Postoperative autologous retransfusion of shed blood in primary total hip and knee arthroplasty

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Postoperative autologous retransfusion of shed blood in primary total hip and knee arthroplasty

A.F.C.M. Moonen

COLOPHON

Thesis:

Postoperative autologous retransfusion of shed blood in primary total hip and knee arthroplasty

Thesis University Maastricht, the Netherlands

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....sport en spel en buitenlucht
en daarna wijs gegeten
lach erbij da's goed voor je hart
dat mag je nooit vergeten....

Voor mijn ouders

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CHAPTER 1

General introduction and thesis outline

A.F.C.M. Moonen

A HISTORY OF BLOOD RETRANSFUSION

Even in ancient times people were aware of the importance of blood. The mythology of the ancient Greeks is replete with tales of exchange transfusion to regain lost youth. The subject was bled and the “ancient veins were filled with a rich elixir”. The latter, brewed in a bronze cauldron, contained “root herbs, seeds and flowers, strong juices and pebbles from farthest shores of the oceans east and west, hoarfrost taken at the full of the moon, a hoot owl’s wings and flesh, a werewolf’s entrails, the fillet of a snake, the liver of a stag and the eggs and head of a crow which had been alive for nine centuries”.⁶

It is generally thought that the first human blood transfusions were performed in France and England in 1667. The French physician Jean-Baptiste Denis was the first to transfuse animal blood into a human subject when he gave lamb’s blood to a young man “possessed of an incredible stupidity”.² Subsequent experiments with animal-to-human transfusion led to one disaster after another. The experiments did, however, yield a reasonably accurate description of incompatible blood transfusions. The experimental failures resulted in a prohibition on blood transfusion by the French Parliament, the Royal Society of London and the Church of Rome. Following the actions of the Royal Society, and the Papal Edict, the practice of blood transfusion fell into oblivion for almost 150 years.

James Blundell, a physician-surgeon practicing in London in the early nineteenth century, is generally credited with reviving the interest in blood transfusion. Alarmed by the unacceptably high number of deaths in his practice caused by post-partum haemorrhage, Blundell looked for ways to replace this blood. Hindered by the lack of infusion equipment and anticoagulant, he devised several pieces of equipment to facilitate transfusion.³ In his experiments, he demonstrated that only blood of the same species should be used for transfusion. Blundell transfused 10 patients, five of whom survived, and was as such the first to demonstrate the potential of blood transfusion as a method to prevent death from haemorrhage.

Blundell’s work reawakened the medical world to the therapeutic potential of blood transfusion. In the latter half of the nineteenth century, the medical world devoted considerable effort to finding better methods of direct or indirect transfusion as well as an adequate method to prevent coagulation. While transfusion was recognised as being beneficial in the treatment of blood loss, the complexity of the procedure and the high morbidity and mortality rates made it no safer than it had been 250 years before. Consequently, it was abandoned in wait of the technologic advances of the twentieth century.

Eventually, in the year 1902 Landsteiner's description of the four different blood groups led to a dramatically reduced risk of death after blood transfusion.⁴

Autotransfusion, or salvage and reinfusion of shed blood, had been used sporadically since 1914 when Theis, a German obstetrician, successfully returned blood lost from ruptured ectopic pregnancies through a gauze filter in three women.⁵ In 1953, Bentley Laboratories developed the first prototype of a cell separation device for autotransfusion. Blood collected by this first "Bentley" machine was contaminated with impurities that often led to coagulopathy, and it was known to produce lethal air embolism. Improvements in this device over the years have led to the current range of cell salvage devices that are used in both the operative and postoperative periods.

Undoubtedly, the realisation that the HIV virus can be transmitted through blood transfusion in the early 1980's opened the eyes of both physicians as well as the public to the inherent risks of allogeneic blood. By that time, it was clear that a new speciality had emerged: 'transfusion medicine'.

TRANSFUSION MEDICINE IN ORTHOPAEDIC SURGERY

Much of the recent literature in the field of transfusion alternatives emanates from orthopaedic departments in Europe and Northern America. This can be attributed to the fact that major orthopaedic operations are usually associated with significant blood loss, making orthopaedic surgeons some of the largest users of blood products. The problems of allogeneic blood transfusion -both the reduced availability of blood as well as the multitude of potential risks -are well documented.⁶⁻¹⁰ Moreover, it has been suggested that transfusion of allogeneic blood is an independent predictor in the development of postoperative infections.^{11,12}

Elective orthopaedic surgery, especially joint replacement and spinal surgery, lends itself well to the use of the many techniques available to help reduce the use of allogeneic blood. In formulating a strategy for blood management, it is important to identify the patients who are most at risk. By far the strongest predictor of the need for transfusion is the preoperative haemoglobin (Hb) level, but age, aspirin use and estimated blood loss are all indicators too.¹³ Estimations of blood loss in correct blood management should also take hidden blood loss into account. Following both primary total hip (THA) as well as total knee arthroplasty (TKA), the mean "true" blood loss up to the third postoperative day has been approximately 1500 mL.¹⁴ This loss eventually causes a fall in the postoperative Hb level of approximately 3.0 g/dL. Nevertheless, even within a well defined situation, i.e. THA or TKA, the

transfusion rate can vary tremendously among different hospitals.

Several techniques for reducing the need for allogeneic blood transfusions are currently in common use. The most frequently used interventions are the decrease of the so-called transfusion trigger,^{15,16} preoperative treatment with epoetin injections,^{17,18} and postoperative cell saving.^{19,20} Although algorithms for reducing allogeneic blood transfusions have already been published,^{21,22} it is still unclear which intervention or combination of measures is the most successful.

THESIS OUTLINE

The studies presented in this thesis aim to establish the role of postoperative cell saving in orthopaedic practice by using an autologous retransfusion system for filtered shed blood in patients after THA or TKA. Additionally, we aim to elucidate possible improvements for the further optimization of when and how to use the retransfusion system. As such, this thesis seeks to answer a number of research questions, which have been formulated as the following aims:

- To determine whether the retransfusion system is safe for use
- To compare the filtering performance of different retransfusion systems
- To elucidate the effect of the position of the drain when using the retransfusion system
- To evaluate the efficiency of the retransfusion system compared to standard therapy
- To establish which patients could benefit from treatment with the retransfusion system as compared to other alternatives
- To document everyday use of the retransfusion system

This thesis starts with an outline of perioperative blood management in elective orthopaedic surgery, presenting an overview of the available interventions that aim to diminish the use of allogeneic blood (**Chapter 2**). **Chapter 3** presents the implementation process regarding blood management in the orthopaedic surgery department of the Maasland hospital in Sittard. The subsequent chapters, forming the main part of this thesis, address the specific research questions described above (**Chapter 4, 5, 6, 7, 8 and 9**). Finally, this thesis closes with a general discussion (**Chapter 10**) and summary (**Chapter 11**).

As all chapters are based on previously published or submitted manuscripts and are intended to be read individually, some repetition is inevitable.

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CHAPTER 2

Perioperative blood management in elective orthopaedic surgery; a critical review of the literature

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Injury 2006;37(3):S11-6

ABSTRACT

Blood loss during orthopaedic procedures can be extensive and the need for allogeneic blood is a common requirement. However, blood transfusion conceals a number of well-recognised risks and complications and blood products have become more expensive because of their specific preparation procedure.

Surgical technique, awareness of the problem and restriction of transfusion triggers are important factors affecting the management of blood loss. Several studies have additionally shown the efficacy of epoetin injections in increasing the preoperative haemoglobin (Hb) level. On the other hand, the true benefit of preoperative autologous donation, acute normovolemic haemodilution and COX-2 selective NSAIDs remains under dispute. Regarding the role of platelet rich plasmapheresis, fibrin sealing and anti-fibrinolytic drugs more data are needed.

Hypotensive epidural anaesthesia seems to be an advantageous method in minimising perioperative blood loss. However, this is not a widely performed technique in orthopaedic surgery. In addition, postoperative blood saving systems after total hip and knee arthroplasty have been reported to significantly minimise allogeneic blood transfusions when compared to controls.

It can be concluded that many interventions diminish more or less allogeneic blood transfusion in elective orthopaedic surgery. Nevertheless, more prospective studies are needed and appropriate algorithms should be applied in perioperative blood loss management.

This review presents an overview of the available interventions which aim to diminish the use of allogeneic blood in elective orthopaedic surgery.

INTRODUCTION

Major orthopaedic operations are usually associated with significant blood loss, and the transfusion of allogeneic blood is not uncommon. However, blood transfusion is far from being considered a zero risk procedure. Instead, it is associated with a number of well-recognised risks and complications such as transfusion errors,¹⁻³ allergic reactions,³⁻⁶ transmission of infectious agents^{4,7,8} and down-modulation of the immune system.⁹⁻¹² Moreover, it has been suggested that transfusion of allogeneic blood is an independent predictor in the development of postoperative infections.^{13,14}

As the primary function of red blood cells is the transport of oxygen and carbon dioxide to and from tissues, it seems that the primary reason for blood transfusion is physiologic, i.e. to provide the additional oxygen delivery (DO_2) needed to correct or prevent the development of tissue hypoxia. Blood transfusion should not be used as a primary means of restoring blood volume or to 'raise hemoglobin (Hb) level' in the absence of a clinically defined need for improved DO_2 . Therefore, the decision should be derived from several factors, such as patient symptoms, vital signs, determination of oxygen delivery-consumption interactions, prediction or estimate of blood loss and the physician's knowledge and experience.

Blood products have become more expensive due to the specific preparation process like donor selection and screening. However, there are still undiscovered infectious factors for which no screening is performed. Concerns of patients and clinicians regarding blood safety have generated the need for application of technologies intended to reduce the amount of allogeneic blood transfusion. Furthermore, the pressure for decreasing the hospitalization cost has increased the interest towards a more restrictive transfusion policy and several interventions are commonly in use. The most frequent interventions are the decrease of threshold under which transfusion is considered necessary (so-called transfusion trigger), preoperative epoetin injections, preoperative autologous blood donation and postoperative cell saving. In this direction the type of anaesthesia also plays an important role by affecting more or less the physiology of bleeding.

Although algorithms to reduce allogeneic blood transfusions have already been published,^{15,16} it is still unknown which intervention or combination of measures is most successful. This critical review of the literature presents an overview of the most important factors which influence perioperative blood management in elective orthopaedic surgery. Various different interventions or therapies are also discussed.

SURGERY

Each surgeon should confine and minimize blood loss in every operation. It is well known that surgical technique plays a major role in maintaining blood loss at a low level.^{17,18} Adequate haemostasis incorporated in a careful and anatomically correct tissue dissection remains the “gold standard” technique for eliminating potential complications. Its impact on transfusion decision is evident: blood that is not lost does not have to be replaced.

