The Effectiveness Of Leucodepleted (In Line) And Leucodepleted (Bedsite) In Reducing Leukocytes And Their Effect On Hemoglobin (Hb) And Red Blood Cell (RBC)

Maulana Baihakhi[1], William Leslie[2], Silvia Fransisca[3*]

[1,2,3] Master of Biomedical Science Study Program, Faculty of Medicine,
Prima University of Indonesia, Medan, Indonesia.
* Corresponding Author:
Email: silviafransisca@unprimdn.ac.id

Abstract.
Blood transfusion currently plays an important medical role in methods of reducing the number of leukocytes in component products, including reducing the number of leukocytes before storage (pre-storage leucodepletion) and reducing the number of leukocytes after storage (post storage leucodepletion). The purpose of this study was to determine whether there was a comparison of hemolysis events and hematocrit quality in leucodepleted (In Line) and leucodepleted (Bedsite) clinical transfusions at the Blood Transfusion Unit at the Indonesian Red Cross in Medan City. This study was an analytic study with a cross-sectional design of 58 people who were divided into two groups, namely the group with leucodepleted in line and the group with leucodepleted bedsite, inclusion and exclusion criteria. The results showed that the incidence of hemolysis after leucodepleted (in line) was 0% and leucodepleted (bedsite) was 0.02%, where the standard percentage of blood hemolysis was <0.8%, the occurrence of hemolysis after the production process of the two products was very small. While the hematocrit before and after leucodepleted decreased by 35.91% in leucodepleted (in line) and 33.33% in leucodepleted (bedsite). Comparison of leucodepleted (In Line) and leucodepleted (Bedsite) hemolysis events was also found. Where the incidence of leucodepleted (in line) hemolysis is not found, so the leucodepleted (in line) blood component has good quality.

Keywords: *Blood Transfusion, Blood Donors, Leukodepleted, Hemoglobin, Red Blood Cell.*

I. INTRODUCTION

Blood transfusion is the process of transferring blood or blood components from one person (donor) to another (recipient). Blood transferred can be in the form of whole blood and blood components. Blood transfusion currently plays an important medical role, both in emergency therapy or in special diseases that require continuous transfusion therapy [1].In today's developing era, blood transfusions no longer provide all the blood components but only provide the necessary blood components, for example, if there is a shortage of red blood cells, only red blood cells are given [2]. However, it should be noted that blood transfusions, on the other hand, can also cause transfusion reactions in the form of hemolytic reactions, febrile reactions, lung sensitivity reactions, anaphylactic allergic reactions, endotoxinemia, pulmonary edema, infection reactions and so on [1] Hemolytic transfusion reaction is a reaction characterized by increased red blood cell damage due to transfusion which is classified into acute hemolytic reactions and delayed type hemolytic reactions [1][2]. Acute type hemolytic reactions occur within 24 hours of transfusion due to incompatibility ABO erythrocytes triggering IgG/IgM antibodies with complement activation leading to intravascular hemolysis and rhesus incompatibility triggering IgG antibodies to rhesus factor causing extravascular hemolysis [2]. While the delayed type of transfusion reaction occurs 3-10 days after the transfusion, it is usually caused by the presence of low levels of antibodies against minor antigens of erythrocytes. Upon exposure to antigenic cells, these antibodies rapidly increase in level and cause extravascular hemolysis [3].Based on the data obtained, the incidence of acute non-hemolytic transfusion reactions varies up to 38% of all platelet and red blood cell transfusions. Reactions that often occur are non-hemolytic fever 1,7% - 30% and allergic reactions 1% -3% [4]. According to the American Society of Hematology in 2016, the incidence of hemolytic transfusion reactions for incompatible products is 1:76,000 and ABO incompatibility is 1:40,000. For transfusion reactions of delayed hemolysis 1:18.000. Non-hemolytic fever reactions 0,1 – 1,0 % and allergic reactions (urtica) 1-3% [5].

