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Universal Leukoreduction Decreases the Incidence of Febrile Nonhemolytic Transfusion Reactions to Cellular Blood Components: A 5 Year Study

Dharmesh Chandra Sharma^{1*}, Sunita Rai¹, Shruti Gupta¹
and Bharat Jain¹

¹Department of Pathology, Blood Bank, G. R. Medical College, Gwalior, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author DCS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SR and SG managed the literature searches; analyses of the study performed the spectroscopy analysis. Author BJ managed the experimental process and supervised the research work. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Background: Febrile nonhemolytic transfusion reactions (FNHTRs) are common complications associated with allogenic transfusion and it is caused by the leucocytes and cytokines released by leucocytes during storage of blood/ blood components. These reactions are generally not life threatening, but they are expensive in their management, evaluation, and associated blood-product wastage. 1st log prestorage universal leukoreduction (ULR) i.e. removal of Buffy coat is a useful and effective procedure in developing countries to control FNHTRs significantly.

Aims and Objects: To know the efficacy of pre-storage 1st log universal leuckoreduction in controlling febrile nonhemolytic transfusion reactions (FNHTRs).

Place and Duration of Study: Study was carried out at Blood Bank, Department of Pathology, G. R. Medical College, Gwalior from January 2009 to December 2013 (5years).

Materials and Methods: Study was divided into control group (Year: 2009) and study group (Years: 2010-13). 14,292 recipients in control group and 45,064 in study group

*Corresponding author: E-mail: dr_dharmesh_sharma@yahoo.com;

were transfused with non-leukoreduced and prestorage 1st log leukoreduced blood/ blood components respectively. Usefulness of prestorage 1st log ULR over non-leukoreduced blood/ blood components was observed, compared and discussed.

Result: In the control group 610 (4.26%) out of 14,292 ($p=0.0003$) and in study group 381(0.84%) out of 45,064 ($p=0.0003$) recipients were reported to have FNHTRs. The comparative study showed significant reduction in FNHTRs from 4.26% to 0.84% (\downarrow 3.42%) ($p=0.000001$).

Conclusion: 1st log Universal Leukoreduction (ULR) is a better option over Selective Leukoreduction (SLR) to prevent FNHTRs and it also helps the transfusion services of under-resourced developing countries in many ways.

Keywords: Blood transfusion; universal leukoreduction; selective leukoreduction; febrile non hemolytic transfusion reaction.

1. INTRODUCTION

Half a century ago, most of the blood transfused was whole blood. In last fifty years, there was a significant shift in strategy of the transfusion of allogenic blood after a concept that blood can be separated in its components; RBCs, WBCs, Platelets, Plasma and Cryoprecipitate [1]. Since blood component therapy came in existence with the thought to transfuse only those components which patients require and keep the rest for the others. At present blood and blood components are treated as drugs because of their use in treating diseases and like drugs, it has adverse effects also [2].

Among all the components, indications of transfusion of White Blood Cells (WBC or leukocytes) in transfusion services are limited or there is no valid indication of transfusion of WBCs except uncontrolled bacteremia, septicemia and eclampsia not responding to antibiotics. On the other hand it produces severe adverse effects to the recipient when transfused along with blood or blood product. These are febrile non-hemolytic transfusion reactions (FNHTRs), alloimmunization, immunomodulation, transmission of cytomegalovirus (CMV), other leukotropic viruses and so on [3-8]. Now a days, the removal of white blood cells (or *leukocytes*) from the blood or blood components supplied for transfusion is recommended. After the removal of leukocytes, the blood product is said to be 'leukoreduced'.

Leukoreduction when performed on each and every supplied blood component is called Universal Leukoreduction (ULR). When it is done for a special group of patients, is called Selective leukoreduction (SLR) [9,10,11]. Several authors describe the usefulness of ULR over SLR [1,12]. Leukoreduction when performed at the time of preparation of components prior to storage is termed as prestorage leukoreduction and when it is performed before or concurrent with administration, is termed poststorage leukoreduction [13,14]. Prestorage leukoreduction is recommended over post storage because of its advantages [12,15-22].