TRANSFUSION TRIGGER

In the past, a liberal transfusion policy without specific triggers was used in the majority of hospitals. Usually the decision was taken according to subjective criteria like fatigue, paleness, or generally not feeling well. The increased awareness of the risks and disadvantages of allogeneic blood transfusion have led to a new blood management which is now widely applied in many hospitals. The basic concepts of management include increased awareness and restrictive transfusion triggers.¹⁹

Following operation, the Hb transfusion trigger depends on comorbidity classification of the American Society of Anaesthesiologists (ASA). If a patient's general condition is compromised, e.g. cardiovascular disease or pulmonary disease, a higher threshold is recommended.²⁰ Administration of allogeneic blood is based on haemoglobin levels instead of subjective complaints.^{20,21} One should always bear in mind that low Hb level does not always justify transfusion, and multiple clinical factors along with haemodynamic parameters should be evaluated in every individual case.^{22,23} Therefore, allogeneic transfusion should be done on patient-specific demand.²⁴

Nowadays, most hospitals in The Netherlands use guidelines which are more or less based on the same values. For most patients this value is a Hb level of 8.1 g/dL. In young patients (<60 yrs) without comorbidity transfusion trigger can be as low as 6.5 g/dL. In compromised patients the trigger is raised to 9.7 g/dL. There is no available evidence for higher triggers.

EPOETIN INJECTIONS AND IRON SUPPLEMENTS

Erythropoiesis is dependent on the hormone erythropoietin which is mainly formed in the human kidney by changes in tissue oxygenation. In most countries, epoetin injections have been approved for application in major orthopaedic surgery. In The Netherlands epoetin has been used in cases of preoperative Hb levels between 10.0 and 13.0 g/dL without iron deficiency.

Regularly, the dosage scheme for elective orthopaedic surgery is 600 IE/kg subcutaneous injection once a week starting 3 weeks before scheduled surgery (i.e. preoperative days -21, -14, -7). Final injections would be administered within 24 hours of surgery if the Hb level is below 15.0 g/dL or direct postoperatively if Hb is above 15.0 g/dL. The old schedule with 300 IE/kg daily for 14 days can be used if the time interval before surgery is less than three weeks. Maximum action of epoetin injections is achieved when patients' iron stores are adequate^{25,26} and for that reason epoetin injection therapy is supported by supplementary oral iron.

One can expect a mean raise in preoperative Hb of approximately 1.9 g/dL.²⁷ According to the above finding, epoetin injections reduce the need for allogeneic blood transfusions after surgery. Several studies have shown the efficacy of epoetin in well-controlled randomised studies²⁷⁻³¹ even in rheumatoid arthritis patients.³² A disadvantage of epoetin injections is the relatively high cost of treatment.

Many studies have investigated potential postoperative markers of iron metabolism to support the hypothesis that erythropoiesis is reduced by the inflammatory effect of surgery.³³⁻³⁵ This is similar to anaemia of chronic disease in which there is poor iron incorporation into red cells despite adequate stores.^{34,35} Oral iron supplementation in the first weeks after surgery seems to be ineffective³⁵ while with intravenous iron application it is possible to increase Hb level postoperatively. So far, little research has been done on the above hypothesis and the majority of studies deal with epoetin injections.³⁶

PREOPERATIVE AUTOLOGOUS DONATION AND ACUTE NORMOVOLIC HAEMODILUTION

Preoperative autologous donation (PAD) is applicable to patients who have been scheduled for elective surgery and will require blood transfusion according to preoperative estimation of blood loss. In PAD the patient needs to donate one or more units of his/her own blood preoperatively. This blood is held in a blood bank and is available for administration during or after surgery.

A few studies of PAD in orthopaedic surgery have been reported in the literature.³⁷⁻³⁹ Although the studies show a reduction in the need for allogeneic blood, they might be influenced by the knowledge of the trial status. Consequently, many questions about the true benefit of PAD are pending. Additional concerns about the use of PAD include handling errors and blood infection.⁴⁰ The overall benefits of PAD in primary joint arthroplasty probably outweigh the harms in specific groups such as in alloimmunized patients after repeated transfusion.

The concept of acute normovolemic haemodilution (ANH) is to lose diluted blood postoperatively and to return the predeposited blood unit.^{41,42} The typical process of ANH is performed one hour preoperatively and includes collection of two to three blood units (500 mL) while the patients received crystalloid and colloid solutions before the beginning of the operation.^{42,43} After surgery the stored blood units are transfused to the patient. An advantage of acute normovolemic haemodilution is that patients are transfused with their own blood which in turn contains clotting factors and contributes to haemostasis.⁴⁴ No current protocols define when ANH or PAD is preferable in elective surgery.

NSAIDS AND ANTI-COAGULATION MEDICATION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to achieve adequate perioperative analgesia. They constitute inhibitors of prostaglandin synthesis and they particularly block cyclo-oxygenase (COX) which is the central enzyme in the prostaglandin formation process. COX-2-selective NSAIDs have, in theory, no undesired COX-1-related side effects and do not impair platelet aggregation and bleeding-time. Only a few studies regarding this topic have been published^{45,46} showing superior results in allogeneic blood transfusion rates after application of COX-2-selective NSAIDs. However, their use in the perioperative period should be considered in patients with expected blood loss and bleeding. The potential protective profile of COX-2 and its true benefit is still under dispute.

Anti-coagulation medication prolongs bleeding time by affecting divergent pathways of the coagulation cascade. Those medicines were usually stopped a few days preoperatively to normalise bleeding time. Patients have started to receive low molecular weight heparin, for thromboembolic prophylaxis, just before surgery, and the duration of treatment depends on the severity of orthopaedic surgery and the estimated time of immobilization.

PLATELET RICH PLASMAPHERESIS, FIBRIN SEALING AND ANTI-FIBRINOLYTIC DRUGS

Platelet rich plasmapheresis (PRP) produces a highly concentrated autologous platelet product and it is considered to be an alternative solution to allogeneic blood transfusion in surgical setting.¹⁴ It involves the patient's own blood which is withdrawn into a plasmapheresis device and after centrifugation is separated into platelet solution, plasma and red blood cells.⁴⁷ The plasma and red cell component is usually re-administered to the patient immediately, whereas the platelet component is collected, temporarily stored and then returned to the patient at the end of surgery.^{47,48}

The basic theory is by applying platelet concentrate to acute wounds the normal healing response can be accelerated. For example, the use of autologous platelet concentrate might reduce the postoperative blood loss from capsule and subcutaneous tissues after total knee arthroplasty. As a result the need for allogeneic could be substantially reduced. More data are needed to support the application of platelet rich plasmapheresis in major orthopaedic surgery.

Fibrin sealants are prepared from autologous human plasma and appear to reduce exposure to allogeneic blood transfusion.⁴⁹ However, a “zero” risk of viral transmission from fibrin sealants cannot be guaranteed even with the use of autologous blood as microbial or viral contamination may occur during the processing phase.⁵⁰

Amongst the available agents for minimising the need for blood transfusion are the anti-fibrinolytic drugs aprotinin and tranexamic acid. Both medicines initiate coagulation and inhibit fibrinolysis.^{51,52} Most of the data have been collected in the context of cardiac surgery and few studies have coped with their effect in orthopaedic surgery.

HYPOTENSIVE EPIDURAL ANAESTHESIA

Hypotensive epidural anaesthesia (HEA) belongs to the available techniques for reducing perioperative blood loss.⁵³ The aims of HEA application are to achieve an epidural dermatome block at least as far as the T2 level and to establish a sufficiently extensive and dense block of the cardio-acceleratory fibres of the thoracic sympathetic chain. Normally this effect could result in some uncertain degree of bradycardia. For that reason, epidurally induced sympathetic block is combined with continuous intravenous infusion of a low-dose epinephrine solution in order to stabilize the circulation status of the patient.

With application of HEA, arterial pressure is reduced whilst heart rate, CVP, stroke volume and cardiac output are maintained in the normal range. Mean artery blood pressure (MAP) could be lowered to 50 mmHg resulting in a reduction of intraoperative blood loss and postoperative wound drainage.^{54,55} By minimising the amount of intraoperative blood loss, surgical exposure could be faster and safer.

Hypotensive epidural anaesthesia can be used in the majority of high-risk patients with hypertension or with poor cardiac function. Even in patients with chronic renal dysfunction, carefully managed HEA seems not to impair renal function after surgery.⁵⁶ Although HEA appears to be an advantageous method in perioperative blood management it is not a widely performed technique in orthopaedic surgery.

INTRAOPERATIVE AND POSTOPERATIVE CELL SAVING

“Intraoperative cell saving” refers to the procedure in which blood collected from surgical sites could be transfused back to the person during or after surgery.^{57,58} The blood is either “washed” before transfusion or transfused “unwashed”, directly after being filtered. Risks from cell salvage include infection and blood clotting problems. Intraoperative blood salvage and autotransfusion is contraindicated in cases of infection, malignancy and estimated blood loss of up to 500mL. Due to high costs associated with the technique, intraoperative cell saving seems suitable for revision surgery.

On the other hand, postoperative cell saving technique includes filtering shed blood which is collected after surgery and could be retransfused to the patient.^{19,59-61} Most cell saving systems consist of a collection and an autologous transfusion bag with filters to entrap blood clots and debris. Regularly, retransfusion of shed blood takes place within six hours after the end of surgery in order to avoid any febrile reactions and bacterial contamination.⁶² After six hours postoperatively, the system is used as regular low-vacuum drain.

In a randomised controlled study by Moonen et al.⁶⁰ patients treated with a postoperative cell saving system following total hip and knee arthroplasty had a significant reduction in allogeneic blood transfusions compared to controls treated with low-vacuum drains. This finding was in accordance with other studies^{59,61} which furthermore pointed out the relatively cheap, safe and easy application of the above system.

CONCLUSION

Ordering and transfusing allogeneic blood involves a complex decision-making process. Consideration should be given to the existing physiologic variables of the patient, the risks of disease transmission, other alternatives, as well as to the patient’s preferences. However, when clearly the blood is indicated administration should not be delayed, thus allowing prompt optimization of the patient’s physiologic states.

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CHAPTER 3

Limited use of blood products; success due to restrictive transfusion policy, education and awareness

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ABSTRACT

The orthopaedic surgery department of the Maasland hospital in Sittard, the Netherlands, has critically examined its blood management. Implementation of a restrictive transfusion policy, education, and awareness of the issue are important factors in the management of blood loss. Within 5 years, the implementation of a combination of different measures has led to a considerable reduction of 73% in the use of blood products. This reduction was attained while preserving the quality of health care given and without increase in complications. This article presents an overview of the implementation process regarding blood management in our orthopaedic surgery department.

INTRODUCTION

In the last few years several publications have argued for a selective transfusion policy. While participating in a study on the efficacy of erythropoietin we realized that a clear transfusion policy was lacking in our orthopaedic surgery department. Before 2000 the policy was quite liberal, and assessment was mainly subjective. Before implementing a new policy we retrospectively analysed a large group of patients with total hip (THP) and total knee prosthesis (TKP). On average 63% of all patients were administered at least one unit of erythrocyte concentrate (EC), usually based on the adage "one is none". Those who received blood were administered an average of 2.7 EC. Our analysis also showed that patients were frequently administered blood on the basis of subjective complaints such as paleness, weakness or fatigue, in some cases even on the third or fourth post-operative day and with a haemoglobin (Hb) level of >10.5 g/dL.