Other efforts to minimize transfusion reactions through modifying the manufacture of blood components and blood products such as the use of washed erythrocyte (WE) and *Leucodepleted*-PRC (LD-

PRC) are now considered capable of preventing reactions related to blood transfusions because they contain only a small number of leukocytes and plasma [6]. Several studies reported that the incidence of transfusion reactions was reduced by using apheretic blood products from single donors and *Leucodepleted* blood products [7].*Leucodepleted* is a filtration method that is 99,99% efficient and practically removes leukocytes, as well as a longer life span of blood components [6]. *Leucodepleted* is also a procedure to reduce the number of leukocytes in blood or blood components to be transfused to a minimum of <1 x 106 leukocytes/unit according to European standards [7].Currently, several methods are known to reduce the number of leukocytes in component products, including reducing the number of leukocytes before storage (pre-storage leucodepletion) and reducing the number of leukocytes after storage (post-storage leucodepletion). To increase the effectiveness of leukocyte filtration, currently the bedsite leucocyte filter can be used closed on blood components prior to storage or immediately after storage by connecting the bedsite leucocyte filter to the satellite bag using a Sterile Connecting Device (SCD). While *Leucodepleted* in-line is a method in which blood products are directly filtered in-line, undergo pre-storage and are centrifuged to obtain *Leucodepleted* (in-line) [6].Based on previous studies, there was a statistically significant decrease in the plasma protein component in *Leucodepleted* products (in-line) of 99,97% and the incidence of hemolysis after the product was manufactured was very small (<0.8%) [6]. Whereas for *Leucodepleted* (bedsite) there was a significant decrease in the number of leukocytes with an average of 2,26 [8]. The quality of the hematocrit plays an important role in blood transfusion. Previous research explained that the hematocrit level in *Leucodepleted* (in line) was 76,9% while *Leucodepleted* (bedsite) was 71,02% [6][8].

II. METHODS

Tabel 1. Definisi Operasional

Variable	Operational Definition	Measuring			
		Instrument	How to	Scale	Results
Hemolysis Events	Hemolysis is the lysis of erythrocytes resulting in the release of hemoglobin. European and US guidelines apply the standard that the percentage of red blood cell hemolysis at the time of transfusion should be lower than 0.8% and 1%.	HemoCue ®	Standardized Photometer Method With Hicn Method (ICSH)	Ratio	g/l unit
Hematocrit Quality	Hematocrit is the number of red blood cells in the blood. Measured after leucodepleted	Sysmex® XP 300	Flow Cytometry Method	Ratio	unit %
Leucodepleted In Line	A procedure to reduce the number of leukocytes in the blood or blood components Leucodepleted in line which screens leukocytes directly when donating blood.	Filter Imugard RC®	Filter leukocytes with sterile connectors	Nominal	Standard < 5 x 10 leukocytes / unit [18]
Leucodepleted bedsites	Leucodepleted bedsite was performed on whole blood stock taken < 24 hours	Filter Imugard RC®	Filter leukocytes with sterile connectors	Nominal	Standard < 5 x 10 leukocytes / unit [18]

The variables in the study consisted of two variables, namely the dependent variable including *Leucodepleted* (in line) and *Leucodepleted* (bedsite). While the independent variables are hemolysis events

and hematocrit quality. This study was an analytical study with a cross-sectional design to compare the incidence of hemolysis and hematocrit quality in Leucodepleted (In Line) and Leucodepleted (Bedsite) clinical transfusions. This research was conducted at the Indonesian Red Cross Blood Transfusion Unit in Medan City, North Sumatra, located at Jalan Palang Merah No. 17 Medan, East Medan District, Medan City, North Sumatra. The time of the study was conducted from August 2019 to September 2019 for sampling and examination of hemolysis events and hematocrit quality at *Leucodepleted* (in line) and *Leucodepleted* (bedsite). Data analysis was carried out in September 2019. The population of this study were all donors who came to UTD PMI Medan City.The sample in this study was divided into 2 groups, namely the group with leucodepleted in line and the group with leucodepleted bedsite inclusion and exclusion criteria. Inclusion criteria (Willing to be a respondent by signing an informed consent, Patients who come to UTD PMI Medan city, Patients who meet the criteria for blood donors and whole blood stocks that are < 24 hours) then Exclusion criteria (Suffering from infectious diseases such as hepatitis A and B, HIV, syphilis, CMV and not willing to participate in the study).

