Implementation of a blood conservation program in the private hospital setting in South Africa

By
Monique du Preez

Dissertation in fulfillment of the requirements for the degree of Magister Scientiae (MSc) in Immunology

In the Department of Immunology
Faculty of Health Sciences, University of Pretoria

Supervisor: Prof M.S. Pepper
Department of Immunology
University of Pretoria

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Summary

Although blood products are a great deal safer these days than in the past, patients receiving allogeneic blood transfusions are still exposed to potential hazards such as infectious diseases and immunomodulatory reactions. Therefore it is important to consider alternatives to allogeneic blood use. This can be done by means of blood conservation alternatives. A successful blood conservation program consists of three integrated phases, namely pre-operative, intra-operative and post-operative stages of patient care. The main objective of this study was to create a transfusion medicine database in order to evaluate the effect of a blood conservation program on the length of hospital stay of patients and the costs incurred in such a program. Five pilot hospitals who had implemented a blood conservation program were compared to five non-pilot hospitals (no blood conservation program). The results show that the average cost related to allogeneic blood usage in pilot hospitals amounted to R 473 274.13, compared to R 777 646.22 for the non-pilot hospitals. Length of hospital stay was also significantly lower in patients receiving blood conservation alternatives compared to patients receiving allogeneic blood. The total costs related to patients of blood conservation was lower, although not significantly, than the total costs of patients using allogeneic blood or both. In this study it was seen that the outcomes were positively associated with the implementation of blood conservation techniques.

The efficacy of two leukodepletion methods for allogeneic blood products namely pre-storage and post-storage filtration, were evaluated. The results revealed that the mean leukocyte count of pre-storage leukodepleted blood samples (n = 30) was 0.12 cells/µl. The mean leukocyte count of the post-storage filtered blood samples (n = 20) was 0.05 cells/µl. Both methods were shown to be successful in the efficient removal of leukocytes.
Declaration

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2. Declare that this Masters dissertation is my own, original work. Where someone else’s work was used (whether from a printed source, the internet or any other source) due acknowledgment was given and reference was made according to departmental requirements.
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Signature ____________________________

Date ____________________________
Acknowledgements

First of all I would like to thank God for giving me the abilities and perseverance necessary to complete this.

An enormous thank you to my supervisor, Prof Michael Pepper, for his guidance and patience. I would not have been able to reach this milestone without your much appreciated help.

I would like to acknowledge the University of Pretoria, Netcare and Filterworks for giving me this opportunity.

Thank you to Mandy Watermeyer and Andrea “Nooky” Naude for their input and hard work throughout this project.

A special thanks to my parents for all their support and motivation.
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<td>Acquired immune deficiency syndrome</td>
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<td>ANH</td>
<td>Acute normovolaemic hemodilution</td>
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<tr>
<td>ATR</td>
<td>Acute transfusion reactions</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>DHTR</td>
<td>Delayed hemolytic transfusion reactions</td>
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<tr>
<td>EACA</td>
<td>Epsilon amino-caproic acid</td>
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<tr>
<td>EBV</td>
<td>Epstein Barr Virus</td>
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<tr>
<td>EPO</td>
<td>Erythropoietin</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FNHTR</td>
<td>Febrile non-hemolytic transfusion reaction</td>
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<td>FS</td>
<td>Fibrin sealants</td>
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<td>HC</td>
<td>High care</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<tr>
<td>HSCT</td>
<td>Hematopoietic Stem cell transplantation</td>
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<td>HTLV</td>
<td>Human T-cell lymphotrophic virus</td>
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<tr>
<td>IBCT</td>
<td>Incorrect blood transfusion</td>
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<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>ID-NAT</td>
<td>Individual donation nucleic acid testing</td>
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<td>Transfusion associated graft-versus-host disease</td>
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<td>TRALI</td>
<td>Transfusion-related Acute Lung Injury</td>
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<td>TRIM</td>
<td>Transfusion related immune modulation</td>
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<td>Description</td>
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<td>TTI</td>
<td>Transfusion transmitted infections</td>
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1. **INTRODUCTION**

Blood is a valuable and important therapeutic component of healthcare, especially in life-threatening situations. Blood transfusions are indicated (a) where a patient has a deficiency of a blood constituent that puts the patient at risk, and (b) if improvement is likely to result from the temporary replacement of the deficiency.

Blood safety and availability are critical in this context. The availability of blood is not always guaranteed and therefore it is important that blood is not used inappropriately or wasted. It still remains a challenge to provide healthcare at a reduced cost while sustaining or improving the quality of care. Although blood products are much safer nowadays with regard to the transmission of infectious diseases, patients receiving allogeneic blood are still exposed to potential hazards, forcing healthcare professionals to search for alternatives.

Blood transfusions have been regarded as an essential part of patient care, but their use is being increasingly questioned as it becomes clear that allogeneic blood administration, although lifesaving, could be a risky medical procedure where the possible risks should be weighed against the benefits. [1-3]

### 1.1 Incorrect blood product transfusion

An adverse reaction due to the transfusion of an incorrect blood product is of concern. This occurs when a patient receives a blood component that did not meet the appropriate criteria or when the product was intended for a different patient. These incidents are usually attributed to human error and are thus avoidable. This is one of the most frequently occurring types of medical error.

In the 2009 Serious Hazards of Transfusion Committee report (SHOT, 2009), 282 cases of incorrect blood transfusion (IBCT) were reported, representing an increase of 7.6 %
since 2008. This resulted in two patients dying and four patients experiencing major morbidity. Of these reported IBCT cases, the most common error was failure to carry out the bedside check. [4] Since 2000, 218 cases of IBCT were reported in South Africa. In 2009, there were only 6 cases reported which represents a drastic decrease compared to previous years. [5]

It is important to realize that not every incorrect blood component transfused results in an adverse reaction. But for the patient who does experience a serious adverse reaction due to an IBCT, the health care costs can increase considerably.

1.2 Shortage of blood

Decreased supply of volunteer blood internationally with a constant increase in demand also contributes to an escalation of costs. For a scarce resource such as blood it is crucial to preserve a balance between demand and supply. Fig. 1 shows an example of the low blood inventory levels experienced in the country.

1.3 Cost of Blood Products

Due to transmissible infectious diseases, a number of screening tests are required to ensure the safety of blood. Blood costs depend on the chain of events necessary to deliver the transfused unit; the more events, the more costly. Fig. 2 illustrates the chain of events in preparation of a unit for transfusion.

Transfusion-related adverse events are costly contributors to health care expenses in both the short- and long-term. Factors contributing to the cost of allogeneic transfusion include the cost of managing transfusion-related complications, increased hospital charges due to extended hospital stay, treating serious medical conditions (such as sepsis) and increased mortality. [7]

1.4 Wastage of Blood

Wastage of blood products is of major concern in the management of medical institutions. An accepted routine in operative management is to order blood in
anticipation of an expected blood loss which usually does not materialize. Unused blood is usually discarded, resulting in substantial blood wastage.

1.5 Blood transfusion risks and hazards

Blood transfusions are however still indispensable in current medical practice even though they have been shown to increase morbidity and mortality. [8,9]

The presence of leukocytes in blood products is responsible for a number of serious adverse effects. These include alloimmunization, non-haemolytic reactions, graft versus host disease and immunomodulation. [10] Leukocytes are also the hosts for several pathogenic viruses such as cytomegalovirus (CMV), human T-cell lymphotropic virus (HTVL I and II), human immunodeficiency virus (HIV) and Epstein Barr virus (EBV). It is possible that transmission and/or reactivation of these viruses may occur during blood transfusions. [7] These post-transfusion effects may be responsible for increased incidences of post-operative infections, increasing hospital stay and therefore increased costs. [11,12]

1.5.1 Noninfectious complications of blood transfusion

Transfusion-related acute lung injury (TRALI)

Transfusion-related acute lung injury (TRALI) is a potentially fatal complication of blood transfusion. It is characterized by a clinical syndrome of acute respiratory compromise with hypoxemia and non-cardiogenic pulmonary edema, progressive dyspnoea and tachypnoea. [13] TRALI may be associated with fever and hyper- or hypotension. [14] The onset of these symptoms typically occurs within 1-6 hours after transfusion. TRALI is however under-recognized and under-reported. There is reason for concern because as reported by the United States Food and Drug Administration (FDA) and by the United Kingdom (SHOT), TRALI has become the leading cause of transfusion-related death. [13]
Immunosuppression

It has been disputed whether allogeneic blood transfusions are capable of activating and/or suppressing the immune system of the recipient. Specific immunomodulatory effects related to transfusions include increased cancer occurrence, and increased post-operative bacterial infections which can lead to increased mortality. This group of immune effects associated with transfusion has been referred to as TRIM (transfusion-related immune modulation) effects. Donor antigen-presenting cells such as monocytes/macrophages play an important role in allo-immunization. This is believed to be related to the expression of class I and class II human leukocyte antigens (HLA) on the surface of the white blood cells. Suppressive effects associated with the change in immune response include decreased CD4/CD8 ratio, impaired natural killer cell function and lymphocyte migration, leading to increased infection rates. The presence of foreign HLA on the surface of leukocytes introduced by blood transfusions causes a shift from a Th1 to a Th2 response. The Th2 cytokine pattern is associated with decreased cytotoxic cell function and inhibition of macrophage activation. With leukocyte contamination, the recipient may also develop antibodies to the foreign HLA in the blood products. This may lead to numerous side-effects such as platelet refractoriness and non-hemolytic febrile transfusion reactions. These immunomodulatory effects caused by leukocyte contamination may therefore result in short- and long-term changes in the immune system, complicating patient care. [8,15]

The downregulating effect of allogeneic blood transfusion on the recipient’s immune system may also lead to enhanced tumor growth in cancer patients. During intra-operative cell salvage in oncological surgery there is always the potential of reintroducing malignant cells during the surgical procedure. This concern for safety during intra-operative cell salvage in oncological procedures is supported by in vitro studies. [16,17] It has been demonstrated that the risk of reintroducing viable tumor cells in these patients may be reduced by the use of leukocyte filters. [17]
This alleged immunomodulatory (TRIM) effect of allogeneic blood transfusion remains contested. Some research studies in the past have shown that, because of this immune suppression, blood transfusions increase the risk of infections and cancer recurrence. However, other more recent studies have not shown these differences and the degree of impact that transfusion has on infection and tumor recurrence is not certain.