FNHTR is one of the most common adverse effects of blood / blood components transfusion. It is caused by the interaction between transfused leucocytes and recipients cytotoxic antibodies as well as release of cytokines by WBC during the storage of blood components [23]. These reactions are generally not life threatening, but they are expensive in their management, evaluation, and associated blood-product wastage.

The usual level of leukoreduction to prevent the febrile non-hemolytic transfusion reaction (FNHTR) is 0.5×10^8 i.e. 1 log reduction, this is known as critical antigenic leukocyte load which can be achieved by removing Buffy coat. However, for preventing alloimmunization or transmission of viruses like CMV, the residual leukocyte level should not be more than 5×10^6 , is called critical immunogenic leukocyte load [24] which can be achieved by filtration.

1st log prestorage universal leukoreduction (ULR) i.e. removal of Buffy coat is a useful, effective and non expensive procedure in under resourced developing countries to control FNHTRs significantly [24].

2. MATERIALS AND METHODS

Present study was carried out at the Blood Bank, Department of Pathology, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India from 2009 to 2013 (5years). Study was divided into two groups; control and study group. Control group constituted of 14,292 blood transfusions from 1st January 2009 to 31st December 2009 (one year) where non-leukoreduced whole blood (WB) / blood components were supplied to the recipients. In study group 45,064 transfusions were performed with leukoreduced Whole Blood Modified (WBM) / blood components during the period of 1st January 2010 to 31st December 2013 (4 years).

Blood and blood components supplied were whole blood (WB), Whole Blood Modified (WBM), Whole Blood Reconstituted (WBR), Packed Red Blood Cells (RBCs), Saline Wash Red Blood Cells (Saline RBCs), Sigm Red Blood Cells (Sigm RBCs), Platelet Concentrate (PC), Buffy Coat Platelets (BP) and Aphaeresis Platelets (AP). All blood/ blood components were screened for transfusion transmitted infections i.e. Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Syphilis and Malaria as per National AIDS Control Organization (NACO) guidelines in India [25]. All blood/ blood components were issued after blood grouping (ABO & Rh) and cross matching by saline / Indirect Coomb's Test (ICT by Gel Technology; Make Tulip) method.

All blood components were prepared by conventional method; centrifugation and separation in close system. Blood was collected in triple bags, quadruple SAGM (an additive solution; saline, adenine, glucose & manitol) bags, top and bottom SAGM bag and aphaeresis bags. For preparation of components, our blood bank is fully equipped with the instruments like; deep fridge centrifuges (*Cryofuse 6000i*: Make- Thermo Scientific), laminar flow (Make- Yarco), plasma extractors, Optipress II (Make- Baxter), dielectric tube sealer (Make- Ljungberg & Kogel AB), sterilized tube connecting device (Make- Terumo Penpol), deep freezers of -40°C and -80°C (Make- Haier & Terumo Penpol) , cryo-water bath (Make- Yarco), electronic balance etc.

In the study group 1st log universal leukoreduction i.e. removal of buffy coat was done with the closed method. In the process of leukoreduction, 5 to 10% loss of RBCs was observed as reported [26]. Between 6 PM to 6 AM, blood was collected in triple bags and it was processed after 6 to 12 hours of collection, leukoreduced WBM was prepared by removal of buffy coat and keeping RBCs and plasma within the unit. Removal of buffy coat from rest of the components was done during its preparation. Saline washed RBCs were prepared by washing the RBCs with 0.9% normal saline (NS) thrice, using sterilized tube connecting device. Whole Blood Reconstituted (WBR) i.e. O +/- cells suspended in AB plasma was prepared for exchange transfusion in Hemolytic Disease of Newborn [27,28]. Platelet concentrate was prepared by conventional method while buffy coat platelets and aphaeresis

platelets were prepared by using automatic plasma extractor and aphaeresis device respectively.