This research is included in the categorical-numerical analytic research thus, the sample size formula is as follows:

$$n = \left[\frac{Z\alpha\sqrt{2PQ} + Z\beta\sqrt{P_1Q_1 + P_2Q_2}}{P_1 - P_2}\right]^2$$

n = number of samples
Alpha (α) = Type one error is set at 5%, one-way hypothesis so Zα = 1.96
Beta (β) = Type two error, set at 20%, then Zβ = 0.84
P2 = proportion in the standard group of 0.5 (reference)
Q2 = 1 – 0,5 = 0,5
RR = 1,5
P1 = RR x P2
P1= 1,5 x 0,5 = 0,75
Q1 = 1 – P1 = 1 – 0,75 = 0,25
P1 – P2 = 0,75 – 0,50 = 0,25
P = (P1 + P2)/2 = (0,75 + 0,50)/2 = 0,63
Q = 1 – P = 1 – 0,63 = 0,37
Based on the calculation results above, it was found that the number of samples was 58.

Sampling was carried out using consecutive sampling technique which is a random sampling of the population as long as it meets the inclusion and exclusion criteria. The data collected is primary data including respondent data collection, hemolysis events and hematocrit quality at *Leucodepleted* (in line) and *Leucodepleted* (bedsite).

How Research Works

As for the workings of this research, the researcher first obtained approval from the ethical committee. then as an initial screening, the subject must meet the requirements as a donor, namely as follows: Minimum age 17 years. First-time donors > 60 years of age and repeat donors > 65 years of age can become donors with special attention based on medical considerations of health conditions. Have a minimum body weight of 45 kg with a systolic blood pressure of 90-160 mmHg and a diastolic of 60-100 mmHg. The difference between systolic and diastolic is more than 20 mmHg. Have a pulse rate of 50-100 times per minute and regular and body temperature of 36,5 – 37,5^{0}C and hemoglobin level of 12,5 – 17 g/dl and the interval since the last blood donation is 2 months. The next stage is to take 450 ml of donor blood (whole blood) and immediately perform leucodepleted in line with a sterile connector. The next step is to check the hematological parameters (routine blood) with the Sysmex® XP 300, where approximately 4 ml of blood will be taken for each sample for haematological examination using the Radio Frequency (RF) / Direct Count (DC) detection method to count erythrocytes and platelets. flow cytometer method with a semiconductor laser to count the number of *leukocytes, neutrophils, reticulocytes* and *platelets*. Then the next step is to *Leucodepleted* bedsite on whole blood blood stock with storage time < 24 hours with a sterile

connector, and Imugard III RC filter made of 1-2µ microporus polyurethane which works mechanically. The blood bag is connected to the filter and the satellite bag using a sterile connector. Then the next step is to examine the incidence of *Leucodepleted* in-line and *Leucodepleted* bedsite hemolysis using the HemoCue® tool.

Data Analysis Method

Data processing is carried out in the following stages: edit data to avoid errors or the possibility of an unfilled questionnaire. Coding the data to facilitate the data entry process, each answer is given a code and a score. Entering data after being coded and checking and repairing before data analysis.Data analysis was carried out with homogeneity and normality tests to determine the difference test to be used. If the data is normally distributed, a parametric sign of difference test is performed, whereas if the data is not normally distributed, a non-parametric sign of difference test is performed.

III. RESULT AND DISCUSSION

Based on the results of the study regarding the comparison of hemolysis events and hematocrit quality in *Leucodepleted* (in line) and *Leucodepleted* (bedsite) clinical transfusions at UTD PMI Medan City, the following haematological parameters (routine blood) were obtained before and after *Leucodepleted*:

Table 1. Hematological Results (Routine Blood) Before and After *Leucodepleted* (In Line) And *Leucodepleted* (Bedsite)