The concept that transfusion might alter host immunity arose from research in the late 1960s that allogeneic blood transfusions enhanced kidney transplant acceptance. Research following this, demonstrated an association between blood transfusions and colorectal cancer recurrence. However, published meta-analyses have produced conflicting results. In 2007, Vamvakas [18] found that in a meta-analysis of nine randomized clinical trials reported up to 2002 (combined despite extreme heterogeneity), there was an association between allogeneic blood and postoperative infection. But when twelve randomized clinical trials reported between 2002 and 2005 were integrated (again despite extreme heterogeneity), no association of allogeneic blood with postoperative infection was found. [19] No association between allogeneic blood transfusion and postoperative infection and mortality was detected across all clinical settings and has only been detected in cardiac surgery. [20] Even though an association of transfused blood and mortality was detected in cardiac surgery, the sub-group analysis contradicts theories about the mechanisms of this transfusion effect.

There is thus currently no overwhelming clinical evidence available to confirm the existence of a TRIM effect that links allogeneic blood transfusion to postoperative infection.

In a more recent study however, performed by Aslam et al., [21] the results suggested that fresh platelets can possibly induce TRIM due to their MHC antigen expression.

This goes to show that currently, TRIM is a highly disputed subject that is actively being researched internationally with the goal of reaching some kind of evidence-based conclusion as to whether such an effect does exist.
Febrile non-haemolytic transfusion reactions

Febrile non-haemolytic transfusion reactions (FNHTRs) have been reported to occur with an incidence of 6.8% following transfusion of erythrocytes and 37.5% after platelet transfusion. [22] They are defined as a rise in body temperature of 1°C or more following transfusion, in the absence of any other familiar causes for the fever. The major cause of FNHTRs is the presence of inflammatory cytokines, especially IL-1, IL-6, IL-8 and TNF-α that are released from donor leukocytes, which mediates fever by upregulating prostaglandin E₂ synthesis. These adverse reactions are due to the formation of immune complexes of the recipient’s antibodies with cells or proteins in the blood product, triggering the patient’s immune system to release these cytokines. [22] This is especially common after platelet transfusion, as platelets are stored at 22°C. [21,22] In 2008, 91 cases of FNHTRs were reported in South Africa. [5]

Platelet refractoriness

Platelet refractoriness is the repetitive failure to respond to platelet transfusions and is a frequent problem for patients that are receiving multiple transfusions. This can occur via immune or non-immune mechanisms. Non-immune causes include septicaemia, fever, disseminated intravascular coagulation and splenomegaly. The main immune cause however is HLA alloimmunization. [23]

A trial was conducted in chronically transfused platelet recipients to determine whether the removal of leukocytes would prevent the formation of antiplatelet alloantibodies and refractoriness to platelet transfusions. The results showed that the reduction of leukocytes by filtration or ultraviolet B irradiation of platelets are both effective in preventing alloantibody-mediated refractoriness to platelets. [23]
Transfusion-associated graft-versus-host disease

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare but often lethal complication of blood transfusion. The interaction between the transfused T-lymphocytes from the donor and the recipient cells bearing either HLA class I or II antigens leads to cellular damage, mostly mediated by natural killer cells. [24]

Table 1 below compares the number of reported adverse events from 2002 to 2008.

Table 1: Results of adverse transfusion reactions recorded from 2002 to 2008 in South Africa

(\textit{TTI} = \textit{Transfusion transmitted infections}, \textit{ATR} = \textit{Acute transfusion reactions}, \textit{IBCT} = \textit{Incorrect blood component transfused}, \textit{DHTR} = \textit{Delayed hemolytic transfusion reactions}, \textit{TRALI} = \textit{Transfusion related acute lung injury}, \textit{TA-GVHD} = \textit{Transfusion associated graft-versus-host disease}, \textit{UCT} = \textit{Unspecified complication of transfusion})

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1.5.2 Infectious complications of blood transfusion

Bacterial contamination

There are a number of bacterial infections that have been shown to be transmitted by transfusion and others that have the potential for transmission. *Rickettsiae* and other small intracellular bacteria can also be transmitted through blood transfusions. [25] The frequency of transfusion-induced sepsis is poorly defined as it is relatively low among red cell recipients, but higher in transfusion with platelet concentrates. [25] Psychrophilic organisms that can multiply at the low temperatures used for storage, may reach high levels in concentrates (such as RBC). The majority of cases of bacterial sepsis seen among recipients of platelet concentrates are attributed to the components being stored at 20°C. [25] Organisms that are involved include skin bacteria such as *Staphylococci* and enteric organisms such as *Salmonella* and *Enterobacter* spp. Sepsis due to *Serratia marcescens* has been reported occasionally, which can be due to contamination of blood containers during the manufacturing process. [25,26]

The estimated risk of bacterial contamination of blood products is 1 in 5 000 for platelets and 1 in 30 000 for red blood cells. [25,26] Since the year 2000 there have been seven cases of bacterial contamination reported in South Africa. As part of the SANBS quality assurance program, 1% of all platelet containing components were screened for bacterial contamination using the BACT ALERT system. The results revealed a low incidence of 0.9% of bacterial contamination. [5]

Hepatitis

Transfusion related hepatitis is caused by a range of viruses that includes hepatitis viruses A to E (HAV, HBV, HCV, HDV, HEV), cytomegalovirus (CMV), Epstein-Barr (EBV) and new viruses such as Hepatitis G (HGV), transfusion-transmitted virus (TTV) and SEN-V. HAV is seldom acquired through blood transfusion which can be attributable to the short stage of viraemia and the absence of a chronic carrier state. HBV is a cause of transfusion transmitted hepatitis that follows transfusion with infected blood products.
Patients suffering from acute infections may be asymptomatic or have viral hepatitis that includes symptoms such as jaundice. Chronic infection with HBV can lead to liver failure and death. [27] HCV is transmitted primarily through blood exposure. Because acute HCV infections are usually asymptomatic, the diagnosis is only made during the chronic phase. [27] Patients with chronic infection are also usually asymptomatic or complain of mild fatigue. The long-term implication of subsequent disease due to HBV or HCV infection can also lead to hepatocellular carcinoma. [28] HDV has no independent existence and cannot be expressed in the absence of HBV as it requires HBV for its replication. It can infect individuals simultaneously with HBV, or it can superinfect already chronic carriers of HBV. Therefore, no further screening for HDV in blood is employed. HEV is an RNA virus which spreads by the faecal-oral route, and not through blood transfusions. GBV-C, formerly called HGV, is a recently discovered virus distantly related to HCV and is mainly transmitted through the parenteral route thus also posing a risk to transfused patients. [28]

Transfusion-associated HCV infection was a worldwide risk before ID-NAT testing became available. It has been estimated that the window period and residual transmission risk of ID-NAT HBV is 24.3 days and 1: 61 500. For HCV transmission it was estimated to be only 2.8 days with a transmission risk of 1: 21 000 000. [29,30]

CMV has the ability to be present in T-cells in a latent phase, which allows transmission during blood transfusion prepared from an infected, but asymptomatic individual at the time of donation. Transfusion-associated CMV infections can lead to severe complications that are expensive to treat and may even be fatal. [14,24,31] Pregnant women infected with CMV can give birth to infants with neurological defects and deafness. Therefore, it is also crucial to provide CMV-free blood to pregnant women requiring blood transfusions. [31]

CMV infection is an important cause of morbidity and mortality despite the introduction of effective antiviral therapies, especially in immunocompromised hematopoietic stem cell transplant (HSCT) recipients. [32,33] CMV-specific CD8 cytotoxic T lymphocytes
play an important role in suppressing CMV reactivation. In healthy individuals, CMV infection is asymptomatic when CMV-specific T cells control the persisting virus. [32] High-risk recipients, characterized by T-cell depletion or treatment with high-dose corticosteroids, are most susceptible to CMV infection. [33,34] Granted, there have been significant improvements in diagnostic and prevention strategies, but HSCT recipients still require constant surveillance and re-evaluation of the viral challenge. Sero-negative donors and blood products or use of leukodepleted blood products are required for the prevention of CMV infection in HSCT recipients. [33, 34]

Drew et al. (2003) [32] found that there was no evidence of activation of cytomegalovirus by allogeneic blood transfusion and very little evidence of possible transmission of new CMV strains.

*Human Immunodeficiency viruses*

The transmission of HIV and the resultant emergence of associated acquired immune deficiency syndrome (AIDS) have transformed transfusion medicine over the past several decades. HIV-1 and HIV-2 are the two etiologic agents. Because HIV has a high genetic diversity, the virus is able to evolve which leads to the emergence of drug resistant mutants. Even though every single unit of donated blood undergoes sophisticated testing for transmissible diseases, there is unfortunately still a window period when the presence of HIV in the blood cannot be detected through testing. Transmission of HIV by blood products has been drastically reduced during the past decade as a result of implementation of sensitive and improved tests for viral antibodies and antigens. Therefore, measures to close the window period were required to further reduce the low residual risk in HIV transmission by blood and plasma. In 2005, SANBS introduced an individual-donation nucleic acid test (ID-NAT) screening for human immunodeficiency virus (HIV) RNA to further reduce the window period for transmission from donations. It has been estimated that the residual transmission risk of ID-NAT HIV is 1:479,000 and the window period risk days is less than 5.5 days. [27,30]
**Human T-cell Lymphotropic viruses**

HTLV was the first human retrovirus isolated and is associated with malignant disease in humans, namely adult T-cell leukemia. It is also associated with myelopathy and tropical spastic paralysis. Currently, the estimated residual risk for HTLV during transfusion in Canada is $1 : 4 \times 300\,000$, and in the United Kingdom it is estimated to be less than $1 : 10\,000\,000$. [35,36] The incidence of HTLV being transmitted through allogeneic blood transfusion is thus very low.