TRANSPARENT POLICY

Our participation in an international study on the efficacy of erythropoietin in moderate anaemia previous to major orthopaedic surgery prompted us to implement a transparent and modern transfusion policy.¹ This policy, formulated in collaboration with the department of anaesthesiology, set a transfusion trigger of 8.1 g/dL below which one EC could be administered. Postoperatively the anaesthesiologist could shift the trigger to 8.9 g/dL or in some cases to 9.7 g/dL. These adjustments were made on the basis of medical history (for instance a history of cardiac problems) and outcome of surgery. The transfusion trigger was allowed to decrease by half a point after approximately 48 hours if the patient had no relevant complaints. An extensive educational campaign was started for the nursing department and for the medical staff. A junior orthopaedic medical doctor monitored the implementation of the new policy in the orthopaedic department. After implementation, the percentage of patients who were administered blood had decreased to 25%, and transfused patients were given 2.3 EC on average.

LAPSE OF ATTENTION

In 2001 the amount of EC administered rose slightly, by 4% after correction for increased production (Fig. 1). The increase was attributed to slackening compliance with the restrictive transfusion policy. The policy received renewed

attention partially due to two new studies that started in 2002: a pilot study of a retransfusion system for wound blood and a study on the relation between declining exercise performance and post-operative Hb reduction.^{2,3} In addition, education emphasized the existence of alternatives for early administration of blood, such as optimizing fluid balance. Following the pilot study mentioned above, a randomised study of a retransfusion system was initiated in 2003 (Bellovac ABT, AstraTech AB, Mölndal, Sweden). The efficacy of the system had already been proven in a non-randomised study.⁴ The system permitted an average of 308 mL per patient to be retransfused. Interim evaluation of the transfusion policy showed that the number of ECs given per transfused patient had declined relative to 2000, the year the restrictive policy was implemented: the rule of thumb “one EC is no EC” was no longer practiced.

Figure 1. Amounts of transfused erythrocyte concentrates (EC)*

* Amounts of transfused erythrocyte concentrates during the implementation of our restrictive blood-use policy, related to the benchmark year 1999. Data are reported as percentages and corrected for the yearly increase in production of THA and TKA.

In 2004 the educational program for medical staff and nursing personnel was repeated. In addition, two projects were initiated to reduce the use of blood even further. In the first project, lasting three months, all blood transfusions given in the orthopaedic ward were reviewed in plenary. This resulted in a 41% reduction in ECs given to the same period of the previous

year. All blood transfusions given were evaluated using patient status research. Criteria such as symptoms, day of transfusion, Hb increase, and deviation from the established transfusion trigger were used to decide whether the transfusion had been justified, possibly justified or not justified. According to these criteria two-fifths of all transfusions were not justified.

COMPLICATIONS

Total use of blood was reduced by 64% in the described period relative to the year 1999 which we used as the benchmark. When the production increase of 31% was discounted, the total number of ECs administered had even declined by 73%. It is important to note that in this period the incidence of complications did not rise.⁵ Also, exercise tests on day 4 after surgery did not show any relevant anaemia-related ECG deviations during maximum effort.³

In addition to the implementation of the restrictive policy, two other important methods were adopted to reduce blood-use. Firstly, patients with moderate anaemia were prescribed erythropoietin before surgery. The indication for prescribing erythropoietin injections before major orthopaedic surgery was a preoperative Hb level of ≤ 13.0 g/dL. Four injections of 40,000 IE epoetin alfa (Eprex, Janssen-Cilag BV, Tilburg, the Netherlands) were given. Secondly, postoperative cell saving was accomplished using a retransfusion system (Bellovac ABT); as this system was used only for study purposes, the indication here was a preoperative Hb level of ≤ 14.5 g/dL. The percentages of patients treated with these methods are listed in table 1.

Table 1. Additional methods in blood management*

Method	Percentage of patients treated (%)					
	1999	2000	2001	2002	2003	2004
Preoperative erythropoietin injections (Eprex)	0	4	3	6	9	12
Postoperative retransfusion system (Bellovac ABT)	0	0	0	3	5	11

* Two additional alternatives, that is Eprex and Bellovac ABT, were used during implementation of restrictive blood-use policy

Because few patients in orthopaedic surgery qualify for a transfusion trigger of 6.4 g/dL, we decided in 2000 to exclude this criterion from the protocol. Firstly, this transfusion trigger is not or hardly applicable for major

orthopaedic surgery, as most patients are elderly and usually exhibit co-morbidities. Secondly, both the medical and the nursing personnel shared the intuition that it would be too risky to allow the Hb level to decline so deeply. In the near future our present policy may possibly be sharpened by implementing the CBO-flexinorm.

CONCLUSION

We conclude that attention for, and education on, blood management are the most important steps in reducing allogeneic blood use. Remarkably, the implementation of a restrictive transfusion policy in our orthopaedic ward took several years. Especially at the start the restrictive transfusion policy was received with apprehension, probably because of previous liberal policy. This defensive attitude relaxed through the years both in medical and in nursing personnel. It proved necessary to regularly repeat the educational program on transfusion policy. Eventually we accomplished a 73% reduction in the use of blood products within 5 years, while preserving the quality of health care given and without increase in complications.

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CHAPTER 4

The amount of haemolysis in retransfusion with the Bellovac ABT system in total hip and knee arthroplasty; a pilot study

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ABSTRACT

The potential risks of allogeneous blood transfusion have led to a more restrictive transfusion policy. One of the alternatives for allogeneous blood transfusion is postoperative cell saving. Using the Bellovac ABT system, wound blood is collected postoperatively during the first 6 hours, whereupon the blood will be returned to the patients.

All samples taken from the transfusion bags exhibited a free haemoglobin level below the critical level of 0.6 g/dL. A high LDH content was found, most probably as a result of tissue damage caused in the area of surgery.

Considering the absence of haemolysis in the transfusion bag the quality of cells in wound salvage blood can be assessed as good.

INTRODUCTION

Over the past few years, blood transfusion policy has attracted increased attention. As it turns out, donating allogeneous blood has more disadvantages than originally thought. Although the chances of contracting a transmissible disease, such as HIV or hepatitis, are very slim, immune reactions and a compromised immune system play an important part in blood transfusions.¹ In addition, the costs of allogeneous blood transfusions are rising due to stricter selection of donors and more extensive pre-treatment of donor blood, such as the depletion of leukocytes.

The need for a blood transfusion after major orthopaedic surgery (like total hip arthroplasty (THA) or total knee arthroplasty (TKA)) can best be predicted using the preoperative haemoglobin (Hb) level. Sixty-nine percent of patients with a preoperative Hb level of less than 13.0 g/dL need a blood transfusion. These odds are 15 times higher than for patients with an Hb level over 15.0 g/dL.²⁻⁵

Besides sharpening transfusion policy, alternatives for allogeneous blood transfusion are being developed.⁶ One of these is postoperative cell saving using the Bellovac ABT system. Postoperative wound blood is collected by means of a drain, filtered, and retransfused to the patient. Debris is removed from the blood by the double filter in the retransfusion system. Retransfusion remains controversial. While a number of studies have stated that it is a safe method, others have reported disadvantages as well.⁷⁻¹⁴

To gain an impression of the quality of retransfused blood, this study has focused on the amount of haemolysis in the transfusion bag.

MATERIALS AND METHODS

The study included 18 patients, of whom 12 had a THA and 6 had a TKA. Mean age was 68 years (range 53-77). Patients with systemic diseases such as rheumatoid arthritis were excluded. Immediately after surgery the retransfusion system (Bellovac ABT, AstraTech AB, Mölndal, Sweden) was connected to two deep wound drains using a Y-coupling. During the first 6 hours after surgery the wound blood was collected in a transfusion bag, passing through a macrofilter with a pore size of 200 µm. If this transfusion bag was filled with wound blood within 6 hours a second transfusion bag was added. Regardless of volume reclaimed, the bags were uncoupled 6 hours post-operatively at the latest. The remaining wound blood was then collected in a regular collector without filter.

One hour before retransfusion, 50 mL of blood was taken from the transfusion bag for further analysis. The critical threshold for retransfusion was

a free Hb level in accordance with the quality requirement for blood in erythrocyte concentrates (i.e. <0.6 g/dL) according to Sanquin.

Besides free Hb level, several other laboratory measurements were performed, including the concentrations of potassium, lactate dehydrogenase (LDH), fibrinogen, lactate, Hb, erythrocytes and leukocytes. In addition, bacteriological assessment was carried out. The results were compared with those for 5 allogeneous erythrocyte concentrates.

Free Hb count was established using the Haemocue haemoglobin system and a spectrophotometer; a Celdyne-4000 was used to determine Hb level and the concentrations of erythrocytes, leukocytes and fibrinogen; an Electra-1400 and Vetros-950 were used to determine the potassium, LDH and lactate concentrations. For the last 2 patients measurements were carried out at 2 different moments: wound blood for analysis was taken from the transfusion bag 3 and 5 hours after surgery.

Retransfusion was performed in those cases where more than 100 mL of wound blood was collected. During the retransfusion, the blood from the wound passed a microfilter with a pore size of 40 μ m. During and after the retransfusion patients were clinically monitored for any transfusion reactions, such as a rise in body temperature of 2°C or cold shivers.

RESULTS

The average amount of wound blood collected in the autologous retransfusion system was 325 mL (range 10-790). As some blood was taken from the transfusion bag for study purposes, an average of 275 mL was retransfused to the 14 patients from whom a sufficient volume of wound blood (>100 mL) had been collected; the other 4 patients were not retransfused.

Table 1 presents the measurement results for the wound blood in the transfusion bags, as well as for the 5 erythrocyte concentrates used in an allogeneous blood transfusion. All samples had free Hb level <0.6 g/dL. Concentrations of potassium and lactate were normal, while fibrinogen was barely detectable. Of note, the concentration of LDH was extremely high; one value reaching nearly 10.000 U/L. Haematocrit was low due to the low number of erythrocytes. Furthermore, the wound blood in the transfusion bag was not free of leukocytes. Bacteriological assessment did not show growth of aerobic or anaerobic micro-organisms in any of the cases.

Figure 1 shows the LDH concentrations in relation to the amount of wound blood collected in the Bellovac ABT system. A trend line has been drawn through all the measuring points. The LDH concentration appears to

Haemolysis in shed blood of retransfusion system

Table 1. Characteristics of shed blood samples and erythrocyte concentrates*

	Shed blood	Erythrocyte concentrates
Haemoglobin (g/dL)	9.3 (5.5-12.1)	20.6
Free Hb (g/dL)	0.27 (0.16-0.48)	<0.16
Haematocrit (L/L)	0.26 (0.14-0.34)	0.69
MCV (fl)	92 (86-100)	99
Erythrocytes ($10^{12}/L$)	2.83 (1.61-3.74)	7.0
Leukocytes ($10^9/L$)	2.9 (1.2-5.3)	<0.1
Potassium (mmol/L)	4.3 (3.4-5.5)	<1.0
LDH (U/L)	4025 (1030-9891)	158
Fibrinogen (g/L)	0.4 (0.0-0.9)	<0.1
Lactate (mmol/L)	3.1 (2.0-5.1)	>24.0

*Data are reported as mean (range). Shed blood samples were taken from the patients' wound blood collection bag using the Bellovac ABT retransfusion system. Erythrocyte concentrates were taken as controls.