FNHTRs are characterized by temperature increase of $\geq 1^{\circ}\text{C}$ (2°F) above the base line (baseline $\leq 37^{\circ}\text{C}$ or $\leq 98.4^{\circ}\text{F}$) during or shortly after transfusion and it can also be accompanied by chills/rigors, hypertension, tachycardia and dyspnea [29,30]. Blood/ blood components were issued along with transfusion reaction card and feedback was recorded in transfusion reaction register as a routine procedure. Whenever adverse reactions were reported, proper inventory and investigation procedures were done to confirm the type of reaction. Registry of FNHTRs was tabulated and its incidence was calculated and discussed. Allergic and other adverse effects of transfusion were not included in the study. Data has been compared statistically by frequency distribution and percentage proportion. Chi square (X^2) test was applied to know the significant (p value) ratio of difference statistically.

3. RESULTS

In 5year study, total 59,356 transfusions were given to the patients. In control group it was 14,292 and in study group it was 45064. In control group, 610 (4.26%) out of 14,292 ($p=0.0003$) transfusions were reported to have FNHTRs while in study group it was 381 (0.84%) out of 45064 ($p=0.0003$). Declining incidence of FNHTRs from control (4.26 %) to study group (0.84%) was 3.42% (\downarrow) ($p=0.000001$) while for different components it was WB/ WBM; 5.50% (240/5333) to 0.88% (42/4770) (\downarrow 4.62%) ($p=0.000001$), Packed RBCs; 4.19% (296/7054) to 0.86% (240/27897) (\downarrow 3.33%) ($p=0.000003$), Sagem RBCs; 4.28% (6/140) to 0.82% (49/5970) (\downarrow 3.46%) ($p=0.000018$), Saline Wash RBCs; 1.01% (1/99) to 0.63% (4/631) (\downarrow 0.38%) ($p=0.6730$), WBR; 3.57% (2/56) to 0.51% (1/196) (\downarrow 3.06%) ($p=0.0624$), Platelet concentrate; 4.03% (65/1610) to 0.84% (32/3777) (\downarrow 3.19%) ($p=0.00001$). Incidence of FNHTRs in buffy coat platelets and aphaeresis platelets was 0.71% (11/1540) and 0.70% (2/283) respectively in study group while facilities for preparation of these components were not present in the year 2009 (control group period) (Table 1, Fig. 1) .

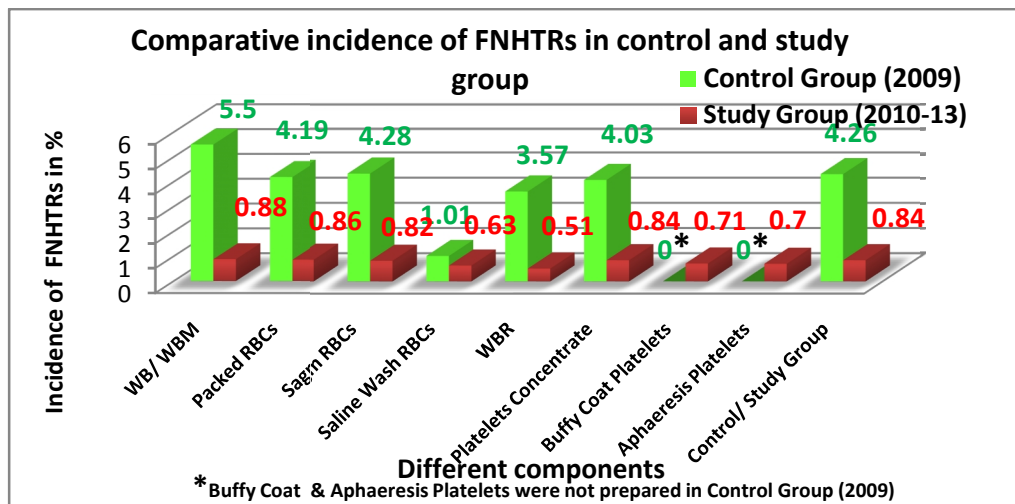


Fig. 1. Comparative incidence of FNHTRs in control and study group

Abbreviations: FNHTRs- Fibril Non Hemolytic Transfusion Reactions, WB- Whole Blood, WBM- Whole Blood Modified, RBCs- Red Blood Cells, Sagem- Saline Adenine Glucose Manitol; additive solution, WBR- Whole Blood Reconstituted