**Variant Creutzfeldt-Jakob disease**

Variant Creutzfeldt-Jakob disease (vCJD) is a degenerative brain disorder that is rapidly fatal once symptoms of progressive dementia and motor disturbances develop. Creutzfeldt-Jakob disease patients can be asymptomatic for a very long time as the incubation period of transfusion-transmitted vCJD is supposedly 6.5 years (derived from the first case of vCJD). There is no definitive data available on the likely transmissibility of vCJD by blood transfusion, but it is believed that circulating B lymphocytes might harbour the prions, making this a possibility. To date, four instances of probable transmission of vCJD by blood transfusion have been identified in the UK. [37,38]

**Parvovirus B19**

Parvovirus B19 is an erythrovirus that infects and lyses red cell progenitors in the bone marrow. In a recent study performed in the USA, the results showed the transmission rate to be approximately 0.12%. [39] Although the risk is low, it can cause a wide range of clinical manifestations such as sudden and severe anaemia, especially in immunocompromised individuals and in patients with underlying chronic haemolytic disorders. [40]
West Nile virus

Current estimates suggest that 80% of infections are essentially asymptomatic with the remaining 20% being relatively mild and flu-like (West Nile fever). [41] Although the current incidence is unknown but believed to be low, about 1 in every 150 infections can result in serious, life-threatening disease termed West Nile encephalitis or West Nile meningoencephalitis. [41,42]

With regard to blood-borne viruses that can be transmitted during transfusions, most exist as latent infections in the leukocytes of individuals who carry the disease but do not have symptoms.

Epstein-Barr virus

Another rare but potential hazard includes the Epstein-Barr virus which lead to transfusion-associated mononucleosis. [43]

Parasites

Malaria is the most common transfusion-transmitted infection in the world. This is because malaria is gradually spreading in terms of the numbers of individuals exposed to it. As there is more travel to and from malarial areas, the number of donors with potential risk is increasing. [43] This can have severe consequences as infection with *Plasmodium falciparum* may prove rapidly fatal.

A literature review from the period 1980–2009 indicated that the median prevalence of malaria among 33,029 blood donors was 10.2% in countries where malaria is endemic. [44] Unfortunately, the critical lack of evidence about the clinical impact of transfusion-transmitted malaria and the absence of an effective screening method are preventing rational decision-making about when and how to screen blood for malaria, especially in endemic areas. [44]
Other

Even though concern has been expressed about the possibility of transmission of other parasitic diseases, there is little convincing published evidence.

*Trypanosoma cruzi* is a protozoan parasite and the etiologic agent of Chagas disease. This parasite spread hematogenously to muscle, with a preference for the heart. Acute disease may occur but is usually relatively mild, generally with flu-like symptoms. In 20 - 30 % of infected persons, Chagas disease will develop leading to fatal cardiac and gastrointestinal complications. [43]

*Babesia microti* is a parasite transmitted by small ticks that causes a disease called babesiosis. Usually babesiosis presents as an asymptomatic disease but can also be characterized by headaches, fatigue and myalgia. More severe symptoms are observed in immunocompromised individuals, infants and the elderly. The FDA received eight reports of deaths due to transfusion-transmitted babesiosis from 2005 onwards. The numbers of deaths reported and Biological Product Deviations Reports suggest that there may be an increased incidence of transfusion-transmitted babesiosis. [45]

In South Africa there have been twenty-two transfusion-transmitted infections reported since 2000. No confirmed cases for transfusion-transmitted infections were reported however in 2007 and 2008. [5]

1.6 Neonates

Premature infants frequently receive multiple blood transfusions leading to the neonatal population being the most heavily transfused of all patients. [46] Transfusions in neonates are done for several reasons such as improving oxygen-delivery, reducing fatigue when feeding and to improve overall growth. As the B-lymphocytes of neonates are still functionally immature, they are often immuno-compromised due to their inability to produce significant amounts of antibodies themselves. [46] Therefore, because of their
immature immune systems, premature infants are exceptionally susceptible to infections. The immunosuppressive effects of allogeneic transfusion may result in life-threatening and costly infectious complications. [46]

1.7 *Jehovah’s Witnesses*

Jehovah’s Witnesses refuse blood and blood products due to their religious beliefs. Allogeneic blood transfusion and stored pre-autologous blood (PAD) are not acceptable to these persons and even in emergencies transfusion is not considered. [47]

1.8 *Alternatives to allogeneic blood transfusions*

Additionally, compatible blood products may be unattainable for transfusion patients with multiple antibodies or may be detrimental for patients with autoimmune hemolytic anemia, particularly auto-erythrocyte sensitization. [47]

The risks of transfusion-transmitted infections combined with the possibility of increased costs and blood shortages, emphasize the need to assess the relative cost-effectiveness of alternative interventions to substitute or reduce allogeneic blood products.

With the introduction of effective blood conservation programs in many countries, the risks of transfusion have been reduced with an improvement in patient care. [9,10] Blood conservation can be defined as a coordinated team approach that introduces alternatives to blood transfusions. This program provides benefits to patients, health-care professionals and the hospitals providing the care.

Despite modern improvements in blood safety, a risk of transfusion-transmitted infections remains, along with threats from new pathogens. [9,10,21] To reduce blood transfusions has consequently become a desired goal in patient care.
1.9 Blood Conservation strategies

An effective blood conservation program consists of three integrated phases, namely pre-operative, intra-operative and post-operative stages of patient care. [9]

1.9.1 Pre-operative stage

This involves structuring a treatment program specific for the required procedure, taking into account the patient’s condition. Martyn et al. [9] have shown that optimizing the patient’s physiological state prior to surgery can lead to reduced blood loss during surgery. By taking into consideration the underlying medical condition and medications that can contribute to increased bleeding, bleeding during surgery can be reduced. Transfusion thresholds based on haemoglobin values can be used to establish a level when blood transfusion is indicated.

Pharmacological agents such as recombinant human erythropoietin (rHuEPO) and iron (with adjuvant vitamin B12 and vitamin C supplements) can be given to maximize blood production prior to surgery. EPO is a protein that increases the production of erythrocytes (red blood cells) in the body. It has been determined in a randomized study of 681 patients, that the frequency of deep venous thrombosis in patients treated with rHuEPO is 4.7% (FDA alert 16 November 2006). [48] In addition, rHuEPO has a negative impact on survival of patients with cancer and kidney disease. This should be taken into account by cautiously balancing the risks against benefits when prescribing and calculating the dose of rHuEPO for patients, especially those with co-morbidities such as renal disease or cancer. [48]

The use of antifibrinolytic agents is another measure that significantly reduces the proportion of patients that needs allogeneic blood. Tranexamic acid (TXA) and epsilon amino-caproic acid (EACA) act as effective inhibitors of fibrinolysis. Both block the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and inhibiting fibrinolysis. [49] Aprotonin is a broad spectrum serine protease inhibitor with
antifibrinolytic properties (bleeding prevention). It inhibits the activation of coagulation and promotes fibrinolysis.

There are concerns that these agents may promote an increase in venous thromboembolism in orthopaedic surgery. However, no evidence was found to support this in a meta-analysis by Zuffery et al. [50] In a recent retrospective analysis, no increase in thromboembolic complications was evident. [49]

In contrast, aprotinin has been recently been withdrawn from the market due to the increased rate of postoperative cardiovascular, cerebrovascular and renal dysfunction events, and death even occurred in some cardiac surgical patients receiving this drug. [50] Aprotinin is limited to trial use in a special treatment protocol (available at: http://www.fda.gov).[48]

Fibrin sealants are made from human plasma derived from either allogeneic or autologous blood. They primarily consist of fibrinogen and thrombin solutions that imitate the ultimate phase of the coagulation cascade and produce a semi-rigid clot. [52] Transmission of viral infection by fibrin sealants has been of concern. However, there are no reported cases of serious viral transmission after the use of fibrin sealants. [52]

Another alternative is pre-operative autologous blood donation, in which the patient’s own blood is collected before surgery, stored and re-infused during or after surgery if necessary. [51]

1.9.2 Intra-operative stage

Acute normovolaemic hemodilution (ANH) is a technique that can be introduced during the intra-operative stage. During the procedure the patient’s blood is intentionally diluted, resulting in fewer red blood cells being lost for any amount of whole blood shed. Blood from the patient is removed before surgery, while the circulating blood volume is maintained with the infusion of acellular fluids and afterwards the collected blood is re-infused. [53] A meta-analysis performed by Carless et al., [54] showed that ANH
decreases the rate of postoperative thrombosis, suggesting that this could be a beneficial effect of ANH. However, the data were insufficient to draw a definite conclusion. Adverse events such as infection, myocardial infarction and mortality seemed to be unaffected by the use of ANH. Unfortunately there were also not sufficient data to draw definite conclusions. [53]

Intra-operative cell salvage is a procedure in which blood shed during surgery is collected, filtered, washed with saline and subsequently re-infused. Appropriate anaesthetic management can also reduce intra-operative blood loss, for example, through controlled hypotension, positioning and ventilation. [52] Pharmacological agents that can be used to reduce intra-operative bleeding include antifibrinolytics, vasoconstrictors and hemostatic agents.