No	In Line (%)				Bed Side (%)			
	Blood ≤ 24 hours Before *Leucodepleted*		Leukodeplted		Blood Store ≤ 24H Before *Leucodepleted*		Leukodepleted	
	Hemolisis	Hematokrit	Hemolisis	Hematokrit	Hemolisis	Hematokrit	Hemolisis	Hematokrit
1	0	40.2	0	39.6	0.253	52.7	0.023	35.9
2	0	41.1	0	39.2	0.046	40.1	0.003	28.3
3	0	39.3	0	38.8	0.161	36.4	0.128	32.7
4	0	34.2	0	32.5	0.303	36.7	0.229	44.1
5	0	34.1	0	32.9	0.058	33.6	0	25
6	0	38.6	0	37.1	0.126	32.7	0	30.8
7	0	35.8	0	34.9	0	34.4	0	28.6
8	0	33.9	0	33.2	0.109	36.6	0	28.8
9	0	34.9	0	33.3	0	34.4	0	28
10	0	39.1	0	37.4	0.045	39.2	0.042	37.2
11	0	36.6	0	35.6	0.09	40.4	0.021	30.1
12	0	32.8	0	32.5	0.118	34.5	0.002	25.7
13	0	35.7	0	35.7	0.191	39.2	0	36.2
14	0	40.2	0	38	0.180	40.6	0.032	30.5
15	0	38.9	0	37.2	0.191	46.1	0.096	53.9
16	0	34.7	0	34.3	0.066	48.5	0.052	29
17	0	37.2	0	35.1	0.170	50.1	0	40.5
18	0	33.8	0	33.2	0.052	36.5	0.052	26.8
19	0	42.2	0	41.0	0.167	48.1	0.023	28.8
20	0	38.0	0	37.5	0.100	37.9	0.092	30.1
21	0	33.3	0	32.7	0.125	63.0	0	45.4
22	0	34.2	0	33.8	0.250	52.2	0	31.7
23	0	36.7	0	34.6	0.043	40.4	0.023	35.4
24	0	40.2	0	38.7	0.159	36.6	0.032	30.0
25	0	34.9	0	34.6	0.300	36.1	0	38.2
26	0	33.8	0	32.4	0.056	33.3	0	29.3
27	0	37.1	0	35.1	0.123	32.5	0	30.7
28	0	39.8	0	34.7	0.123	34.1	0	35.8
29	0	36.9	0	34.2	0.106	36.2	0.012	31.6
30	0	34.1	0	32.1	0.118	34.4	0.123	29.0
31	0	34.5	0	33.9	0.042	39.2	0.054	30.8
32	0	41.8	0	40.0	0.124	38.4	0.021	33.5
33	0	33.7	0	32.6	0.119	34.6	0	30.9
34	0	37.3	0	35.7	0.190	39.0	0	30.2

35	0	36.2	0	35.2	0.178	40.4	0	32.2
36	0	34.8	0	33.8	0.188	46.0	0	37.1
37	0	35.2	0	34.8	0.064	48.3	0	31.7
38	0	35.1	0	33.3	0.165	50.0	0	42.1
39	0	41.2	0	39.8	0.057	36.3	0	31.2
40	0	37.9	0	37.5	0.165	46.1	0.042	32.2
41	0	37.3	0	36.9	0.108	31.7	0.032	28.5
42	0	39.3	0	38.4	0.123	60.2	0	44.1
43	0	37.9	0	37.6	0.055	32.5	0	35.6
44	0	32.2	0	33.6	0.123	34.2	0.021	32.3
45	0	37.4	0	36.2	0.133	36.4	0.036	33.9
46	0	36.7	0	35.5	0.105	34.2	0	30.1
47	0	33.3	0	32.6	0.132	39.0	0	33.1
48	0	35.2	0	34.8	0	41.2	0	32.8
49	0	34.4	0	33.9	0.110	33.1	0.066	29.5
50	0	39.1	0	37.7	0.115	37.1	0.023	34.3
51	0	33.2	0	32.1	0.198	41.3	0.024	30.6
52	0	41.4	0	40.8	0.185	46.0	0	34.5
53	0	33.6	0	32.5	0.188	47.3	0	40.0
54	0	38.0	0	37.1	0.068	49.3	0.012	39.5
55	0	35.9	0	35.6	0.166	35.6	0	33.1
56	0	40.9	0	40.7	0.050	47.6	0.034	37.3
57	0	44.2	0	43.3	0.165	37.5	0	32.6
58	0	45.8	0	45.2	0.102	62.1	0	41.1