Table 1. Incidence of FNHTRs in control and study group

S. no.	Blood components transfused	Control group (Year: 2009)			Study group (Year:2010-2013)			↓ Incidence of FNHTRs from control to study group
		No. of transfusions	No. of FNHTRs	Incidence of FNHTRs	No. of transfusions	No. of FNHTRs	Incidence of FNHTRs	
1.	WB / WBM	5333	240	5.50	4770	42	0.88	4.62 ($p=0.000001$)
2.	Packed RBCs	7054	296	4.19	27897	240	0.86	3.33 ($p=0.000003$)
3.	Sagm RBCs	140	6	4.28	5970	49	0.82	3.46 ($p=0.000018$)
4.	Saline wash RBCs	99	1	1.01	631	4	0.63	0.38 ($p=0.6730$)
5.	WBR	56	2	3.57	196	1	0.51	3.06 ($p=0.0624$)
6.	Platelet concentrate	1610	65	4.03	3777	32	0.84	3.19 ($p=0.00001$)
7.	Buffy coat platelets	-	-	-	1540	11	0.71	-
8.	Aphaeresis platelets	-	-	-	283	2	0.70	-
1 to 8.	Total	14292	610	4.26	45064	381	0.84	3.42 ($p=0.000001$)

Abbreviations: FNHTRs- Febrile Non Hemolytic Transfusion Reactions, ↓ incidence – declining incidence, WB- whole blood (in Control group), WBM- whole blood modified (in study group), RBCs- Red Blood Cells, Sagm- Saline Adenine Glucose Manitol(additive solution) ,WBR- Whole Blood Reconstituted

4. DISCUSSION

Before the year 2010, transfusion services of our institute was supplying non-leukoreduced whole blood and its components to the recipients. Only in selected cases of multiple transfusions like hemato-oncology patients, thalassemia etc, saline washed RBCs were supplied and whenever patient's attendant could bear the expenses of the procedure, prestorage or poststorage leukoreduction filters were used to supply the leukoreduced RBCs i.e. selective leukoreduction (SLR). Since 2010, we have chosen the policy of universal leukoreduction and we are doing 1st log ULR by removal of buffy coat layer during the preparation of blood components. The residual leukocytes in the units were 500- 800/cu mm i.e. removal of approximately 90% of leukocytes from the units supplied. This dose is well below the critical antigenic load i.e. $.5 \times 10^8$ to prevent the FNHTRs [24]. By doing that, rate of FNHTRs came down significantly in the study group (0.84%) over control group (4.26%) with the reduction of 3.42% (↓) which was comparable with the study done by Perrotta PL et al. & King KE et al. [30,31]. Significant reduction of FNHTRs in study group over control group was reported in WB/ WBM, Packed RBCs, Sagsm RBCs and platelet concentrates while it was non-significant in case of saline washed RBCs and WBR because of the fact that saline washed procedure in both the components already reduced the WBC in study group.

Our study also supports the finding of several recent studies [32,33]. Prestorage leukoreduction is currently the most widely accepted mode over post storage leukoreduction because it eliminates the scope of inflammatory cytokines (interleukin 1, interleukin 6 and tumor necrosis factor) release from leukocytes during storage, hence efficient in the prevention of FNHTRs [34,35,36]. It also minimize the risk of leukotropic transfusion transmitted virus as leukocytes disintegrate and release the intracellular organism after 72hours of storage in blood components [32,37] and HLA alloimmunization in multi-transfused patients as it removes the intact leucocytes [38,39].