Figure 1. Relation LDH concentration and amount of shed blood*

* Data are presented as the relation between amount of shed blood collected and LDH concentration. The regression line is based on analysis of all samples.

decrease with increasing amount of wound blood collected. The LDH level for the last two patients was measured at two different moments (3 and 5 hours after surgery) and showed a decrease in that period of time.

No transfusion reactions such as allergies, fever or symptoms of shock occurred in any of the patients during hospitalization.

DISCUSSION

A low free Hb level in transfusion blood is important in connection with the prevention of liver damage. Therefore, the collected wound blood has been tested against haemolysis parameters. All samples from this study had a free Hb level below the critical threshold as set for allogeneous blood products. This concurs with the results of previous studies, which also found low free Hb level in collected and filtered wound blood.¹⁰

Besides the free Hb level, the potassium concentration in the transfusion bag was also low. The free Hb and potassium level suggest that only a limited amount of haemolysis occurs in the wound blood. However, we also found extremely high concentrations LDH (an intracellular enzyme released in cell lysis). When this was noted during the research it was decided to perform two LDH measurements for the last 2 patients, at 3 and 5 hours after surgery; these measurements showed a decreasing LDH concentration. It seems plausible that in the first 3 hours a lot of LDH ends up in the transfusion bag as a result of tissue damage during surgery. In the hours that follow, the release of LDH seems to decline, which produces a diluting effect if wound blood production continues (Figure 1). We have not found studies in literature reporting measurements of LDH concentration in wound blood.

The amount of fibrinogen in the transfusion bag is low; this would suggest a low probability of thromboembolic complications. Retransfusing high lactate concentrations can increase load in both the pulmonary as well as the cardiovascular system. However, the lactate concentration in the wound blood is very low, which indicates there is not much cell activity in the transfusion bag.

It seems likely that the presence of leukocytes will not cause transfusion reactions as they are the body's own cells. Many questions remain about the role of interleukins in retransfusion. In particular, several studies have assessed the safety of retransfusions based on the interleukin concentrations in the transfusion bag.^{11,12} These measurements have not been carried out in our study, as we have focused on the amount of haemolysis.

Whether retransfusion is useful or not was not a subject of our research. However, from the literature on blood doping it is known that with normal Hb

level the administration of erythrocytes improves both oxygen intake capacity and endurance.¹⁵ It seems plausible that postoperative autologous retransfusion in patients with a high preoperative Hb level will increase postoperative Hb level. No connection has as yet been reported between Hb level and duration of hospitalization.¹⁶ However, with the accelerated rehabilitation programs presently used in orthopaedics, this connection could materialize. Further research is needed for establishing correct indication criteria.

In summary, it can be concluded that, considering the absence of haemolysis in the transfusion bag, the quality of the cells in the collected blood can be assessed as good. As such, it seems safe to return the collected wound blood to the patient without additional laboratory assessment. Further research will be necessary to determine the amount of postoperative Hb increase and the resulting decrease in the number of allogeneic blood transfusions. Additionally, the cost efficiency of the retransfusion system will have to be determined.

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CHAPTER 5

Filters in autologous blood retransfusion systems affect the amount of blood cells retransfused in total knee arthroplasty; a pilot study

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ABSTRACT

A pilot study was undertaken to evaluate whether filters integrated in postoperative retransfusion systems affect the amount of blood cells retransfused after total knee arthroplasty. Twenty-two consecutive patients received either the Donor retransfusion system (n=12 patients) or the Bellovac ABT retransfusion system (n=10). Both systems differ with respect to the type of filter, a Pall Lipiguard filter and a Sangopur filter, respectively. At the beginning of the retransfusion, blood samples were taken before and after the filter. The filter of the Donor system significantly decreased the amount of leukocytes and erythrocytes, whereas the filter of the Bellovac system did not. As a result the haemoglobin level of retransfused blood with the Donor system was significantly lower than with the Bellovac system.

It can be concluded that the type of filter integrated in two postoperative autologous blood retransfusion systems significantly affected the amount of blood cells retransfused in patients undergoing total knee arthroplasty.

INTRODUCTION

Blood loss during orthopaedic procedures may be extensive and may require transfusion of allogeneic blood. One of the alternatives to allogeneic blood transfusion is postoperative re-infusion of drained blood. In the Netherlands several postoperative cell saving systems are widely used in patients undergoing total knee arthroplasty (TKA). Currently, the Bellovac ABT retransfusion system is the system most used in the Netherlands, while the Donor retransfusion system is gaining popularity. Both the Bellovac and Donor systems are based on the same principle, namely postoperative collection of blood, filtration of shed blood and retransfusion of filtered autologous blood. Although both systems have the same principles, they differ with respect to the type of filter, suction pressure and handling procedures. The filter of the Donor retransfusion system is a Pall Lipiguard filter, and the filter of the Bellovac system is a Sangopur filter. In a recently published randomised study, So-Osman et al concluded that the Donor system and the Bellovac system were equal in efficacy and safety.¹⁰ Except for the amount of leukocytes, shed blood samples before and after filtering in both systems were comparable with regard to the amount of thrombocytes and the haemoglobin (Hb) level, but erythrocyte counts were not made.

This pilot study was designed to evaluate the filters integrated in the Donor and the Bellovac system with respect to the retransfused blood cells in patients undergoing TKA. The primary objective was to compare differences in the amount of leukocytes and erythrocytes after filtering in both postoperative retransfusion systems.

MATERIALS AND METHODS

From November 2006 to February 2007 all patients scheduled for elective TKA for primary osteoarthritis (OA) in our clinic were included in this prospective non-randomised observational pilot study. Patients with haematological diseases, coagulation disorders or with known malignancy or infection on admission and those with previous surgery to the joint were excluded. Other alternatives to allogeneic blood transfusions were not allowed. Known rheumatoid arthritis and former arthroscopy of the knee with meniscectomy were not exclusion criteria. After oral and written study information was given, informed consent was obtained.

Twenty-two patients were enrolled in the study. The first 12 patients were assigned to receive the Donor retransfusion system (van Straten Medical,

Nieuwegein, the Netherlands) and the next ten consecutive patients were assigned to receive the Bellovac ABT retransfusion system (AstraTech AB, Mölndal, Sweden). The Donor retransfusion system is a closed wound drainage system which consists of an 800 mL collection container for shed blood and a retransfusion system with an integrated Pall Lipiguard filter. This depth filter consists of a polyester screen media consisting of a cascade with variable pore size with the least size of 40 microns. The Donor system has a continuous pre-evacuated vacuum pressure of -150 mmHg during collection of shed blood. The Bellovac system consists of a suction bellow connected to a 500 mL collection bag for postoperative shed blood and a retransfusion system. Blood coming out of the wound first passes a filter of 200 microns before entering the collection bag and passes a Sangopur filter during retransfusion. The Sangopur filter consists of a gradual screen filter with a pore size of 80 and 40 microns. The vacuum pressure of the Bellovac system is intermittent with a maximum suction pressure of -90 mmHg.

All patients received an uncemented Scorpio TKA (Stryker Netherlands, Waardenburg, the Netherlands). Operations were done by three different surgeons, all experienced in joint replacement and using standard medial parapatellar arthrotomy. A tourniquet was used during surgery and was released after wound closure. One deep drain was placed at the end of surgery, and was connected to the retransfusion system after closure of the wound. Collection and retransfusion of postoperatively shed blood was in accordance to product guidelines by which all retransfusion occurred within six hours after surgery. The minimum amount of collected shed blood had to exceed 150 mL after which retransfusion occurred. The amount of collected and retransfused blood was recorded.

At the beginning of the retransfusion blood samples were taken out of the collection container (Donor) or bag (Bellovac) (T_1 , see table 2), and out of the retransfusion line connected to the patient during retransfusion (T_2 , see table 2). Once the blood samples had been taken, they were passed to the department of clinical chemistry and haematology for analysis. The following laboratory parameters were assessed: Hb, free Hb, haematocrit (Ht), mean corpuscular volume (MCV), erythrocytes, leukocytes, and thrombocytes using a Sysmex XE-2100 (Goffin-Meyvis, Etten-leur, the Netherlands).

Blood Hb levels were measured preoperatively and after surgery on Day 1 and 3 according to standard measurements in hospital policy by taking intravenous blood samples. Furthermore all allogeneic blood transfusions given to our population were in accordance to hospital policy (flexinorm, CBO consensus guidelines, 2004) that is based on the Hb transfusion trigger

depending on the American Society of Anaesthesiologist (ASA) classification and age. All allogeneic blood transfusions were recorded.

All complications, including possible transfusion reaction which occurred during admission were recorded.

Patients who used anticoagulation (acenocoumarol or acetylsalicylate) stopped their intake seven days preoperatively. All patients received low-molecular-weight heparin (nadroparin) for thrombo-embolic prophylaxis starting just before surgery and continuing six weeks postoperatively. The rehabilitation program conformed to standard hospital policy and discharge out of the hospital was planned at Day 5 after surgery.

The results were analysed statistically with the paired t-test for all blood sample measurements within the patients to analyse the effect of the filter. Different filtering rates, defined as the level before filtering minus the level after filtering, between both groups were analysed with the Student's test. A p-value less than 0.05 was considered indicative of a significant difference.

RESULTS

Twenty-two consecutive patients undergoing elective TKA were enrolled in the study. Their average age was 67 years (range 49-82). The proportion of females among the patients was perceptibly higher than the males in both groups. Details of the patient characteristics are presented in table 1. All patients were ASA 2 or 3 category and both groups were similar in terms of gender, age and preoperative Hb levels.

Table 1. Patient characteristics in both retransfusion groups*

	Donor (n=12)	Bellovac ABT (n=10)
Male / female	4 / 8	3 / 7
Age (yrs)	67 (49-82)	67 (55-79)
Preoperative Hb (g/dL)	14.0 ± 1.9 (11.8-17.1)	13.9 ± 1.5 (11.9-17.1)

* Values are presented as mean ± standard deviation (range)

In three patients blood samples were not taken out of the retransfusion system. In two of those three patients the amount of shed blood in the collection device six hours after surgery did not exceed 150 mL (one patient in both groups). In the third patient (Bellovac group) 200 mL of shed blood was

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collected but neither blood samples, nor retransfusion of shed blood took place, because the nurse was not familiar with the procedure. In total 19 blood samples were taken out of the collection device and out of the retransfusion line.

The average amount of collected blood was 449 ± 242 (SD; range, 40-800) mL in the Donor group and 334 ± 167 (SD; range, 40-600) mL in the Bellovac group (NS). As a result a little more blood was retransfused, after taking the blood samples, to the patients in the Donor group compared to the patients in the Bellovac group (445 mL versus 322 mL), although this difference was not statistically significant.