1.9.3 Post-operative stage

There are several strategies that can be introduced in the post-operative period to reduce blood loss and to increase blood production and oxygen delivery while minimizing oxygen consumption. Maintaining normothermia, avoiding hypertension and taking note of drug interactions that may increase bleeding, all contribute greatly to the successful management of patient after-care.
CHAPTER 2: METHODOLOGY

This dissertation consists of two parts. The first part examines the implementation of a blood conservation program in the private hospital setting, and the second part evaluates the efficacy of currently available leukodepletion methods.

2.1 OBJECTIVES

The main objectives of this study are outlined below:

First part of the dissertation:
- To establish and interrogate a transfusion medicine database in order to evaluate the effectiveness of a blood conservation program.
- To determine the impact of blood conservation on the length of hospital stay.
- To determine the impact of blood conservation on overall cost during hospital stay.

Second part of the dissertation:
- To compare the efficacy of leukocyte removal in pre-storage leukodepletion versus post-storage leukodepletion (see Chapter 4).

2.2 CREATING THE DATABASE

This was a prospective, observational study of patients undergoing surgery who were in need of blood transfusion. A transfusion medicine pilot project was initiated on 1 July 2006 that ran until the end of Sept 2007 (15 months).

The development of this database was outsourced to a software engineer. I was involved in the design of the structure of the database, including (1) processes for capturing the data (such as age, procedure, finances, etc.) and (2) mechanisms required for satisfactory information processing in order to allow the outcomes to be measured.
2.2.1 **Extraction of data**

All data was electronically captured into a data management system specifically developed for the study. Medical records of patients were entered into the database by blood conservation coordinators at the Netcare Hospitals during the time period 1 July 2006 to 30 Sept 2007. This database consists of non-sensitive data including patient demographic information, surgery data, costs, transfusion data and complications. The database was updated continuously throughout the period of the study. Data collected from these entries was analyzed and the results reported in an anonymous fashion according to a number of key elements.

Due to the large number of patients, spelling mistakes and different wording used by the coordinators when typing the data, e.g. “hip replacement left” / “left hip replacement” / “replacement left hip”, extraction of data proved to be difficult and inaccurate. This resulted in a delay in obtaining meaningful and trustworthy information.

As a solution to these problems, a method of merging the M25 Report (which includes all admissions to all Netcare Hospitals) and All Stock Reports (consumables / items used only for saving blood) into the database was developed. This offered much needed additional information with improved consistency and accuracy thereof.

2.2.2 **Inclusion and exclusion criteria**

The following orthopedic procedures were chosen:

- knee replacements
- hip replacements
- spinal surgeries.

These surgeries were chosen because they are easier to identify with fewer procedural codes than for example the variety of cardiovascular procedures. Patients undergoing knee and hip replacements and spinal surgeries were used since they are the most common surgical procedures among transfused patients. For the purpose of this study, the spinal surgeries included were anterior / posterior spinal lumbar fusions, spinal
decompression and Smith-Robinson fusions. Excluded were all cervical fusions because there is very little bleeding compared to other spinal regions where fusions are done, and therefore blood conservation techniques are rarely practiced.

Advance routine ordering of blood “just to be prepared”, has been used especially for orthopedic procedures. There are various alternatives to blood usage in orthopedics which can be employed selectively according to each individual patient’s needs.

### 2.2.3 Sample size

Medical records of 2,641,098 patients were entered into the database by blood conservation coordinators at the Netcare Hospitals during the 15-month study period. Data collected from these records were used to compare allogeneic blood and BCP consumables usage between the pilot and non-pilot hospitals.

A total of 2,683 patients that met the inclusion criteria were enrolled and their records were used to calculate the effect of blood conservation on the length of hospital stay and costs involved. These patients were only selected from the pilot hospitals as there were blood conservation coordinators present who could help with making the necessary data available for capturing and analysis.

**Data extracted from the M25 Report**

- Patient: hospital, file number,
- Procedure: code, description, ICD 10 code
- Admission date
- Financials: Fee for service / per diem, total hospital
- Length of stay (LOS): divided into intensive care unit (ICU), high care and general ward days and the total days

**Data extracted from the Allstock Report**

- Patient: hospital, file number
- Procedure: code, description, ICD 10 code
Date: month and actual date product billed
Consumables used: NAPPI code, stock code, quantity billed, total cost of product billed (per product)
Length of stay: divided into ICU, high care and general ward days and the total days in hospital

Data from SANBS
Patient: receiving ward in which hospital
Product: blood product issued, quantity, costs
Date: month issued

Additional notes
Notes made by the blood conservation coordinators included:
Co-morbidities
Volume of blood loss
Blood results such as the hemoglobin value
Pre-autologous donation, post-op drains, cell salvage
Additional procedures
Complications

After a pilot trial of collecting data from the notes made by the blood conservation coordinators, it was found that the data was inconsistent and it was decided to abandon this method.

The LOS was calculated as the sum of days spent in the general ward, intensive care unit (ICU) and high care (HC).

Total cost used was the hospital bill that includes the costs of blood products and their transport and cost of blood conservation equipment such as cell saver kits and filters.
2.3 SCREENSHOTS OF DATABASE

Important demographics of the patient were captured in Fig. 3 such as age, weight, medications etc. Also shown is a link stating whether this patient received blood conservation or not. Religion is also useful as Jehovah’s witnesses for example are against blood transfusion.

![Blood Conservation Patient History Assessment]

* - modified to preserve patients identity
Figure 4 shows previous surgeries undergone by this patient, any allergies and any comorbidities.

**Fig. 4: Patient demographics – Medical history**

This screen (Fig. 5) shows the procedure that this patient was admitted for in hospital.

**Fig. 5: Procedure date and description**
The screen below (Fig. 6) provides all links related to procedure that the patient was admitted for, such as blood conservation alternatives received for example cell savers, drains etc., financial implications as well as length of stay.

**Fig. 6: Links related to surgery**

The breakdown of this patient’s length of stay in hospital (shown in Fig. 7)

**Fig. 7: Length of stay**
A breakdown of the finances involved including the total hospital bill, ward and theatre fees related to blood conservation and costs related to blood products, is shown in Fig. 8.

![Fig. 8: Finances](image)

### 2.4 APPROVAL FROM THE RESEARCH ETHICS COMMITTEE

Approval for this study was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee. Ethical approval was also obtained from Netcare for the extraction of data from the blood conservation database for the purpose of this study (Ethical Approval – Appendix A).
CHAPTER 3: RESULTS OF IMPLEMENTING A BLOOD CONSERVATION PROGRAM

3.1 LIST OF CONSUMABLES AND PHARMACEUTICALS USED IN BLOOD CONSERVATION

Below is a list of the consumables and pharmaceuticals used in the Netcare blood conservation program. Consumables are used during the intra-operative phase to reduce the blood loss during surgery. During the pre-operative phase, pharmaceuticals are used to increase the production of red cells prior to surgery.

<table>
<thead>
<tr>
<th>Consumables</th>
<th>Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell savers</td>
<td>Iron sucrose</td>
</tr>
<tr>
<td>Post operative drains</td>
<td>Erythropoietin (EPO)</td>
</tr>
<tr>
<td>Filters</td>
<td></td>
</tr>
</tbody>
</table>

3.2 PILOT HOSPITALS

To closely monitor the trend and progression of blood conservation in a private hospital setting, it was decided to select a limited number of hospitals (named pilot hospitals).

The five pilot hospitals selected were:

- Netcare Krugersdorp Hospital
- Netcare Pretoria-East Hospital
- Netcare Sunninghill Hospital
- Netcare Unitas Hospital
- Netcare Universitas Hospital
All of these pilot hospitals were provided with a person to implement a blood conservation program, called blood conservation coordinators.

### 3.3 NON-PILOT HOSPITALS

To compare the results of the above-mentioned pilot hospitals, five private hospitals, comparable in size, which did not have blood conservation programs, were selected as controls.

The five non-pilot hospitals selected were:
- Netcare Milpark Hospital
- Netcare Greenacres Hospital
- Netcare Union Hospital
- Netcare Garden City Clinic
- Netcare St Augustine’s Hospital

Figs. 9 to 23 show the different blood conservation products (BCP) used in all patients in each of the five pilot hospitals, as well as the total number of BCP used compared to patient occupancy. In Figs. 24 to 28, blood usage in the non-pilot hospitals is shown as a comparison to the pilot hospitals. Blood usage in the figures below refers to red blood cell concentrates only.
3.4.1 RESULTS FOR PILOT HOSPITALS

Netcare Krugersdorp Hospital

In Fig. 9 below, it can be seen that there was a slight decrease in the usage of allogeneic blood in Krugersdorp Hospital.

*Fig. 9: Netcare Krugersdorp Hospital blood usage vs. hospital occupancy*
Fig. 10 below shows that there was an increase in the usage of BCP consumables that appeared to be independent of patient occupancy.

*Fig. 10: Netcare Krugersdorp Hospital BCP consumables vs. hospital occupancy*
Fig. 11 below shows the different BCP consumables as well as the number of units of each consumable used.

*Fig. 11: Netcare Krugersdorp Hospital blood conservation products usage*
Netcare Sunninghill Hospital

In Fig. 12 below it can be seen that there was a very slight decrease in the usage of allogeneic blood in Netcare Sunninghill Hospital.

Fig. 12: Netcare Sunninghill Hospital blood usage vs. hospital occupancy
Fig. 13 below shows that there was a slight increase in the usage of BCP consumables that appeared to be independent of patient occupancy.