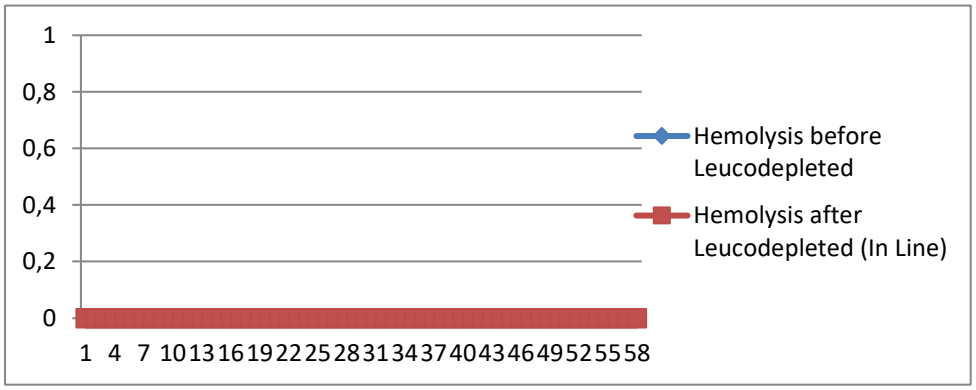

Fig 1. Comparison of Hemolysis Values before and after *Leucodepleted* (Inline)

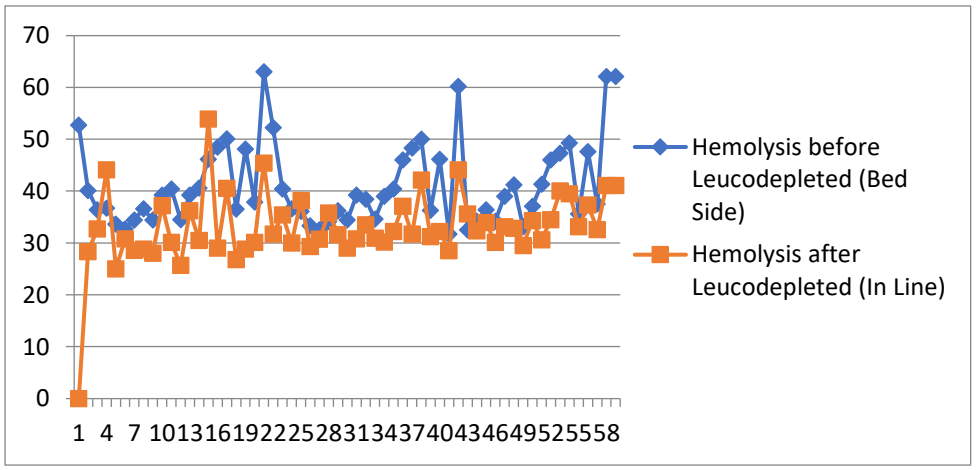

Fig 2. Comparison of Hemolysis Values before and after *Leucodepleted* (Bedside)

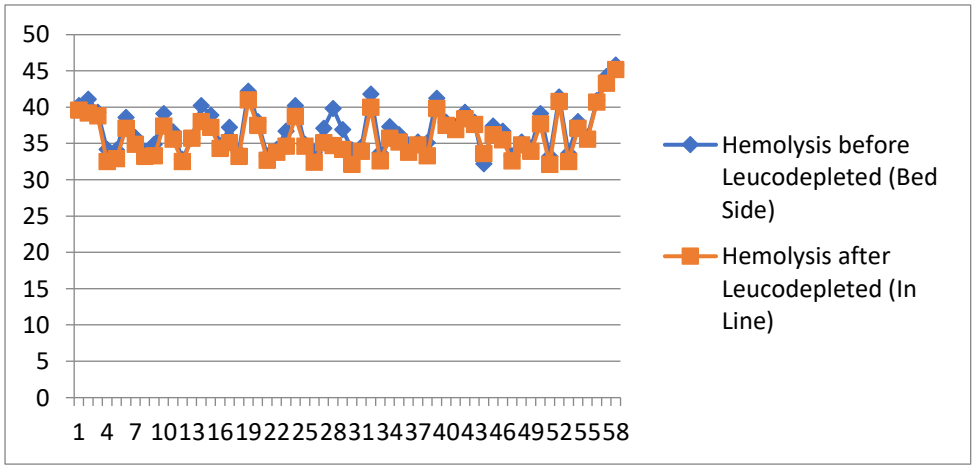

Fig 3. Comparison of Hematocrit Values before and after *Leucodepleted* (In Line)