Blood sample analysis for both postoperative retransfusion systems is shown in table 2. Filtering shed blood with the filter in the Donor group

Table 2: Data of blood samples from shed blood before and after filtering

	Donor system (n=11)			Bellovac ABT system (n=8)			p-value
	T ₁	T ₂	Filtering	T ₁	T ₂	Filtering	
	Mean $\pm$ SD (Range)	Mean $\pm$ SD (Range)	rate Mean $\pm$ SD	Mean $\pm$ SD (Range)	Mean $\pm$ SD (Range)	rate Mean $\pm$ SD	
Haemoglobin (g/dL)	10.5 ± 1.8 (8.1-13.7)	8.9 ± 2.0 (6.6-12.2)	1.6 ± 1.0	10.8 ± 1.9 (6.9-13.0)	11.0 ± 2.5 (7.1-14.3)	-0.2 ± 1.4	0.004
Free Hb (g/dL)	0.16 ± 0.08 (0.0-0.5)	0.16 ± 0.07 (0.2-0.3)	0.0 ± 0.07	0.16 ± 0.05 (0-0.1)	0.16 ± 0.05 (0.2-0.3)	-0.01 ± 0.05	0.522
Haematocrit (L/L)	0.32 ± 0.05 (0.20-0.41)	0.28 ± 0.06 (0.21-0.38)	0.05 ± 0.03	0.33 ± 0.06 (0.21-0.38)	0.33 ± 0.07 (0.22-0.44)	0 ± 0.03	0.003
MCV (fl)	93 ± 4.3 (88-101)	93 ± 4.5 (88-101)	0 ± 0.63	96 ± 5.3 (87-104)	96 ± 5.3 (88-104)	0.1 ± 0.8	0.297
Erythrocytes ($10^{12}/L$)	3.5 ± 0.6 (2.8-4.6)	3.0 ± 0.7 (2.3-4.2)	0.5 ± 0.3	3.4 ± 0.7 (2.2-4.3)	3.5 ± 0.8 (2.2-4.6)	-0.1 ± 0.4	0.003
Leukocytes ($10^9/L$)	6.9 ± 1.8 (2.9-9.3)	3.0 ± 1.8 (0.4-5.3)	$4.3 \pm 2.0^*$	6.7 ± 2.2 (2.4-9.7)	6.5 ± 2.2 (2.3-9.1)	0.2 ± 0.7	<0.001
Thrombocytes ($10^9/L$)	42 ± 16 (25-64)	26 ± 10 (15-41)	16 ± 11	45 ± 13 (27-65)	45 ± 12 (28-67)	0 ± 4	<0.001

T₁ = Sample of collection device before filtering; T₂ = sample of retransfusion line after filtering (Pall Lipiguard filter in the Donor system, Sangopur filter in the Bellovac system) at beginning of retransfusion; filtering rate = difference between T₁ and T₂, defined as the level before filtering minus the level after filtering, in which a negative value means an increase of that value; SD = standard deviation; * = significant difference within patients; p-values are analysing different filtering rates between both groups.

showed a significant decrease in the amount of leucocytes by 56% (from 6.9 to $3.0 \times 10^9/\text{L}$), whereas after filtering with the filter in the Bellovac group this was only 3% (from 6.7 to $6.5 \times 10^9/\text{L}$). This filtering rate for leucocytes was significantly different between both groups ($p < 0.001$). Furthermore, the amount of erythrocytes in blood samples after filtration using the Donor filter was decreased by 16% (from 3.5 to $3.0 \times 10^{12}/\text{L}$), whereas it was not after filtration using the Bellovac filter (from 3.4 to $3.5 \times 10^{12}/\text{L}$). Again, this filtering rate for erythrocytes between both groups was significantly different ($p = 0.003$). The same counted for the filtering rate for thrombocytes between both groups, in which the Pall Lipiguard filter of the Donor system decreased the amount of thrombocytes from 42 to $26 \times 10^9/\text{L}$ (38%).

The Hb level of blood samples in the Donor retransfusion system decreased from 10.5 ± 1.8 g/dL to 8.9 ± 2.0 g/dL (NS), whereas the Hb level in the Bellovac system remained unchanged after filtering, i.e. from 10.8 ± 1.9 g/dL to 11.0 ± 2.5 g/dL (NS). On average, the filter in the Donor system caused a decrease in Hb of 1.6 g/dL, whereas there was no decrease in Hb using the filter in the Bellovac system. This difference in filtering rate for Hb between both groups caused by the difference in type of filter was significant ($p = 0.004$).

Among all blood samples the free Hb content remained under the critical level of 0.6 g/dL. The MCV of blood samples in the collection device as well as in blood samples after filtering had normal levels and was comparable to the MCV in blood samples taken from the patient.

Preoperative Hb levels in both groups did not differ, i.e. 14.0 ± 1.9 g/dL in the Donor group and 13.9 ± 1.5 g/dL in the Bellovac group (NS). On the first day after surgery, Hb levels had decreased in both groups, to 11.9 ± 1.5 g/dL in the Donor group and to 11.6 ± 2.1 g/dL in the Bellovac group (NS). At Day 3 after surgery, Hb levels further decreased to 10.8 ± 1.1 g/dL and 11.2 ± 2.4 g/dL in the Donor group and Bellovac group, respectively (NS). No patient in the Donor group received allogeneic blood transfusions compared to one patient in the Bellovac group who received two erythrocyte concentrates. No visible side-effects, allergic or haemolytic reaction occurred after retransfusion. In the Donor group one patient was readmitted one week after discharge because of a possible wound infection. Micro-organisms were not found in cultures. After clinical improvement oral antibiotics were stopped and the patient was discharged. In the Bellovac group one patient showed a small dehiscence of the wound, without clinical signs of infection. Due to observation of the wound the hospital stay was prolonged. No thrombo-embolic events occurred in the population.

DISCUSSION

This pilot study evaluated whether the type of filter integrated in two postoperative retransfusion systems affected the amount of blood cells retransfused in patients undergoing TKA. We have shown that patients treated with a retransfusion system received autologous shed blood with different constituents depending on the type of filter. This was shown by a significant reduction in the amount of leukocytes when using the filter as integrated in the Donor system. This reduction is in accordance with the result described in literature.^{2,10} Although both systems have filters with similar minimum pore size, filtering shed blood using the filter as integrated in the Bellovac system had no influence upon the amount of leukocytes retransfused. In the past, a few studies have been published in which the authors concluded that retransfusion of autologous shed blood alters the activity of the polymorphonuclear leukocytes.^{4,5} Although a positive effect of retransfusion is described⁹, the clinical effect of retransfusion of activated leukocytes is still unknown.⁸

Whereas the reduction of leukocytes was expected to occur using the Donor system, the reduction of both erythrocytes and thrombocytes was surprising as the average size of both blood cells is only 7.8 and 3.0 microns, respectively.⁶ Though erythrocytes pass through, the Lipiguard filter partly functions as a sponge as erythrocytes obviously are absorbed in this sponge since their concentration in the retransfused blood is reduced. Thereby, their primary function to recover blood is hampered. While So-Osman et al concluded that the Donor and Bellovac systems were equal¹⁰, our study showed significant differences in filtering rates for leukocytes, erythrocytes and thrombocytes between both retransfusion systems caused by the type of integrated filter.

As a result of the difference in the amount of erythrocytes, there was a difference in the Hb level in the blood samples in both systems. The filtering rate for Hb level, defined as the Hb level before filtering minus the Hb level after filtering, was significantly different in the Donor system compared to the filtering rate for Hb level in the Bellovac system. Therefore, it might be suggested that retransfusion of shed blood filtered by the Sangopur filter in the Bellovac system, causes a bigger increase of Hb level in systemic blood samples of the patients. Nevertheless, the systemic Hb levels were slightly lower at Day 1, but were higher at Day 3 after surgery in patients treated with retransfused blood from the Bellovac system compared to the Donor system. However, conclusions about differences in systemic Hb level after retransfusion in both systems can not be made because of small sample size. In addition, this

study was not designed to evaluate differences regarding the need for allogeneic blood transfusions in both systems.

The filter in the Bellovac retransfusion system appears beneficial because of an increased rate of retransfused blood cells. However, this interpretation is doubtful. The filter is supposed to reduce the amount of potential emboli sources by reducing emulsified fat, cell aggregates and debris. In our study none of the patients experienced any thrombo-embolic complications. However, no measurements were performed to objectivate possible effects.

Not only the kind of filter but also the suction drainage of Bellovac and Donor system differs. The American Association of Blood Banks (AABB) recommends a suction level for closed wounds no higher than 100 mmHg, because if the vacuum suction is set too high, red blood cells will be lysed.¹¹ In our study we have not found indications for haemolysis in both retransfusion systems, as shown by the low free Hb and normal MCV levels. Although suction pressure does not seem to be clinically relevant regarding haemolysis, it might be relevant regarding collecting shed blood volumes, since the calculated true Hb (volume * Hb concentration) in retransfused blood might be different in both systems, because there was a trend towards collecting more shed volume in the Donor system. However, the study of So-Osman et al showed opposite results by which the Bellovac system collected and re-infused more shed blood volume compared to the Donor system.¹⁰

Though several studies have shown the efficacy of different postoperative blood cell saving systems after TKA^{1,3,7,12}, larger sufficiently powered studies are necessary to compare retransfusion systems regarding presumed differences in shed volumes, systemic Hb level after retransfusion and differences in need for allogeneic blood transfusions.

In summary, using either a Donor retransfusion system or a Bellovac retransfusion system, blood with different amounts of blood cells was retransfused to the patient. The filter integrated in the Donor system significantly decreased the amount of leukocytes and erythrocytes. As a result the Hb level of retransfused shed blood with the Donor system was significantly lower than with the Bellovac system. It can be concluded that the type of filter integrated in two postoperative autologous blood retransfusion systems significantly affected the amount of blood cells retransfused in patients undergoing TKA.

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CHAPTER 6

Drain position in autologous blood retransfusion after total hip arthroplasty affects the amount of shed blood collected and retransfused; a prospective randomised clinical trial

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ABSTRACT

Background and purpose

Though the clinical efficiency of postoperative cell saving already was demonstrated after total joint arthroplasty, various amounts of shed blood are retransfused. This prospective randomised clinical trial was designed to evaluate the effect of the drain position as a possible confounding factor on the amounts of shed blood in patients treated with a retransfusion system after total hip arthroplasty.

Methods

One hundred patients were enrolled in the study and were randomly allocated into the intra-articular or into the subfascial group. The amount of collected and retransfused shed blood was recorded along with allogeneic blood transfusions.

Results

In the intra-articular group, on average, 349 mL of filtered shed blood was collected six hours after surgery whereas in the subfascial group 194 mL was collected ($p < 0.001$). As a result, significantly more blood was retransfused in the former group. The total amount of shed blood at drain removal at twenty-four hours after surgery was 518 mL and 311 mL in both groups respectively ($p < 0.001$). The allogeneic transfusion rate showed an equal percentage of 20% in either group.

Interpretation

We conclude that the intra-articular drain position collected more shed blood compared to the subfascial drain position in patients treated with a retransfusion system after total hip arthroplasty. However, there was no relationship between increased volume of shed blood retransfused and reduced need for allogeneic blood transfusion, raising the question whether the tamponading effect of post-surgical haematoma is counteracted by low-vacuum wound drainage when drains were removed at twenty-four hours after surgery.