Fig. 13: Netcare Sunninghill Hospital BCP consumables vs. hospital occupancy
Fig. 14 shows the different BCP consumables as well as the number of units of each consumable used.

Fig. 14: Netcare Sunninghill Hospital BCP consumables usage
Netcare Universitas Hospital

Fig. 15 below shows that blood usage in Netcare Universitas Hospital remained relatively constant.

Fig. 15: Netcare Universitas Hospital blood usage vs. hospital occupancy
Fig. 16 below shows that there was a slight increase in the usage of BCP consumables that appeared to be independent of patient occupancy.

![Graph showing BCP consumables vs. hospital occupancy from July 06 to September 07.](image)

**Fig. 16: Netcare Universitas Hospital BCP consumables vs. hospital occupancy**
Fig. 17 below shows the different BCP consumables as well as the number of units of each consumable used.

Fig. 17: Netcare Universitas Hospital BCP consumables usage
Netcare Pretoria East Hospital

In Fig. 18 below we see that there is a major decrease in blood usage.

Fig. 18: Netcare Pretoria East Hospital blood usage vs. hospital occupancy
Fig. 19 below shows that there was a considerable increase in the usage of BCP consumables, with patient occupancy being relatively constant.

![Graph showing BCP consumables vs. hospital occupancy from July 06 to September 07](image)

**Fig. 19: Netcare Pretoria East Hospital BCP consumables vs. hospital occupancy**
Fig. 20 below shows the different BCP consumables as well as the number of units of each consumable used.

Fig. 20: Netcare Pretoria East Hospital BCP consumables usage
Netcare Unitas Hospital

In Fig. 21 below there is a major decrease in blood usage which appears to be independent of patient occupancy.

Fig. 21: Netcare Unitas Hospital blood usage vs. hospital occupancy
Fig. 22 below shows a slight increase in the usage of BCP consumables which appears to be independent of patient occupancy.

Fig. 22: Netcare Unitas Hospital BCP consumables vs. hospital occupancy
Fig. 23 below shows the different BCP consumables as well as the number of units of each consumable used.

![Bar chart showing BCP consumables usage from July 2006 to September 2007.](image)

**Fig. 23: Netcare Unitas Hospital BCP consumables usage**
3.4.2 Results for Non-pilot Hospitals

Netcare Milpark Hospital

Blood usage remained constant for Netcare Milpark Hospital as seen in Fig. 24 below.

![Blood usage vs. hospital occupancy chart](chart.png)

*Fig. 24: Netcare Milpark Hospital blood usage vs. hospital occupancy*
Netcare Greenacres Hospital

For Netcare Greenacres Hospital, a slight increase in allogeneic blood usage can be seen in Fig. 25 below.

Fig. 25: Netcare Greenacres Hospital blood usage vs. hospital occupancy
**Netcare Union Hospital**

Fig. 26 below shows an increase in blood usage for Netcare Union Hospital.

![Graph showing blood usage vs. hospital occupancy](image_url)

**Fig. 26: Netcare Union Hospital blood usage vs. hospital occupancy**
Netcare Garden City Clinic

Fig. 27 below shows an increase in blood usage for Netcare Garden City.

Fig. 27: Netcare Garden City Clinic blood usage vs. hospital occupancy
Netcare St Augustine’s Hospital

For Netcare St Augustine’s Hospital, a slight increase in allogeneic blood usage can be seen in Fig. 28 below.

![Graph showing blood usage vs. hospital occupancy](image)

**Fig. 28: Netcare St. Augustine’s Hospital blood usage vs. hospital occupancy**
3.4.3 Statistical Analysis

Linear regression was used to assess for an increase or decrease in allogeneic blood usage and is displayed a linear trendline in Fig. 9 to 28. The trendline was calculated using following the equation: $y = mx + b$.

To determine whether the difference in allogeneic blood usage in the pilot hospitals versus non-pilot hospitals was significant, SigmaPlot programme version 12.0 was used for the statistical data analysis. To determine which method is best suitable to assess whether the two groups are statistically different from each other, the following tests were performed:

Normality Test (Shapiro-Wilk): Passed ($p = 0.521$)

Equal Variance Test: Failed ($p = 0.041$)

Therefore, the Mann-Whitney Test was performed on the data. The difference in the median values between the two groups was observed to be greater than would have been expected by chance. There was a statistically significant difference ($p \leq 0.001$) between the pilot and non-pilot hospitals’ blood usage.
3.5 RESULTS OF IMPLEMENTING BLOOD CONSERVATION PROGRAM

Fig. 29 below compares the average blood usage in pilot and non-pilot hospitals. It can be seen that there was considerably more blood used in non-pilot hospitals.

![Average blood usage in pilot vs. non-pilot hospitals](image)

*Fig. 29: Average blood usage in pilot vs. non-pilot hospitals*

Fig. 30 below reveals an increase in the number of BCP patients in pilot vs. non-pilot hospitals over a period of time. As can be seen, there was an increase in the number of blood conservation patients in pilot hospitals compared to those of the non-pilot hospitals. This could be due to the presence of the blood conservation coordinators in the pilot hospitals which raises awareness of blood conservation. This directly correlates with Fig. 32, which shows an increase in the growth of blood conservation.
Fig. 30: Non-pilot hospitals vs. Pilot hospitals BCP patients
Fig. 31 below shows a slight increase in the usage of autologous cell savers in the pilot hospitals from July 2006 – September 2007. This can probably be ascribed to an increased awareness of blood conservation.

![Chart showing usage of autologous cell savers from July 2006 to September 2007.](chart)

*Fig. 31: Autologous cell saver usage in pilot hospitals*

As there is an increase in the number of patients receiving blood conservation alternatives, we wanted to see if this was the only reason for the increase in cell saver usage.
In Fig. 32 below it is clear that occupancy remained relatively constant, with a definite increase in cell saver usage. The increase in blood conservation was thus independent of patient occupancy.

*Fig. 32: Cell saver usage vs. occupancy*
As can be seen in Fig. 33 below, there was a definite increase in the number of blood conservation patients in 2007 in all the pilot hospitals when compared to 2006. This can be attributed to an increased awareness of blood conservation in 2007, and increased implementation of a blood conservation program through the presence of the coordinators during this period.

![Number of Blood Conservation patients](image)

*Fig. 33: Growth of blood conservation program in pilot hospitals*

### 3.6 LENGTH OF STAY AND COST DATA

During the 15-month study period, a total of 2683 patients were enrolled in this study. Of these, 775 patients underwent knee replacements, 875 patients underwent hip replacements and 1033 patients underwent spinal surgeries. The detailed results below were obtained only from the pilot hospitals as there was a blood conservation program implemented and blood conservation coordinators present who could help with making this data available for capturing and analysis.
Table 2 and 3 summarize the procedures with their means for the LOS and total costs in each transfusion category.

Table 2: Mean values of length of stay for the different procedures and transfusion categories

<table>
<thead>
<tr>
<th>Procedure</th>
<th>BC Only n</th>
<th>LOS (days)</th>
<th>Blood Only n</th>
<th>LOS (days)</th>
<th>BC and Blood n</th>
<th>LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee replacements</td>
<td>535</td>
<td>7.37</td>
<td>128</td>
<td>8.98</td>
<td>112</td>
<td>10.12</td>
</tr>
<tr>
<td>Hip replacements</td>
<td>298</td>
<td>8.35</td>
<td>415</td>
<td>10.28</td>
<td>162</td>
<td>11.02</td>
</tr>
<tr>
<td>Spinal procedures</td>
<td>477</td>
<td>9.52</td>
<td>277</td>
<td>12.52</td>
<td>279</td>
<td>14.32</td>
</tr>
</tbody>
</table>

Table 3: Mean values of total costs for the different procedures and transfusion categories

<table>
<thead>
<tr>
<th>Procedure</th>
<th>BC Only n</th>
<th>Cost</th>
<th>Blood Only n</th>
<th>Cost</th>
<th>BC and Blood n</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee replacements</td>
<td>535</td>
<td>73476.83</td>
<td>128</td>
<td>80477.82</td>
<td>112</td>
<td>86010.49</td>
</tr>
<tr>
<td>Hip replacements</td>
<td>298</td>
<td>81107.75</td>
<td>415</td>
<td>83253.64</td>
<td>162</td>
<td>93431.28</td>
</tr>
<tr>
<td>Spinal procedures</td>
<td>477</td>
<td>78927.49</td>
<td>277</td>
<td>95996.58</td>
<td>279</td>
<td>124072.60</td>
</tr>
</tbody>
</table>
Table 4 illustrates the different hypotheses in view of the differences between the length of stay and the costs for the different categories and also demonstrates significant differences calculated by Mann-Whitney Test using SigmaPlot 12.0.

The null hypothesis that blood conservation alternatives had no effect on length of stay and costs was tested by probability testing with a statistical significance level of 5 % (two sided) for each orthopedic category.