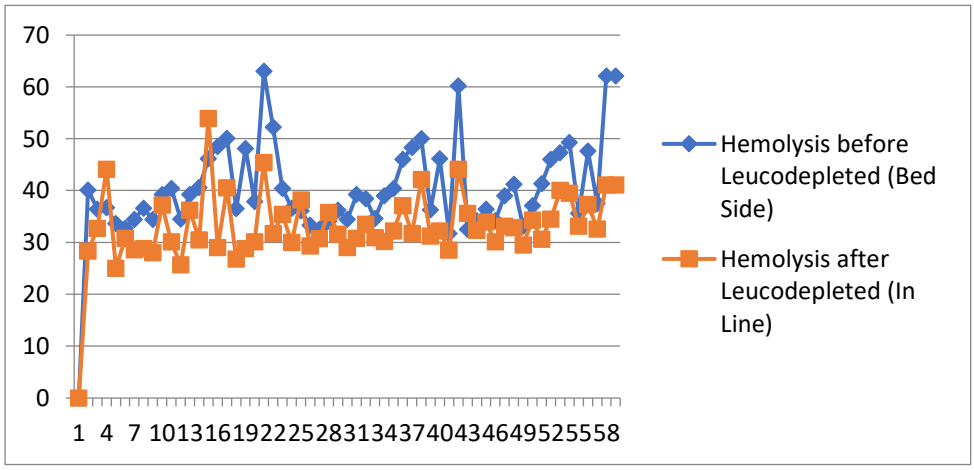

Fig 4. Comparison of Hemolysis Values before and after *Leucodepleted* (Bedside)

Table 2. Hematological parameters (routine blood) before and after *Leucodepleted* (In line) and *Leucodepleted* (Bedsite)

Parameters		**Leukodepleted (*In Line*) (n=58)**		**Leukodepleted (*Bedsite*) (n=58)**	
		Before	**After**	**Before**	**After**
Hemoglobin (Avg ±SD)	(g/dl)	13,08 ± 1,22	12,24 ± 1,51	13,92 ± 1,71	11,54 ±1 ,71
Hematokrit (Avg±SD)	(%)	36,99 ± 3,05	35,91 ± 2,96	40,76 ± 7,55	33,33 ± 5,41
Eritrosit (Avg±SD)	(x10/µL)	4,57 ± 0,53	4,12±0,54	4,75 ± 0,81	4,14 ± 0,88
Leukosit (Avg±SD)	(x10/µL)	0 ± 0	0 ± 0	6,53 ± 1,44	0 ± 0
Hemolisis (Avg±SD)		0 ± 0	0 ± 0	0,12 ± 0,06	0,02 ± 0,04

From the results of routine blood tests prior to *Leucodepleted*, it was found that there was no hemolysis in the *Leucodepleted* (in line) and the average hematocrit level in the *Leucodepleted* (in line) was 36.99% while in the *Leucodepleted* (bedsite) the average hemolysis was 0,12 and the average level of hematocrit at *Leucodepleted* (bedsite) of 40,76%. For routine blood tests after *Leucodepleted*, it was found that there was no hemolysis in the *Leucodepleted* (in line) and the average hematocrit level in the *Leucodepleted* (in line) was 35,91% while in the *Leucodepleted* (bedsite) the average hemolysis was 0,02 and the average hematocrit level on *Leucodepleted* (bedsite) of 33,33%.