When the unit of blood (approximately 450 ml) is collected; about 2 billion (2×10^9) WBCs are present. Even with blood component processing, 90% of these cells remain with the RBCs, primarily as granulocytes; 8% of the cells remain with the platelets as mononuclear cells; and 2% of cells remain in an aliquot of fresh frozen plasma. The intent of leukoreduction is to reduce the number of white blood cells in the aliquot but the 0.0005% of the cells left after leukoreduction leaves 5000 residual leucocytes. Filtering of white cells can lead to a 5-10% loss in the number of RBCs recovered per unit. These losses may be justified, however, because they are balanced in part by the improved quality of leucoreduced RBCs unit [26]. Similar loss of RBCs was also reported in our study using 1st log leukoreduction i.e. removal of Buffy coat.

Removal of Buffy coat significantly reduces the FNHTRs, however the limitation of this technique is that it can only reduces the chances but cannot prevent the alloimmunization, immunomodulation, transmission of cytomegalovirus (CMV) and other leukotropic viruses [1,12,24]. In under-resourced developing countries like India, main hurdle for ULR by leukofiltration is the expense of the procedure and it is only limited to SLR. Under these circumstances ULR by removal of Buffy coat is a clinically useful option because of 1) No processing expenses transfer to the patients. 2) Incidence of alloimmunization, immunomodulation, transmission of cytomegalovirus (CMV) and other leukotropic viruses is very low [12]. Author has rarely reported these reactions in his 33 years of clinical practice. 3) Reduction in over all transfusion reactions. 4) Prevents the wastage of precious human resources i.e. blood/ blood components. 5) Prevents the extra cost of management of

FNHTRs. 6) Reduces the panic of transfusion reaction among hospital staff and patients, hospital stay of patients and the extra load on overburdened hospital management.

5. CONCLUSION

We concluded that prestorage even 1st log universal leukoreduction of allogenic cellular components is better option over selective leukoreduction by filtration in under-resourced developing countries like India. It reduces the incidence of FNHTRs significantly and also helps in preventing the other adverse effects of WBCs when transfused along with the cellular components of blood. Hence we recommend that 1st log universal leukoreduction is a clinically useful procedure where universal leukoreduction by filtration or other expensive methods is not practically possible.

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CONSENT

The author(s) declare that written informed consent was obtained from the patients before being recruited for this research.

ETHICAL APPROVAL

All author(s) hereby declare that all procedure have been examined and approved by the appropriate ethics committee of Gajra Raja Medical College, Gwalior, India and research have therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sharma RR, Marwaha N. Leukoreduced blood components: Advantages and strategies for its implementation in developing countries. *Asian J Transfus Sci.* Jan. 2010;4(1):3–8. doi: 10.4103/0973-6247.59384 PMID: PMC2847337
2. Dense M. Harmening, Test Book on Modern Blood Banking and Transfusion Practices, 3rd Edition, Jaypee Brothers Medical Publishers LTD, New Delhi. 2009;317.
3. Schiffer CA, Dutcher JP, Aisner J, Hogge D, Wiernik PH, Reilly JP. A randomized trial of leukocyte-depleted platelet transfusion to modify alloimmunization in with leukemia. *Blood.* 1983;62:815–20. [PubMed]
4. Sniecinski I, O' Donnel MR, Nowicki B, Hill LR. Prevention of refractoriness and HLA-alloimmunization using filtered blood products. *Blood.* 1988;71:1402–7. [PubMed]
5. Andreu G, Dewailly J, Leberre C, Quarre MC, Bidet ML, Tardivel R, et al. Prevention of HLA immunization with leukocyte-poor packed red cells and platelet concentrates obtained by filtration. *Blood.* 1988;72:964–69. [PubMed]