INTRODUCTION

Prosthetic orthopaedic surgery is associated with considerable blood loss and blood transfusions are frequently necessary. The potential risks involved have stimulated the search for alternatives to diminish the use of allogeneic blood transfusions. A frequently used alternative is postoperative cell saving by using a retransfusion system. Though the clinical efficiency already was demonstrated after total joint arthroplasty, various amounts of shed blood are retransfused in patients after total hip arthroplasty (THA).¹⁻⁴ Considering drainage after THA, some surgeons prefer the intra-articular position of the drain while others prefer the subfascial position mainly based on different assumptions regarding infection risks. This difference in drain position seems to influence the amounts of collected blood indicating that the drain position of a retransfusion system is a possible confounder. As a result, this may influence the efficiency of the retransfusion system due to a possibly different need for allogeneic blood transfusions in these patients.

To our knowledge, there are no studies analysing the effect of the position of the drain on the amount of shed blood in patients treated with a retransfusion system. This prospective randomised clinical trial was designed to evaluate the effect of the intra-articular and subfascial drain position on the amounts of shed blood in patients treated with a retransfusion system after THA. Primary objective was to compare differences in the amounts of shed blood collected during the first operative day in both groups. Secondary objective was to evaluate the need for allogeneic blood transfusions in either group.

MATERIALS AND METHODS

Between June 2007 and May 2008, all patients scheduled for elective THA were selected for this prospective randomised clinical trial. Patients with haematological diseases, coagulation disorders or with known malignancy on admission were excluded. The use of other alternatives than postoperative cell saving to reduce allogeneic blood transfusions was excluded. Informed consent was obtained, and the study was approved by the local hospital ethics committee (Date of issue, May 21st 2007; Registration number, NL17352.096.07).

A total of one hundred patients were enrolled and all were randomly allocated to the intra-articular or subfascial groups by block randomization and sealed envelopes which were labelled with a consecutive case number from 1 to 100. At the end of surgery, just before wound closure, the envelope was opened and patients were assigned to one of the groups. As a consequence the drain was

placed in the intra-articular or subfascial position. The drain had a fixed manufactured length with 80 small holes in the last 13 centimetres of the drain. Until complete wound closure additional haemostasis was not further allowed. Then the drain was connected to the retransfusion system (Bellovac ABT, AstraTech AB, Mölndal, Sweden). This system comprises a suction bellow (intermittent vacuum pressure between 0 and -90 mmHg) connected to a transfusion bag with a 40- μ m filter. The filtered blood was returned either when the bag was full (500mL) or six hours postoperatively when the collected blood exceeded 100 mL. The amount of blood collected and retransfused (T_6) was recorded by blinded ward nurses. After retransfusion six hours after surgery, the system was used as a regular low vacuum drainage system. The additional shed blood collected was recorded at twelve (T_{12}) and at twenty-four (T_{24}) hours after surgery when all drains were removed independently of the production of shed blood.

Patients received an uncemented THA (ABG-II®, Stryker Netherlands, Waardenburg, the Netherlands) or cemented THA (Exeter®, Stryker) depending on their age. The operations were done by three different surgeons, all experienced in joint replacement. Patients on anticoagulants (acenocoumarol or acetylsalicylate) stopped these five days before surgery. All patients received low-molecular-weight heparin for thromboembolic prophylaxis starting after surgery and continuing for six weeks. Antibiotic prophylaxis was given fifteen minutes before operation followed by two more postoperative doses at eight and sixteen hours after surgery.

Before surgery haemoglobin (Hb) levels were obtained in all patients at screening three weeks prior to surgery by taking intravenously blood samples. After surgery the Hb levels were measured on the first and third days in both groups. Allogeneic blood transfusions were administered according to hospital policy. Postoperatively, the anaesthesiologist determined the Hb transfusion trigger that is 8.1 or 9.7 g/dL, depending on the ASA classification. All allogeneic blood transfusions were recorded. Complications including transfusion reactions, wound healing problems and wound infections were recorded. The rehabilitation program conformed to a standard policy, with discharge from hospital planned for five days after surgery. The length of follow-up varied from one to 12 months.

Before the study, a sample size calculation was performed based on unpublished data. An increase of 250 mL of retransfusion of shed blood was considered the smallest clinical difference. With the level set to 0.05 and the power at 0.80, it was calculated that forty-one patients were needed in each group. Compensating for dropout fifty patients per group were included. The results were analyzed statistically using Student's t-test for analyzing the differences in amounts of shed blood collected in both groups. The Fisher exact

test was used for testing the proportions of those receiving allogeneic blood transfusions. A p-value less than 0.05 was considered a significant difference.

RESULTS

Of the total of one hundred patients, five patients (4 intra-articular and 1 subfascial) were excluded since the amount of shed blood on the various moments of measurements was not recorded adequate. In total, an uncemented THA was performed in 86% (82/95) patients and a cemented THA in the others. There were no statistical differences between the groups in terms of age, gender, height, weight, preoperative Hb level, type of surgery, type of anaesthesia or postoperative transfusion trigger (Table 1).

Table 1. Patients and surgical characteristics*

Characteristic	Intra-articular group (n=46)	Subfascial group (n=49)
Age (years)	70 ± 8 (53-86)	69 ± 8 (47-82)
Sex (male/female)	16 / 30	17 / 32
Height (cm)	168 ± 9 (148-182)	169 ± 9 (150-190)
Weight (kg)	78 ± 15 (54-118)	81 ± 17 (55-128)
Preoperative Hb (g/dL)	13.8 ± 1.5 (11.1-17.4)	14.2 ± 1.3 (11.3-16.1)
Type of surgery (uncemented THA / cemented THA)	40 / 6	42 / 7
Type of anaesthesia (spinal / general)	43 / 3	48 / 1
Postoperative transfusion trigger (g/dL)	8.4 ± 0.7 (8.1-9.7)	8.4 ± 0.7 (8.1-9.7)

* Data are reported as mean ± SD (range). There were no significant differences between both groups.

Retransfusion and allogeneic transfusions

In the intra-articular group, a mean of 349 ± 195 mL (SD; range, 50-1000) of filtered shed blood was collected at T6 whereas in the subfascial group, a mean of 194 ± 157 mL (SD; range, 0-500) was collected six hours after surgery ($p < 0.001$) (Fig. 1). The total amount of shed blood was 518 ± 281 mL (SD; range, 70-1500) and 311 ± 248 mL (SD; range, 0-900) when the drain was removed in both groups respectively ($p < 0.001$). This mend that two-thirds (349/518 mL in the intra-articular group and 194/311 mL in the subfascial group) of the total amount of shed blood was collected at T₆. More than 85% (462/518 mL versus 266/311 mL) was collected within the first twelve hours in either group (Fig. 1) compared to the total drainage at 24 hours after surgery.

Figure 1. Perioperative Hb level*

* Data are reported as average amounts of shed blood collected at various moments of measurements. T₆ = collected till six hours after surgery. T₁₂ = additional amount collected between six and twelve hours after surgery. T₂₄ = additional amount collected from twelve hours after surgery till drain removal at twenty-four hours after surgery. Statistical significant differences between both groups are indicated by §.

Retransfusion was not started in some patients. One patient in the subfascial group did not receive shed blood because the system was disconnected. In addition, the percentage of patients in which the amount of shed blood did not exceed the 100 mL threshold six hours after surgery was 4% (2/46) in the intra-articular group and 41% (20/49) in the subfascial group. In all the other patients a retransfusion was started. As a result, the average amount of retransfused blood was significantly different in either group, that was 343 mL versus 168 mL (p<0.001).

In the intra-articular group 20% (9/46) of the patients received at least one allogeneic blood transfusion compared with 20% (10/49) in the subfascial group. Of all these transfused patients, five in either group had a preoperative Hb level below 13.0 g/dL at screening.

Hb levels

The preoperative levels of Hb were a mean of 13.8 ± 1.5 g/dL (SD; range, 11.1-17.4) in the intra-articular group and 14.2 ± 1.3 g/dL (SD; range, 11.3-16.1) in

the subfascial group. The number of patients with preoperative Hb levels below 13.0 g/dL was 24% (11/46) and 14% (7/49) in both groups respectively.

On the first day after surgery the Hb levels had decreased to 11.0 ± 1.3 g/dL (SD; range, 8.2-14.0) in the intra-articular group and to 11.0 ± 1.2 g/dL (SD; range, 8.4-13.2) in the subfascial group. By the third day the levels had decreased to 10.2 ± 1.7 g/dL (SD; range, 6.1-13.2) in the intra-articular group and to 10.5 ± 1.3 g/dL (SD; range, 7.6-13.2) in the subfascial group. These reductions were not significantly different between both groups.

Complications

No transfusion reactions were observed. The total number of clinical complication was similar among both groups. In three patients assigned to the intra-articular group and in two patients assigned to the subfascial group, a deep wound infection was recorded. After early surgical debridements none of the prosthesis needed to be removed in these patients. In one patient in the subfascial group the THA was dislocated which was treated with an abduction brace after closed reduction. Two patients, one in either group, had a periprosthetic fracture after a fall during follow up. Both patients were treated with surgical osteosyntheses.

DISCUSSION

Though the clinical efficiency of a retransfusion system already was demonstrated after total joint arthroplasty, various amounts of shed blood retransfusions are reported.¹⁻⁴ The drain position as a possible confounder is supposed since our results showed that patients treated with an intra-articular position of the drain had a significant higher amount of shed blood compared to patients treated with a subfascial drain. As significantly more shed blood was retransfused to patients in the intra-articular group it was expected that less patients in this group would need allogeneic blood. However, an equal transfusion rate was found in either group. A possible explanation can be the additional blood loss in the period after retransfusion since the additional amount of drained blood was higher in patients with the intra-articular drain position compared to the subfascial drain position in the period beyond six hours after surgery. By this, the purpose for prolonged drainage of the wound after retransfusion at six hours after surgery can be discussed. To illustrate, in accordance to a large meta-analysis incorporating 3495 patients it was suggested that drainage in total joint arthroplasty enhances blood loss since active drainage for twenty-four to forty-eight hours was associated with a greater need for allogeneic blood transfusions compared to treatment without

drains.⁵ However, their conclusion that routine use of wound drainage may be more harmful than beneficial has to be interpreted with caution since the included studies showed an overall transfusion rate of 40% in patients treated with a drain indicating a liberal transfusion policy. Nowadays a more restrictive transfusion policy is used as is performed in our study. Still, our transfusion rate was 20% independent of the position of the drain. This high rate is partly explained by a large number of included patients with preoperative Hb levels below 13.0 g/dL since it was concluded in literature that these patients have more chance in receiving allogeneic blood.⁶

The preference of surgeons for the intra-articular or subfascial drain position is mainly based on different assumptions regarding infection risks. Theoretically, low vacuum drainage will evacuate a developing haematoma from the operative field and promote wound healing by providing less culture medium for infections.^{7,8} Drains may, however, act as an entry route for bacteria into the wound.^{9,10} It has been concluded that if drainage is maintained for more than 12 hours, there is an increased risk of contamination of the drain by bacteria. No organisms were isolated from samples of the drain tip at 12 hours. However, at 24 hours, 17% of the drain tips yielded bacterial growth.¹¹ In our study five patients (3 intra-articular and 2 subfascial) developed a deep infection. The high infection rate was reason of concern. As we did not culture the tip of the drain after removal a causal relation could not be proved. Nevertheless, with reference to the infection risk, it makes sense to consider earlier drain removal than twenty-four hours after surgery. In addition, regarding evacuating the haematoma, nothing is to be gained by continuing drainage beyond 12 hours since our results showed that less than 15% of the total amount of drained blood is collected in that period. It is not considered that the additional drained volume over the second 12 hour period, which is approximately 50 ml, is sufficiently large to constitute a risk to wound healing. Therefore, further studies to determine when to remove the drain of a retransfusion system following THA, are needed.