Table 4: The hypotheses tested with their p-values

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS in Blood conservation &lt; LOS in Blood (knee)</td>
<td>0.043*</td>
</tr>
<tr>
<td>LOS in Blood conservation &lt; LOS in Both (knee)</td>
<td>0.003*</td>
</tr>
<tr>
<td>LOS in Blood &lt; LOS in Both (knee)</td>
<td>0.093</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Blood (knee)</td>
<td>0.703</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Both (knee)</td>
<td>0.482</td>
</tr>
<tr>
<td>Costs in Blood &lt; Costs in Both (knee)</td>
<td>0.007*</td>
</tr>
<tr>
<td>LOS in Blood conservation &lt; LOS in Blood (hip)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>LOS in Blood conservation &lt; LOS in Both (hip)</td>
<td>0.013*</td>
</tr>
<tr>
<td>LOS in Blood &lt; LOS in Both (hip)</td>
<td>0.620</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Blood (hip)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Both (hip)</td>
<td>0.348</td>
</tr>
<tr>
<td>Costs in Blood &lt; Costs in Both (hip)</td>
<td>0.107*</td>
</tr>
<tr>
<td>LOS in Blood conservation &lt; LOS in Blood (spine)</td>
<td>0.001*</td>
</tr>
<tr>
<td>LOS in Blood conservation &lt; LOS in Both (spine)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>LOS in Blood &lt; LOS in Both (spine)</td>
<td>0.566</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Blood (spine)</td>
<td>0.125</td>
</tr>
<tr>
<td>Costs in Blood conservation &lt; Costs in Both (spine)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Costs in Blood &lt; Costs in Both (spine)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

*Significant (p < 0.05)
The mean LOS for knee replacements with blood conservation was 7.37 days, allogeneic blood transfusion 8.98 days and the use of both was 10.12 days. For hip replacements, the mean LOS with blood conservation was 8.35, for blood only it was 10.28 days and for both it was 11.02 days. Patients undergoing spinal surgery had a mean LOS of 9.52 days with blood conservation only, 12.52 days with blood only and 14.32 days with both procedures. As shown in Table 4, the LOS of patients for blood conservation in all three procedures was significantly lower than for allogeneic blood transfusion or both.

Patients undergoing knee replacements had a mean total cost of R 73 476.83 with blood conservation, R 80 477.82 with blood only and R 86 010.49 using both procedures. The mean total cost for hip replacements with blood conservation was R 81 107.75, for allogeneic blood transfusion it was R 83 253.64 and using both it was R 93 431.28. For spinal surgeries, the mean total cost with blood conservation was R 78 927.49, for blood only it was R 95 996.58 and with both it was R 124 072.60.

3.7 DISCUSSION

Decisions about transfusing RBCs must be made with a full understanding of the risks and benefits involved. The estimated risks of infection have dramatically decreased in recent years as increased test sensitivity has reduced the infectious window periods. Clinicians should however be vigilant of the possibility of infection and risks from new pathogens.

Blood costs depend on the chain of events necessary to deliver the transfused unit; the more events, the more costly. Factors that also contribute to the cost of allogeneic transfusion include the cost of managing transfusion-related complications, increased hospital charges due to extended hospital stay, treating serious medical conditions (such as sepsis) and increased mortality. [3,55] On the basis of these observations, it was decided to assess the possibility of improving patient outcomes and increasing economic
benefits through the systematic implementation of a comprehensive blood conservation program.

In a study by Veenith et al. (2010), a dose-dependant relationship was seen between blood transfusion and the length of hospital stay in patients undergoing cardiac surgery. They stated that this might be attributed to the inflammatory and immunosuppressive effect of transfusion, together with the inflammation already present during cardiopulmonary bypass. [20]

In 2002, a provincial blood conservation program was implemented in Ontario, Canada. Transfusion coordinators were placed in 23 hospitals throughout the province. In most of these hospitals there was a decrease in usage of allogeneic blood at the 12 month analysis. Results of the analysis also showed that patients who received allogeneic transfusions had significantly higher post-operative infection rates and increased length of stay. Overall, the implementation of this program resulted in good patient satisfaction, improved patient safety and was shown to be cost-effective. [56]

As demonstrated in the results of this study, in all the pilot hospitals there was a definite decrease in allogeneic blood usage, in addition to an increase in the usage of BCP consumables. An important factor to mention with regard to these findings is that all of this was independent of hospital occupancy. This can in all likelihood be attributed to the presence of a blood conservation administrator and increased awareness of blood conservation in these five hospitals.

Length of hospital stay was significantly ($p \leq 0.05$) lower in patients who received blood conservation than patients using allogeneic blood in all three surgical procedures chosen for this study. The costs related to patients receiving blood conservation during knee and spine surgery were lower than those receiving allogeneic blood; however this was not statistically significant.
Glenngard *et al.* (2005) found that autologous transfusions are more costly than allogeneic transfusions in terms of administration but less costly when it comes to complications. [57]

In several studies investigating allogeneic vs. autologous blood transfusions, it was found that the length of hospital stay following allogeneic transfusion was significantly longer. [58,59] A loss of production by the patient is linked to the longer hospital stay which is also costly to the community. A longer stay in hospital is however multi-factorial, and in this study, other factors that may have an impact on the hospital stay of the patients were not measured.

Numerous outliers were present. This can be due to unforeseen complications arising during surgery or post-operative complications not related to transfusions.

The hospitals that participated in this study are a representative cross-section of private hospitals in South Africa, including larger and smaller hospitals. Therefore, it can be said that the results reflect the general blood conservation vs. no blood conservation trend in the private sector.

Our results show that there is an association between the administration of allogeneic blood transfusion and the length of hospital stay. While the data presented shows that the length of hospital stay was shorter in patients who received blood conservation therapies, further studies are needed to demonstrate cause and effect. Regrettably, we do not have the data currently to interrogate cause and effect and for now we have to rely on the published literature.

Questions that need to be addressed in future research include:

- Is the increased length of hospital stay attributable solely to adverse effects of blood transfusion?
Could the reasons that resulted in the extended length of hospital stay be due to post-operative complications e.g. haemorrhage?

Could it be that the surgery was more complex in patients receiving blood transfusion, resulting in longer hospital stay?

### 3.8 CONCLUDING REMARKS

Allogeneic blood transfusions are crucial in the treatment of patients with trauma and major blood loss. In less extreme conditions, however, the safety of allogeneic blood transfusions is challenged. As mentioned, there are a number of safe and cost-effective therapeutic alternatives which doctors should consider for the potential management of patients without using allogeneic blood transfusion. This philosophy will offer patients safe and effective therapy that will minimize the risks of allogeneic blood and help preserve our decreasing blood resources for those who are truly in need.

In this study, it is seen that the length of hospital stay and hospital costs are positively affected by the implementation of blood conservation techniques.

The total costs related to patients who received blood conservation was lower, although not significantly, than the total costs of patients using allogeneic blood or both. When taking into account the benefits provided by blood conservation and the risks involved with allogeneic blood transfusions, the fact that blood conservation is not more expensive than allogeneic blood motivates that blood transfusion alternatives should actually be considered more often.

In view of the results demonstrated in this study, I would like to propose a hypothesis that blood conservation therapies reduce the length of hospital stay compared to allogeneic blood transfusions. Further studies will need to be performed to interrogate cause and effect in this regard.
Since health practitioners need to weigh the benefits and risks of blood conservation and blood transfusions to be able to decide on the most appropriate treatment option for the highest level of patient safety, in light of the findings of this study practitioners should seriously consider blood conservation alternatives for the health benefit of their patients. A positive impact on blood product management would be possible if all of the components of a quality system could be developed and implemented (i.e. blood transfusion alternatives, appropriate product use with minimal/no wastage).

**Summary of results**

- Since the implementation of a blood conservation program in the pilot hospitals, there has been an increase in the use of blood conservation consumables, independent of patient occupancy, and in some hospitals this was accompanied by a decrease in the use of blood and blood products.
- There was a definite increase in the number of blood conservation patients in the pilot hospitals which could be ascribed to increased awareness of blood conservation programs due in large part to the presence of the blood conservation coordinators.
- The length of hospital stay of blood conservation patients was significantly lower than that of patients receiving allogeneic blood.
- The costs involved in blood conservation were relatively similar to those associated with the use of blood and blood products.
- Higher blood costs were incurred by the non-pilot hospitals than the pilot hospitals during the period of this study.
CHAPTER 4: LEUKODEPLETION

4.1 LEUKOCYTE DEPLETION FILTERS

Many of the adverse reactions associated with allogeneic blood transfusion can now be prevented with leukocyte depletion filtration technology. Although leukodepletion has had an improved effect on mortality and transfusion reactions and is compulsory in many countries, this practice has not yet been universally adopted. [60,61] Leukocyte-depleted blood is commonly prepared by passage through a leukocyte filter. By making use of different properties regarding the material, size, surface charge etc. of the filter, the filters will entrap leukocytes.

4.1.1 History of leukocyte filters

The pathologist Fleming was the first to design a filter using a cotton wool plug for the removal of leukocytes from whole blood. Fig. 34 shows the apparatus that he used which strongly resembles the structure of modern filters. [60]

![Fig.34: Leukocyte depletion filter as used by Fleming in 1928 [61]](image)

In 1961, Swank made an observation that contributed to transfusion-related filtration techniques. He observed using a microfilter as a model that high pressures were needed
to force blood through the filter. Also, microscopic examination revealed that the openings in the filter were occluded by debris and aggregates of white blood cells and platelets. [61]

4.1.2 Filter technology

Early filters were made of cotton wool or cellulose, but they had several drawbacks. These materials tend to activate the complement C3 system leading to vasoconstriction and increased capillary permeability. [61] The efficacy of the filter was dependant on the flow across the filter. Therefore it was a time-consuming process that took up to 30 minutes for one unit of blood.

Modern filters today have a rapid flow rate and an improved leukocyte removal of up to 99.995%. [61,62]

For an explanation of these superior flow properties of this new generation of filters, aspects of the materials and design used must be discussed. Two methods of filtration currently exist. The first is known as screen filtration. These filters are made from layers of woven polyester filter material, and trap the leukocytes in the smaller pores. Secondly, depth filtration makes use of polyester or polyurethane materials to promote adhesion of leukocytes to the surface of the filter. The efficacy and capacity of the filters are influenced by the means by which the leukocytes are trapped inside the filter. The specific properties that have been attributable to the leukocyte-reducing action of these materials are:

• The size of the mesh network that they create, which is likely to lead to retention of large or inflexible cells
• Surface structure
• Charge effects which are expected to induce the binding of cells to the fiber surfaces, resulting in successful removal of leukocytes. [61]

The most important mechanism is adhesion, whereby the negatively-charged leukocytes are attached to the filter materials by Van der Waal’s and electrostatic forces. This
method of adhesion is an active process and is advantageous because a bigger pore size with higher flow rates is achievable. [61]

Coating of these materials with a substance such as methacrylate can improve the efficacy of filtration by modifying the surface charge. [61,63] This creates a more positive surface charge resulting in stronger bonds with the negatively charged leukocytes. Optimal contact between the white blood cells and fibres is vital as it subsequently leads to adhesion.