6. van Marwijk Koov M, van Prooijen HC, Moes M, Bosma-Stants I, Akkerman JW. Use of leukocyte -depleted platelet concentrates for the prevention of refractoriness and primary HLA alloimmunization < a prospective, randomized trial. *Blood*. 1991;77:201–5. [PubMed]
7. Yazer MH, Podlosky L, Clarke G, Nahirniak SM. The effect of Prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reaction to platelet concentrates and RBC. *Transfusion*. 2004;44:10–5. [PubMed]
8. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusion. The Trial to Reduce Alloimmunization to platelet Study Group. *N Engl J Med*. 1997;337:1861–9. [PubMed]
9. Federowicz I, Barrett BB, Andersen JW, et al. Characterization of reactions after transfusion of cellular blood components that are white cell reduced before storage. *Transfusion*. 1996;36:21-28.
10. Uhlmann EJ, Isgriggs E, Wallhemfechtel M, et al. Prestorage universal leukoreduction of red blood cells does not affect non-hemolytic transfusion reaction rates. *Transfusion*. 2000;40(suppl):58S
11. Oksanen K, Kekomaki R, Ruutu T, et al. Prevention of alloimmunization in patients with acute leukemia by use of white cell–reduced blood components: a randomized trial. *Transfusion*. 1991;31:588-594.
12. Joseph D. Sweeney, MD, FACP, FRCPath Universal Leukoreduction of Cellular Blood Components in 2001? *Am J Clin Pathol*. 2001;115:666-673
13. Dzik S. Leukodepletion blood filters: filter design and mechanisms of leukocyte removal. *Transfus Med Rev*. 1993;2:65-77.
14. Dzik WH. Current trends: evolving concepts in transfusion medicine: leukoreduced blood components: you can filter now or you can filter later. *Transfus Sci*. 1992;13:207-210.
15. Brecher ME, Pineda AA, Torloni AS, et al. Prestorage leukocyte depletion: effect on leukocyte and platelet metabolites, erythrocyte lysis, metabolism, and in vitro survival. *Semin Hematol*. 1991;28(suppl):3-9.
16. Heaton WAL, Holme S, Smith K, et al. Effects of 3-5 log₁₀ prestorage leukocyte depletion on red cell storage and metabolism. *Br J Haematol*. 1994;87:363-368.
17. Heddle NM, Blajchman MA, Meyer R, et al. A randomized trial comparing plasma removal to two types of prestorage leukoreduction to prevent reactions to platelets. *ransfusion*.1999;39:231-238.
18. Sweeney JD, Kouttab NM, Penn CL, et al. A comparison of prestorage WBC-reduced whole-blood–derived platelets with bedside-filtered whole-blood–derived platelets in autologous progenitor cell transplant. *Transfusion*. 2000;40:794-800. omponents: you can filter now or you can filter later. *Transfus Sci*. 1992;13:207-210.
19. Ledent E, Berlin G. Inadequate white cell reduction by bedside filtration of red cellconcentrates. *Transfusion*. 1994;34:765-768.
20. Popovsky MA. Quality of blood components filtered before storage and at the bedside: implications for transfusion practice. *Transfusion*. 1996;36:470-474.
21. Sweeney JD, Dupuis MP, Mega AJ. Hypotensive reactions in bedside filtered red cells, but not prestorage filtered red blood cells in patients taking ACE inhibitors. *Transfusion*. 1998;38:410-411.
22. Beard MJ, Seghatchian J, Cardian R, et al. Leucofiltration of sickle cell trait blood “the blocker”: NBS London & S.E. experience. *Transfus Sci*. 2000;22:71-73.