In conclusion, the intra-articular drain position collected more shed blood compared to the subfascial drain position in patients treated with a retransfusion system after THA. However, there was no relationship between increased volume of shed blood retransfused and reduced need for allogeneic blood transfusion, raising the question whether the tamponading effect of post-surgical haematoma is counteracted by low-vacuum wound drainage when drains were removed at twenty-four hours after surgery.

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CHAPTER 7

Retransfusion of filtered shed blood in primary total hip and knee arthroplasty; a prospective randomised clinical trial

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ABSTRACT

Background

Allogeneic blood transfusions are associated with a number of well-recognised risks and complications. Postoperative retransfusion of filtered shed blood is an alternative to (reduce) allogeneic blood transfusion. The objectives of this study were to evaluate the clinical efficacy of retransfusion of filtered shed blood and to evaluate the complications, in particular febrile reactions.

Study design and methods

In this clinical trial 160 patients undergoing primary total hip or knee replacement were randomly assigned to receive either a retransfusion system (Bellovac, AstraTech AB) or a regular drain (Abdovac, AstraTech AB). Patients with a preoperative hemoglobin (Hb) level between 13.0 and 14.6 g/dL were included. The shed blood was returned 6 hours after operation. After surgery the anaesthesiologist determined the transfusion trigger. When Hb level dropped below this trigger, an allogeneic blood transfusion was given. The following data were obtained: number of allogeneic blood transfusions, total volume of blood collected in the bag used for retransfusion, perioperative Hb levels, febrile reaction, and other complications.

Results

In the control group 19 percent of the patients received at least one allogeneic blood transfusion. In the study group this percentage was 6 percent of the patients ($p=0.015$). Comparing total knee and total hip arthroplasty (control vs. study) the percentages were, respectively, 16 percent versus 2 percent ($p=0.040$) and 21 percent versus 11 percent (NS). On average 308 mL filtered shed blood was retransfused in the study group. In the study group 18 percent of patients had febrile reactions compared to 20 percent in the control group.

Conclusion

Postoperative retransfusion of filtered shed blood is effective for decreasing allogeneic blood transfusions after total hip and knee arthroplasty. There was no relationship between retransfusions and postoperative febrile reactions.

INTRODUCTION

Prosthetic surgery is associated with considerable blood loss, and allogeneic blood transfusions are frequently necessary. Allogeneic blood transfusion are associated with a number of well-recognised risks, with serious complications like transfusion related acute lung injury, which can cause death after an allogeneic blood transfusion.^{1,2} Other hazards include allergic reactions, transmission of infectious agents, and immunomodulatory effects.^{1,2} All these potential risks of allogeneic blood transfusions have lead to a more restrictive transfusion policy. Besides the restrictive policy several interventions to diminish the use of allogeneic blood are commonly in use. Frequently used alternatives are preoperative epoetin alfa injections,³⁻⁵ preoperative autologous blood donation,⁶⁻⁸ and perioperative^{9,10} and postoperative cell saving.^{11,12} Although algorithms to reduce allogeneic blood transfusions are published,¹³ it is still unknown which intervention or combination of measures is most successful. Of all methods, postoperative cell saving with a retransfusion system of filtered shed blood is a relatively cheap and easy method.

Blood collected from surgical wounds, however, contains large concentrations of inflammatory mediators,¹⁴ which are believed to mediate febrile reactions.¹⁵ Although the safety of retransfusion of filtered shed blood was disputed in the past,¹⁶⁻¹⁸ retransfusion is considered safe nowadays.¹⁹⁻²¹

The clinical efficacy has previously been described in comparison with a historic cohort¹¹ but large randomised clinical trials are lacking. This randomised clinical trial was designed to evaluate the clinical efficacy of retransfusion of filtered shed blood by defining the proportion of patients receiving allogeneic blood transfusions. Furthermore, postoperative hemoglobin (Hb) levels and possible complications, in particular febrile reactions, were evaluated.

MATERIALS AND METHODS

We undertook a prospective randomised clinical trial involving 160 patients undergoing consecutively scheduled primary total knee (TKA) or total hip arthroplasty (THA). Patients gave their informed consent after receiving oral and written patient information. Our hospital ethical committee approved the study.

Patients with a preoperative Hb level between 13.0 and 14.6 g/dL were included. Other inclusion criteria were no severe heart disease, no immunocompromised disease, no chronic renal failure, and a low risk of thromboembolism. The use of other alternatives than postoperative cell saving to (reduce) allogeneic blood transfusions was excluded.

Before surgery all 160 patients were randomly allocated into a retransfusion group with a postoperative retransfusion system (Bellovac ABT, AstraTech AB, Mölndal, Sweden) or into a control group with a regular postoperative low-vacuum drain (Abdovac, AstraTech AB). A treatment allocation schedule was randomly generated and then concealed in sealed envelopes that were labeled with a consecutive case number from 1 to 160. Blocking and stratification were not used.

At the end of surgery, two Redon lines were placed, one intra-articular and one subcutaneous. Both lines were connected to a Bellovac retransfusion system or Abdovac system. The Bellovac retransfusion system consists of a collection suction bellow (-90 mmHg), which was vacuumed for 6 hours after surgery, and an autologous transfusion bag with a 200-µm filter to entrap blood clots and debris. Before retransfusion the blood was let through a 40-µm filter. Reinfusion of shed blood was started 6 hours after the end of surgery when the collected blood exceeded 100 mL or when the transfusion bag was full (500 mL), whichever occurred first. After 6 hours postoperatively the system was used as regular low-vacuum drain like the Abdovac system in which collected blood was discarded.

Patients who used anticoagulation (i.e., acenocoumarol or acetylsalicylate) stopped their intake 7 days preoperatively. All patients received low-molecular-weight heparin for thromboembolic prophylaxis, starting just before surgery and continuing 6 weeks postoperatively.

After surgery the anaesthesiologist determined the Hb transfusion trigger, that is, 8.1, 8.9, or 9.7 g/dL, depending on comorbidity classified in the ASA classification and according to hospital policy (Table 1). When Hb level dropped below this trigger an allogeneic blood transfusion was given.

Table 1. Criteria for transfusion trigger

Hb level, 8.1 g/dL (study, n=50; control, n=49)
ASA* 1
ASA 2 and 3, and uncomplicated surgery
Hb level, 8.9 g/dL (study, n=29; control, n=30)
ASA 2 and 3, and significant blood loss during surgery (more than 500 mL)
Hb level, 9.7 g/dL (study, n=1; control, n=1)
ASA 2 and 3, and minor complications during surgery (i.e., ST deviation on electro cardiogram)
ASA 4

* ASA = classification according to the American Society of Anaesthesiologist

The following data were obtained in both groups: number of allogeneic blood transfusions, total volume of blood collected in the bag used for retransfusion, Hb levels (i.e., preoperative and postoperative on Days 1, 3, and 5), complications, and febrile reaction (i.e., any increase in body temperature above 38.0°C). Body temperature was recorded twice daily until patients were discharged. When patients received allogeneic blood or shed blood, body temperature was measured according to hospital protocol, i.e., just before starting, just after starting, during, and after (re-)transfusion.

Primary outcome was the proportion of patients receiving at least one allogeneic blood transfusion in the postoperative period. Secondary outcomes were postoperative Hb levels and complications, in particular febrile reactions.

Before the study a power analysis was performed. The sample size of the study was calculated with retrospective data from our orthopaedic department²² showing that 35 percent of the controls and 15 percent of the study group would need a transfusion. With alpha level set to 0.05 and a power of 0.80, it was calculated that 74 patients per group were needed. Compensating for dropout 80 patients per group were included. The results were analysed statistically using the Fisher exact test for testing proportions in receiving allogeneic blood transfusions. Other results were analysed with the t test. A p value less than 0.05 was considered a significant difference. Adjustment for multiple tests of significance was not made.

RESULTS

A total of 160 patients were enrolled in the study, 80 in each group. There were no significant differences between both groups regarding age, body mass index, type of surgery, type of anaesthesia and transfusion trigger (Table 2). Interestingly, comparing type of surgery, a marked asymmetry between study group and control group was seen, that is, more THA in the study group and more TKA in the control group.

Of all patients, a primary TKA was performed in 52 percent (83/160) and primary THA in 48 percent (77/160). In most patients (88%) spinal anaesthesia was used; others had general anaesthesia.

A few inclusion failures occurred. Five patients with higher preoperative Hb levels than 14.6 g/dL were included. In the study group three patients had an Hb level of 14.8 g/dL and one had a level of 15.0 g/dL. In the control group, one patient had a preoperative Hb level of 15.5 g/dL. All patients were included for further evaluation according the intension-to-treat principle.

Hb transfusion triggers were determined by the anaesthesiologist after

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Table 2. Patient and surgical characteristics*

Characteristic	Study (n=80)	Control (n=80)
Age (years)	69.0 ± 9.5 (36-83)	69.5 ± 7.3 (52-83)
Sex (male/female)	10/70	13/67
Body mass index (kg/m ²)	28.9 ± 4.8 (21-40)	27.7 ± 4.6 (19-38)
Type of surgery (THA/TKA)	45/35	32/48
Type of anaesthesia (spinal/general)	72/8	68/12
Transfusion trigger (g/dL)	8.4 ± 0.41 (8.1-9.7)	8.4 ± 0.41 (8.1-9.7)

* Data are reported as mean ± SD (range). Patients in the study group were using a postoperative retransfusion system (Bellovac ABT) and patients in the control group were using a postoperative low-vacuum drain (Abdovac). There were no significant differences between both groups.

surgery. The mean transfusion trigger in both groups was 8.4 g/dL (Table 2). Fifty patient in the study group and 49 patients in the control group had a transfusion trigger of 8.1 g/dL. Allogeneic blood transfusions were performed when the Hb level dropped below the trigger of 8.9 g/dL in 29 patients in the study group and 30 patients in the control group. In both groups there was one patient with a transfusion trigger of 9.7 g/dL.

Retransfusions and allogeneic transfusions

In the control group 19 percent (15/80) of the patients received at least one allogeneic blood transfusion. In the study group this percentage was 6 percent (5/80) of the patients. This was a significant difference ($p=0.015$). Comparing TKA (control vs. study) the percentages were, respectively, 16 percent (5/32) versus 2 percent (1/45), which was also a significant difference ($p=0.040$). In THA the percentages were 21 percent (10/48) versus 11 percent (4/35), which was not significant.