A further consequence of the physical properties of the filter material is that leukocytes mainly get caught at the crossing points of the filter fibres. [61-63] Producing more crossing points requires that thinner fibres are used, but thinner fibres lead to increased resistance resulting in flow reduction. This shows how complicated the design of filters is and the factors that need to be considered.

Interactions between the different cell populations have also been observed to play a role in contributing to depletion. [61]

In leukocyte-reduced blood components, leukocyte counts are usually well below the level of detection of standard haematology analysers. Flow cytometry is a more accurate and sensitive method of detecting leukocytes. Flow cytometry utilizes fluorescent dyes such as propidium iodide that are used to measure cellular DNA content. These dyes are intercalated into the DNA helical structure, and the fluorescent signal emitted is directly proportional to the amount of DNA present. In view of the fact that red blood cells and mature platelets do not contain DNA, the signal obtained represents the leukocyte population in the blood sample. According to the Council of Europe guidelines, an acceptable count of residual leukocytes in leukodepleted blood components is $<1 \times 10^6$ cells/unit. [63,64]

Leukocyte depletion can be performed either immediately after the collection of whole blood before it is stored (pre-storage leukodepletion), or just before transfusing the blood product to the patient (post-storage leukodepletion). There are still a number of questions
with regard to whether the leukodepletion should be performed before storage or just before transfusion after storage.

The aim of this study was specifically to test the efficacy of removing leukocytes with the two available types of leukocyte depletion namely pre-storage leukodepletion and post-storage leukodepletion.

4.2 MATERIALS AND METHODS

Bedside filtration was used in this study as the method of post-storage leukoreduction of blood. The company Pall Pty. Ltd. (South Africa) generously provided us with filters for this study. These filters are used for bedside leukocyte reduction.

Blood samples were collected at Netcare Pretoria East Hospital within 7 days of donation (the shelf life of blood is between 7 and 21 days as mentioned in Van de Watering et al., 1998). [65] The RC1 filter from Pall was used in this study. One filter was used to filter 1 unit of blood.
Fig. 35: Pall RC1 Bedside Filter (www.filterworks.co.za, accessed on 30/08/2008)

To assemble: Hang the RBC unit bag on an IV pole
   Close the inlet clamp
   Place the administration set clamp close to the drip chamber and close completely
   Remove protective cap from administration set spike and insert into the RBC bag
Fig. 36: Assembled filter with blood bag (Photo taken by Monique du Preez)

To prime filter and drip chamber:

Ensure that the filter and drip chamber hang vertically
Open inlet clamp
The filter and drip chamber will fill automatically

4.2.1 Study design

Pre-storage leukodepletion:

- 30 leukodepleted blood samples supplied by SANBS were used as controls within 7 days from donation.

Bedside filtration:

- 20 Bedside RC1-filtered blood samples were collected at the bedside by the blood conservation coordinator of Pretoria East hospital assisting with the transfusion.
The filtered samples (< 500µl) were collected from the tubing once the transfusion was completed. Thus, patient safety was never compromised.

- 20 Non-filtered blood samples were collected before filtration for comparison
- All blood samples were collected aseptically using Baxter sampling site couplers.

4.2.2 Analysis

Whole blood was filtered by gravity flow with the filters in a vertical position at room temperature. Samples were analyzed on an FC500 flow cytometer (Beckman Coulter, South Africa) using the Leukosure Enumeration Kit from Beckman Coulter.

The samples were processed as indicated on the product insert of the Leukosure Enumeration Kit. In summary, the samples were lysed and permeabilized using the Leukosure Lyse Reagent to get rid of RBCs after which the Leukosure Stain reagent which contains propidium iodide and RNAse was added. Since mature RBCs and platelets do not contain DNA, the stained cells represent the leukocyte population of the blood. A single platform enumeration method was used by adding a known volume (100 µl) of LeukoSure Fluorospheres to an identical volume (100 µl) of sample to be tested. The samples were analyzed within one hour of preparation.

The acceptable level for residual leukocytes is less than 3 cells/µl. This is below the level of detection for most standard counting methods. The LeukoSure Enumeration Kit was configured to utilize the sensitivity of flow cytometry to specifically enumerate residual leukocytes at the levels required to guarantee the quality control of leuko-reduced blood.

All samples were analyzed in duplicate. In the analysis, non-filtered versus leukocyte-depleted, filtered samples were analyzed. The absolute count was then calculated by the flow cytometry software using the following formula:
Absolute count (cells/µl) = (Total number of cells counted divided by Total number of fluorospheres counted) multiplied by the concentration of the Leukosure fluorospheres assayed.

### 4.3 RESULTS

Table 5: Leukocyte count of SANBS leukodepleted blood samples

<table>
<thead>
<tr>
<th>SANBS samples</th>
<th>Duplicate 1 (cells/µl)</th>
<th>Duplicate 2 (cells/µl)</th>
<th>Mean leukocyte count (cells/µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sample 2</td>
<td>0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Sample 3</td>
<td>5</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>Sample 4</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Sample 5</td>
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<td>0</td>
</tr>
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<td>Sample 6</td>
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</tr>
<tr>
<td>Sample 7</td>
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<tr>
<td>Sample 8</td>
<td>1</td>
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<td>0.5</td>
</tr>
<tr>
<td>Sample 9</td>
<td>0</td>
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<tr>
<td>Sample 10</td>
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<tr>
<td>Sample 11</td>
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<tr>
<td>Sample 12</td>
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<td>Sample 13</td>
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<td>Sample 14</td>
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<td>Sample 15</td>
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<td>Sample 16</td>
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<td>Sample 17</td>
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<td>Sample 18</td>
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<td>Sample 19</td>
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<td>Sample</td>
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<td>--------</td>
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</tr>
<tr>
<td>Sample 21</td>
<td>0</td>
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<td>Sample 22</td>
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<td>Sample 24</td>
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<tr>
<td>Sample 25</td>
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<td>Sample 26</td>
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<td>Sample 27</td>
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<td>Sample 29</td>
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</tr>
<tr>
<td>Sample 30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The mean leukocyte count of the SANBS leukodepleted blood samples was 0.12 cells/µl as illustrated in Table 5. In sample 3, duplicate 1, the leukocyte count detected in the sample was 5 cells/µl. This is considered to be an outlier and is a very rare occurrence.
Table 6: Leukocyte count of non-leukodepleted blood samples filtered with Pall bedside filters

<table>
<thead>
<tr>
<th>Pall-filtered samples</th>
<th>Pre-filtration</th>
<th>Post-filtration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duplicate 1 (cells/µl)</td>
<td>Duplicate 2 (cells/µl)</td>
</tr>
<tr>
<td>Sample 1</td>
<td>1356</td>
<td>1580</td>
</tr>
<tr>
<td>Sample 2</td>
<td>5239</td>
<td>4897</td>
</tr>
<tr>
<td>Sample 3</td>
<td>6418</td>
<td>7206</td>
</tr>
<tr>
<td>Sample 4</td>
<td>4011</td>
<td>4107</td>
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<tr>
<td>Sample 5</td>
<td>2200</td>
<td>2008</td>
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<tr>
<td>Sample 6</td>
<td>2041</td>
<td>2375</td>
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<tr>
<td>Sample 7</td>
<td>4876</td>
<td>4984</td>
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<td>Sample 8</td>
<td>1824</td>
<td>1904</td>
</tr>
<tr>
<td>Sample 9</td>
<td>1288</td>
<td>1156</td>
</tr>
<tr>
<td>Sample 10</td>
<td>6000</td>
<td>6004</td>
</tr>
<tr>
<td>Sample 11</td>
<td>6919</td>
<td>6701</td>
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<tr>
<td>Sample 12</td>
<td>4001</td>
<td>4025</td>
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<tr>
<td>Sample 13</td>
<td>2089</td>
<td>2125</td>
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<tr>
<td>Sample 14</td>
<td>2244</td>
<td>2178</td>
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<tr>
<td>Sample 15</td>
<td>4304</td>
<td>4356</td>
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<td>Sample 16</td>
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<td>5799</td>
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<td>Sample 18</td>
<td>4587</td>
<td>4369</td>
</tr>
<tr>
<td>Sample 19</td>
<td>2116</td>
<td>2194</td>
</tr>
<tr>
<td>Sample 20</td>
<td>3613</td>
<td>3589</td>
</tr>
</tbody>
</table>
As shown in Table 6, the mean leukocyte count of the pre-filtered blood samples was 2817 cells/µl. In 19 out of the 20 filtered samples the leukocyte count was measured to be 0 cells/µl, with one filtered sample’s count being 1 cell/µl. The mean leukocyte count for the Pall filtered samples was 0.05 cells/µl.

The following 2 figures indicate flow cytometric data of the leukocyte count in the blood samples. Region B, as shown below, is the calculation of all the leukocytes present in the blood sample. In this study we used this value as an indication of the efficacy of filtration.

Fig. 39 and fig. 40 make use of FL3 Lin vs. Ratio that provides additional discrimination of nucleated leukocytes from platelets, red cells or debris. Events that occur on the diagonal in this figure represent non-specific debris and are eliminated from the analysis. Region B shows the residual WBC count of a pre-filtration sample.