Table 3. Normality and Homogeneity Test Results

Variable	Normality test	Information
Hemolysis Events	0,000	Not normally distributed
Hematocrit Quality	0,000	Not normally distributed

The results above show the normality test p = 0,000 (p <0,05) so that the data is not normally distributed and when the homogeneity test is carried out it is obtained p = 0,000 (p <0,05), namely the data is not homogeneous, it can be concluded that the test carried out is the non-parametric, namely the Kruskall Wallis Test.The following is the result of data analysis regarding the comparison of hemolysis and hematocrit quality to *Leucodepleted* (in line) and *Leucodepleted* (bedsite):

Table 4. Comparison of hemolysis and hematocrit events in *Leucodepleted* (In Line) and *Leucodepleted* (Bedsite) with the Kruskall Wallis Test

Variabel	N	Avg ± S.D	P
Hemolysis Events	58	0,01 ± 0,03	0,000
Hematocrit Quality	58	34,62 ± 4,53	0,000

From these results, it was obtained that the value of p = 0,000 (p <0,05) then H0 was rejected so that it could be concluded that there was a comparison of hemolysis and hematocrit events in *Leucodepleted* (in line) and *Leucodepleted* (bedsite).

DISCUSSION

From the results of the examination, it was found that the incidence of hemolysis after *Leucodepleted* (in line) was 0% while *Leucodepleted* (bedsite) was 0,02%. This shows that the incidence of hemolysis is small. Based on previous studies [15,6], the presence of hemolysis in blood transfusions describes a damage or disruption of the integrity of the blood cell membrane which causes the release of hemoglobin. European (2010) and United States (2005) guidelines apply the standard that the percentage of hemolyzed RBCs at the time of transfusion should be lower than 0,8 and 1,0%, to ensure that no component of hemolysis is transfused to the patient.Based on the results of the analysis, it was found that the value of p = 0,000 (p <0,05) so that there was a significant difference between the events of *Leucodepleted* (in line) and *Leucodepleted* (bedsite) hemolysis. It can also be seen from the results of the examination of *Leucodepleted* (in line) hemolysis events that were not found. So that *Leucodepleted* (in line) blood components have good quality against hemolysis events. Where this situation is in accordance with research [6] which states that the *Leucodepleted* component (in line) has good quality and is safely given to clinical transfusion patients and also to multiple transfusion patients with different indications.While *Leucodepleted* (bedsite), the incidence of hemolysis is 0.02%.

This is consistent with research [7] which states that hemolysis can be caused by several factors, namely blood processing, improper storage conditions, bacterial hemolysin, antibodies that cause complement lysis, damage to cell membranes, or abnormalities in donor blood [7]. Based on these factors, leukocyte removal is preferable if the time between blood collection and *Leucodepleted* is shortened. This occurs because, during storage, leukocytes degranulate, fragment or die releasing their contents which can cause transfusion reactions such as hay fever and allergies. Cytokines in particular such as IL-8 which accumulate during storage have been implicated in several bedsite filtration failures thereby triggering blood hemolysis [8][16].Based on the results of the study, it was found that the hematocrit value decreased before and after *Leucodepleted* both in line and bedsite. Data analysis also showed a value of p=0,000 (p<0.05) where there was a difference in hematocrit for *Leucodepleted* (in line) and *Leucodepleted* (bedsite). These results are in line with studies by [6][17] which stated that in the *Leucodepleted* component there is a decrease in hematocrit. This happens because in the process of making *Leucodepleted* there are anticoagulants so that the blood will become dilute and the hematocrit level will decrease.

IV. CONCLUSION

The conclusion in this study is that based on the haematological parameters it was found that the incidence of hemolysis after *Leucodepleted* (in line) was 0% and *Leucodepleted* (bedsite) was 0,02%, where the standard percentage of blood hemolysis was <0,8%, the occurrence of hemolysis after the manufacturing process both products are very small. While the hematocrit before and after *Leucodepleted* decreased by

35,91% in *Leucodepleted* (in line) and 33,33% in *Leucodepleted* (bedsite). There is a comparison of the incidence of *Leucodepleted* (in line) and *Leucodepleted* (bedsite) hemolysis. Where the incidence of *Leucodepleted* (in line) hemolysis is not found, so that the *Leucodepleted* (in line) blood component has good quality, there is a comparison of the quality of *Leucodepleted* (In Line) and *Leucodepleted* (Bedsite) hematocrit.

V. ACKNOWLEDGMENTS

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