving PRC in patients related to the expression of SDF-1 and TGF in patients could not be evaluated.

## CONCLUSION

The increase of SDF-1 and TGF- $\beta$ 1 levels in PRC by days of storage time has a potential role as the indicator for storage lesion at Sanglah General Hospital-Blood Bank, Bali, Indonesia. However, future studies with bigger sample size and longitudinal evaluation need to be considered to evaluate the particular relation between the storage time of PRC to the SDF-1 and TGF- $\beta$ 1 expression.

## CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

## ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia, with the number 1940/UN14.2.2.VII.14/LP/2019 prior to the study being conducted.

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## AUTHOR CONTRIBUTION

All authors contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the study results through publication.

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