23. Bordin JO, Heddle NM, Blajchman MA. Biologic effects of leukocytes present in transfused cellular blood products. *Blood* 1994;84:1703-21.
24. Leucoreduction-The future of blood components -Medical Buyer
Available:http://www.medicalbuyer.co.in/index.php?option=com_content&task=view&id=3102&Itemid=49
25. National AIDS Control Organization. Standards for Blood Banks and Blood Transfusion Services. New Delhi: Ministry of Health and Family Welfare Government of India; 2007.
Available:http://www.iapsmgc.org/userfiles/10_Standards_for_Blood_Banks_and_Blood_Transfusion_Services.pdf
26. Marc J Shapiro. To filter blood or universal leukoreduction: what is the answer? *Crit Care*. 2004;8(Suppl 2): S27–S30. PMC3226148.
Available:<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3226148doi:10.1186/cc2453/>
27. Sharma DC, Rai S, Mehra A, Kaur M, Sao S, Gaur A, Sapra R. Study of 25 Cases of Exchange Transfusion by Reconstituted Blood in HDN, *Asian Journal of Transfusion Science*. 2007;2(1):56-58. doi:10.4103/0973-6247.33448
28. Dharmesh Chandra Sharma, Sunita Rai, Sudha Iyengar, Bharat Jain, Satya Sao, Ajay Gaur, Rahul Sapra. Efficacy of Whole Blood Reconstituted (WBR) in Exchange Transfusion (ET) in Hemolytic Disease of New Born (HDN) —A Study of 110 Cases. *Open Journal of Blood Diseases*. 2013;3(1):15-20. DOI: 10.4236/ojbd.2013.31004,
Available: <http://www.scirp.org/journal/PaperDownload.aspx?paperID=29292>
29. Roback JD (ed). Non-infectious complications of blood transfusion. Chapter 27, AABB Technical Manual, 17th edition. AABB, Bethesda; 2011.
30. Perrotta PL, Snyder EL. Non-infectious complications of transfusion therapy. *Blood Rev*. 2001;15:69-83.
31. King E, Karen R Sue Shirey, Sandra K Thoman, Debra Bensen-Kennedy, Warren S. Tanz, Paul M Ness. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs *TRANSFUSION*. 2004;44.
32. Dzik WH, Anderson JK, O'Neill EM, et al. A prospective, randomized clinical trial of universal WBC reduction. *Transfusion*. 2002;42:1114-22.
33. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA*. 2003;289:1941-9.
34. Heddle NM, Blajchman MA, Meyer RM, Lipton JH, Walker IR, Sher GD, et al. A randomized controlled trial comparing the frequency of acute reactions to plasma - removed platelets and Prestorage WBC- reduced platelets. *Transfusion*. 2002;42:556–66. [PubMed]
35. Muyile L, Joos M, Wouters E, De Bock R, Peetermans ME. Increased tumor necrosis factor alpha (TNF alpha), interleukin 1, and interleukin 6 (IL-6) levels in the plasma of stored platelet concentrates: Relationship between TNF alpha and IL-6 levels and febrile transfusion reactions. *Transfusion*. 1993;33:195–9. [PubMed]
36. Rebullia P, Dzik WH. Multicenter evaluation of methods for counting residual white cells in leukocyte-depleted red blood cells. *Vox Sanguinis*. 1994;66:25–32. [PubMed]
37. Paglino JC, Pomper GJ, Fisch GS, Champion MH, Snyder EL. Reduction of febrile but not allergic reactions to red cells and platelets following conversion to universal Prestorage leukoreduction. *Transfusion*. 2004;44:16–24. [PubMed]

38. Williamson LM, Wimperis JZ, Williamson P, Copplestone JA, Gooi HC, Morgenstern GR, et al. Besides filtration of blood products in the prevention of HLA alloimmunization-a prospective randomized study. *Blood*. 1994;83:3028–35.[PubMed]
39. Sintnicolaas K, van Marwijk Kooij M, van Prooijen HC, van Dijk BA, van Putten WL, Claas FH, et al. Leukocyte depletion of random single- donor platelet transfusions does not prevent secondary human leukocyte antigen- alloimmunization and refractoriness: A randomized prospective study. *Blood*. 1995;85:824–8. [PubMed]

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