![Flow Cytometric Results](image)

**Table: Flow Cytometric Results**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cells/µl</th>
<th>%Gated</th>
<th>X-Mean</th>
<th>X-Mode</th>
<th>Y-Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>8116</td>
<td>100</td>
<td>158</td>
<td>7</td>
<td>779</td>
</tr>
<tr>
<td>B</td>
<td>4059</td>
<td>50.02</td>
<td>239</td>
<td>234</td>
<td>877</td>
</tr>
</tbody>
</table>

*Fig.39: Flow cytometric results from non-leukodepleted SANBS sample*
In Fig. 40, region B shows the residual WBC count of a filtered sample.

**Fig.40: Flow cytometric results from filtered blood sample**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cells/µl</th>
<th>%Gated</th>
<th>X-Mean</th>
<th>X-Mode</th>
<th>Y-Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>119</td>
<td>100</td>
<td>69.6</td>
<td>8</td>
<td>515</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0.04</td>
<td>231</td>
<td>219</td>
<td>840</td>
</tr>
</tbody>
</table>

4.4 DISCUSSION

Blood transfusions are generally given after surgery, after which the transfused leukocytes, activated during storage, are introduced to an already activated inflammatory response system, and as a result aggravate tissue damage through the further release of cytokines and oxygen radicals. [65] The immunosuppressive effect of blood product transfusion may also predispose patients to infections. [66] In a study done by Murphy *et al.* (1992), the authors observed that patients who acquired infections used more hospital resources, adding to expenditure on health care; in addition they received a greater amount of transfusion products than non-infected patients. [67]
The frequent occurrence of infections seen amongst those patients transfused with allogeneic blood was confirmed by Jensen et al. (1992) in a study done on colorectal surgery patients. Their results also support the observation that the immunosuppressive effect of transfusion is mediated by leukocytes; when leukoreduced blood products were transfused, the infection rates dropped from 23% down to less than 3% as seen in non-transfused patients. [68]

According to the Council of Europe guidelines, less than $1 \times 10^6$ WBC should be present in a leukoreduced blood product bag. In the UK this value is $5 \times 10^6$ cells / unit. Outside of these, in an ordinary leukoreduced unit of blood, the WBC count is expected to be $< 3$ cells/µl to ensure validation. [64]

Leukofiltration of blood is done either at the time of collection and processing (pre-storage), or at the bedside (post-storage). Pre-storage leukoreduction is currently the most widely accepted mode.

Looking specifically at commonly used pre-storage leukoreduction, the advantages of pre-storage over post-storage leukoreduction are as follows:

- Immediate availability of leukoreduced blood components
- Eliminates the possibility of inflammatory cytokine accumulation formed by the leukocytes during storage
- Reduced risk of HLA-alloimmunization in transfused patients by prevention of leukocyte fragments produced during storage passing through filters with alloimmunization of the recipient against donor antigens
- Ease in consistently maintaining leukocyte quality control in the laboratory rather than at the patient's bedside.

Advantages of bedside filtration include:

- Costs involved
- Can be done selectively for the patient groups recommended for leukoreduced blood components
- Easy to use whether they at the bedside in hospital, in the regional blood center or even at home for home-care transfusions
- Rapid flow rate – not time-consuming

A study by Pruss et al. (2004) demonstrated that pre-storage leukodepletion of blood components is more successful than post-storage leukodepletion in preventing febrile reactions but not allergic reactions. The rates of febrile NHTRs after buffy coat depleted RBC and post-storage leukodepleted RBC transfusions were very similar, but significantly higher than that of pre-storage leukodepleted RBCs. [22]

Safety concerns related to bedside filtration include the failure to adequately remove leukocytes due to uncontrolled filtration times and temperatures. Also, as a post-storage procedure, it has been associated with precipitous hypotension in the transfused recipient, particularly patients on medications that inhibit angiotensin converting enzyme (ACE inhibitors). [69,70] However, this is an infrequent adverse effect but should be kept in mind when transfusing patients susceptible to precipitous hypotension. With regard to the first concern mentioned, namely efficiency, in this study the pre-storage leukodepletion and the bedside filtration both resulted in effective removal of leukocytes as the acceptable count of residual leukocytes is < 1 x 10^6 cells / unit.

At the time of performing this study, the cost of a unit of SANBS leukodepleted blood was R 2 179.60 excl VAT. The cost of a unit of red cells packed blood was R 1 333.89 excl VAT, and the price of a RC1 Pall filter (including administration set) R 543.10. Thus:
SANBS leukodepleted blood unit: R 2 179.60
RC1 Pall filtered blood unit: R 1 333.89 + R543.10 = R 1 876.99
This gives one a cost saving of R 302.61.

As bedside filters are also covered by medical aids, there is not much cost implication to the hospital or patient by making use of bedside filtration.
However, post-storage filtration does not remove leukocyte fragments that are formed during storage and it does not prevent the production of inflammatory cytokines during storage, but it does remove the micro-aggregates formed by the leukocyte fragments and platelets. Another advantage of pre-storage filtration is that because the blood is filtered at the time of collection, it prevents the accumulation of bioactive substances released by stored leukocytes that have been associated with patient anaphylactic reactions. [71]

Another important finding is that the red cell recovery with pre-storage filtration is significantly better than what is achieved with bedside filtration. The red cell recovery with the bedside filters was observed to decrease even more when the bedside filters were used at room temperature. Bearing in mind that bedside filtration is normally performed on products at room temperature since they are used only at the time of the transfusion, this decreased red cell recovery is important. [22]

Although the preferred method of filtration is pre-storage leukodepletion, not every unit of whole blood from SANBS is leukodepleted before storage (as shown in Table 6) and we assume that this is due to the cost that would be involved in leukodepleting every unit that is supplied by SANBS. Bedside filtration has shown to be cost-effective and effective in removing leukocytes from blood but unfortunately it lacks the benefits beyond just effective leukocyte removal that have been proven with pre-storage leukodepletion. [71]
4.5 CONCLUDING REMARKS

Hospitals are considering all options for cutting costs including scrutiny of their blood use. Bedside filters have been shown to be an effective method for leukodepletion with reduced costs. However, further studies need to be conducted to evaluate the outcome of the build-up of hazardous substances released by the stored leukocytes on patients who are subjected to bedside filtration rather than pre-filtration by SANBS. Thus, despite the reduction in cost, the physiological implications of bioactive products released by stored leukocytes in non-filtered blood suggest that the small additional cost may be justified to pre-filter all units of blood provided by SANBS.
CHAPTER 5: Final conclusions and perspectives

I had the opportunity to study the effect of blood transfusion alternatives in a South African private hospital setting in relation to the usage of allogeneic blood products. Although selected hospitals were considered in my study, the results reflect the general blood conservation vs. no blood conservation trend. The following conclusions can be drawn from my results:

- The implementation of a blood conservation program has been shown to have a beneficial effect on the length of hospital stay without increasing costs.
- A large variety of outcomes can be measured in the future using this database and method of analysis to give reports on for example, the comparison between different hospitals, attending doctors, patient groups, age groups, etc.
- Both methods currently available for leukodepletion (pre-storage and post-storage) have been shown to be efficient in the removal of leukocytes.
- Overall, pre-storage leukodepletion filters have better clinical outcomes when compared to bedside filters (post-storage).
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Universiteit van Pretoria
University of Pretoria

Faculty of Health Sciences Research Ethics Committee
University of Pretoria
HW Snyman Building, (South) Level 2-34 Pretoria
Private Bag X169 Pretoria 0001

Date: 5/11/2007

PROTOCOL NO. 118/2007(a)
PROTOCOL TITLE Analysis and Monitoring of Blood Conservation in Netcare Hospitals
INVESTIGATOR
Person: Monique du Preez Phone: 012-3192425 E-Mail: dereet@unitas.netcare.co.za
Cell: 0846576947

DEPARTMENT Immunology; Pretoria Academic Hospital; University of Pretoria

STUDY DEGREE M.Sc Immunology

SUPERVISOR Prof M S Pepper E-Mail: ronald.anderson@up.ac.za

SPONSOR None.

MEETING DATE 26/09/2007

This Protocol and Informed Consent and all the attachements have been considered by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria on 31/10/2007 and found to be acceptable.

*Advocate AG Nienaber (female)BA(Hons) (Wits); LLB; LLM (UP); Dipl.Dataometrics (UNISA)
*Prof V.O.L. Karusseit MBChB; MFGP (SA); M.Med (Chir); FCS (SA); Surgeon
*Prof M Kruger (female) MB.ChB(Pret); Mmed.Paed.(Pret); PhD (Leuven)
Dr N K Likibi MB.ChB; Med Adviser (Gauteng Dept of Health)
Snr Sr J. Phatshili (female) BCur (El.Al) Senior Nursing-Sister
*Dr L Schoeman (female) B pharm, BA Hons (Psy), PhD
*Prof J.R. Snyman MBChB, M Pharm; Med: MD; Pharmacologist
*Dr R Sommers (female) MBChB; M.Med (Int); MPhar; Med;
Prof TPJ Swart BChD, MSc (Odont), MChD (Oral Path) Senior Specialist; Oral Pathology
*Dr A P van Der Walt BChD, DGA (Pret) Director: Clinical Services of the Pretoria Academic Hospital
*Prof C W van Staden MBChB; Mmed (Psych); MD; FTCL; UPLM; Dept of Psychiatry

DR R SOMMERS; MBChB; M.Med (Int); MPhar Med.
SECRETARIAT of the Faculty of Health Sciences Research Ethics Committee - University of Pretoria

* = Members attended the meeting on 31/10/2007.