On average, 308 ± 193 (SD; range, 0-850) mL of filtered shed blood was retransfused in the study group. In TKA, on average, 378 mL was retransfused versus 203 mL in THA.

According to hospital policy, patients were transfused with allogeneic blood transfusions based on the determined Hb transfusion trigger. The five patients in the study group who received allogeneic blood transfusions were transfused with 2.2 units on average (range, 1-4 units) compared to the 15 patients in the control group who received 1.5 units on average (range, 1-3 units; NS).

In six patients randomly assigned to the Bellovac system, retransfusion was not

completed due to several reasons. In three of these cases, the Abdovac system was used instead of the Bellovac system; in two cases the quality of the shed blood was considered dubious and therefore not retransfused. In one patient 6 hours after surgery was expired so the blood was not returned to that patient.

Hb levels

Preoperative Hb levels were on average 14.0 ± 0.44 (SD; range, 13.2-15.0) g/dL in the study group and 14.0 ± 0.43 (SD; range, 13.2-15.5) g/dL in the control group (Fig. 1). On the first day after surgery, Hb levels had decreased in both

Figure 1. Course of perioperative Hb levels*

* Patients in the study group (◆) were using a postoperative retransfusion system (Bellovac) and patients in the control group (■) were using a postoperative low-vacuum drain (Abdovac). Standard deviation is printed as error bars (± 1 SD). There were no significant differences between both groups.

groups, that is, to 10.5 ± 1.1 (SD; range, 8.0-13.5) g/dL in the study group and to 10.1 ± 0.96 (SD; range, 7.7-13.2) g/dL in the control group. On Day 3 after surgery, Hb levels even decreased to 9.9 ± 1.2 (SD; range, 6.9-13.5) g/dL in the study group and to 9.6 ± 1.2 (SD; range, 6.7-12.2) g/dL in the control group. At Day 5, the Hb level increased to 10.1 ± 1.2 (SD; range, 7.2-13.4) g/dL in the study group and to 9.9 ± 1.1 (SD; range, 7.5-12.6) g/dL in the control group. There were no significant differences between both groups.

Febrile reactions

Febrile reaction was defined as an increase in body temperature above 38.0°C. In the study group 18 percent (14/80) of patients had febrile reactions. Almost the same percentage was found in the control group, that is, 20 percent (16/80). Patients with a retransfusion of more than 500 mL shed blood showed a percentage febrile reaction of 20 percent (4/20).

In the study group, one patient who did receive a retransfusion of 750 mL had a body temperature of 39.2°C. His temperature at the start of the retransfusion was already 38.9°C. Because this increase measured only 0.3°C, the elevated temperature was considered to be a febrile reaction but not a transfusion reaction.

Complications

The total amount of clinical complications was similar among both groups (Table 3). There were two patients with deep wound infections, one in each group. Both had surgical debridement and eventually the prosthesis needed to be removed in both patients. No thromboembolic events occurred in the population. No allergic reactions or haemolytic reactions were seen. A minimal difference was found in terms of haematoma, prolonged discharge of the wound, and superficial wound infections, that is, seven patients in the study group versus four in the control group (NS).

Table 3. Clinical complications*

Complication	Study (n=80)	Control (n=80)
Superficial wound problem	7 (8.8)	4 (5.0)
Deep wound infection	1 (1.3)	1 (1.3)
Cardiovascular	3 (3.8)	4 (5.0)
Neurological	1 (1.3)	0
Gastrointestinal	0	2 (2.5)
Total	12 (15)	11 (13.8)

* Data are reported as number (%). Superficial wound problem included haematoma, prolonged discharge of the wound and superficial wound infections. Both deep wound infections led to removal of the prosthesis. Cardiovascular complications included angina pectoris and cardiac arrhythmias. The neurological complication was a neuropraxia of the superficial peroneal nerve. Gastrointestinal complications were defined as dyspepsia. There were no significant differences between both groups.

DISCUSSION

In this study we have shown that patients treated with a postoperative retransfusion system (Bellovac) after TKA or THA had a significant reduction in allogeneic blood transfusions compared to controls treated with regular postoperative low-vacuum drains (Abdovac). This was shown by a significant absolute risk reduction of 13 percent (19% to 6%) in allogeneic blood transfusions (Table 4).

Table 4. Risk reduction (%) of receiving at least one allogeneic blood transfusion*

Group	ARR	p Value	RRR	NNT
Total group	13 (19-6)	0.015	68%	7.7
TKA	14 (16-2)	0.040	88%	7.1
THA	10 (21-11)	0.204	48%	10

* Significant differences between both groups are given. ARR = absolute risk reduction; RRR = relative risk reduction; NNT = numbers needed to treat

Nowadays most hospitals use restrictive transfusion triggers due to the awareness of risks and complications of allogeneic blood transfusions.^{1,2} This awareness and restrictive policy might be the most important factor in reducing allogeneic blood transfusions. The liberal policy with variable Hb transfusion triggers used in the past is a major confounding factor in retrospective studies or studies with historical cohorts. Owing to the many recent developments in blood management, new prospective randomised studies are needed. Therefore our prospective randomised clinical trial provides valuable information without the previously mentioned confounding factor. Patients in our study were transfused according to hospital transfusion policy, which is based on current Dutch consensus in blood management policy.

Recently, the efficacy of a retransfusion system was shown by Strümper and coworkers.¹¹ Compared to a historical cohort, they reported a reduction from 35 to 22 percent for patients treated with a postoperative retransfusion system (Bellovac). This reduction was most pronounced in TKA (19% to 6%). We also noticed a significant reduction in allogeneic blood transfusions. Our reduction is in accordance with their findings; the overall results are not. The transfusion rate in our control group is even below the transfusion rate in the intervention group reported in the study of Strümper and coworkers.¹¹ The low

percentage allogeneic blood transfusion seen in our control group (19%) shows the restrictive transfusion policy based on the current Dutch consensus. But on top of this restrictive policy, a high relative risk reduction (RRR) of 68 percent was seen in patients who received a retransfusion of filtered shed blood (Table 4). In TKA this reduction was even more pronounced, i.e., relative risk reduction of 88 percent. The absolute risk was decreased to only 2 percent. We also saw a clear absolute risk reduction in THA treated with the Bellovac system (i.e., 21% to 11%).

As mentioned before, there was a marked asymmetry between study group and control group in terms of the type of operation carried out. If treatment allocation had been stratified by the type of operation, this asymmetry would have been minimized. The observed imbalance by treatment group for the type of operation could have biased the study results; however, such a bias would be in favour of the control group. In this study, all TKAs were performed under tourniquet. Less blood loss was seen during surgery, but more blood was collected after surgery. Because of the low number of TKAs in our study group, less shed blood was retransfused compared to our control group. Therefore, the actual difference between study and control group might be underestimated and barely have any consequences for the validity of the results obtained.

By use of different determined Hb transfusion triggers (i.e., 8.1 or 8.9 or 9.7 g/dL), we were able to include a rather heterogeneous group of patients reflecting a normal population undergoing primary TKA and THA.

Interpreting the differences in course of Hb levels postoperative in both groups is difficult because there are significantly more allogeneic blood transfusions in the control group, which increases the Hb level. At the same time, the amount of blood collected in the Bellovac retransfusion system (i.e., 308 mL on average) was relatively small to increase Hb levels significantly. Therefore, we believe that the postoperative retransfusion system (Bellovac) was effective in reducing allogeneic blood transfusions but not useful in trying to reach high postoperative Hb levels. This is in accordance with the study of Pilot and colleagues²³ in which they concluded that aiming for high postoperative Hb level to enhance recovery is not useful.

In this trial we included only patients with preoperative Hb levels between 13.0 and 14.6 g/dL. Because preoperative Hb level is a good predictor for postoperative transfusion needs,²⁴ it is known that patients with Hb levels above 14.6 g/dL have less chance in receiving any allogeneic blood transfusion. If we would have included patients with Hb levels above 14.6 g/dL, the population at risk would be relatively smaller and a much larger study population would have been needed to have sufficient power. If patients have

preoperative Hb levels of below 13.0 g/dL, they routinely receive epoetin alpha (Eprex) injections in our hospital. To prevent potential bias, no other alternatives than postoperative cell saving to reduce allogeneic blood transfusions were allowed. The clinical efficiency of use of a postoperative retransfusion system in patients with preoperative Hb levels of below 13.0 g/dL should be demonstrated in the future.

As shown, five patients were enrolled in the study who should not have been included according to the inclusion criteria. In the study group there were four preoperative Hb levels of just above 14.6 g/dL (i.e., range, 14.8-15.0 g/dL). In the control group, one preoperative Hb level was much higher than this level for inclusion (i.e., 15.5 g/dL). All patients were used for analysis based on the intention-to-treat principle. We believed that those few inclusion failures were not of influence on the overall results.

Postoperative febrile reactions are general reactions seen in major orthopaedic surgery. Our results show that there is no difference in developing febrile reactions with a postoperative retransfusion system (Bellovac) or use of a regular postoperative low-vacuum drainage system (Abdovac). In both groups almost the same percentages of patients with febrile reactions were found, that is, 18 percent in the study group versus 20 percent in the control group. Also, retransfusion of more than 500 mL of filtered shed blood did not increase this percentage. Several studies imply an important role of cytokines when returning filtered shed blood.^{14,15} Although our study did not measure cytokines, the absence of an increase in febrile reactions probably shows that the meaning of those cytokines when returning shed blood remains disputed.

Comparing the total amount of complications in both groups, there were no differences although the study was not powered to detect differences in such complications. In combination with the absence of an increase in febrile reactions, we consider the Bellovac retransfusion system to be safe. Long-term effects remain to be seen, especially regarding the immunomodulatory influence of receiving autologous shed blood. This effect should cause fewer wound healing problems. Although the overall complication rate was similar between groups, there was a difference regarding complications in terms of wound healing problems, haematomas, and infections (study group, eight; control group, five), which, however, was not significant.

In summary, we conclude that postoperative retransfusion of filtered shed blood in primary TKA and THA is an effective and safe way to decrease allogeneic blood transfusions. In TKA the use of allogeneic blood can almost be reduced to nil. Furthermore, there was no relationship between postoperative retransfusion of filtered shed blood and postoperative febrile reactions or other complications.

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CHAPTER 8

Preoperative injections of epoetin alpha versus postoperative retransfusion of autologous shed blood in total hip and knee replacement; a prospective randomised clinical trial

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ABSTRACT

This prospective randomised clinical trial evaluated the effect of alternatives for allogeneic blood transfusions after total hip replacement and total knee replacement in patients with preoperative hemoglobin levels between 10.0 g/dL and 13.0 g/dL. A total of 100 patients were randomly allocated to the Eprex (preoperative injections of epoetin) or Bellovac groups (postoperative retransfusion of shed blood). Allogeneic blood transfusions were administered according to hospital policy.

In the Eprex group, 4% of the patients (two patients) received at least one allogeneic blood transfusion. In the Bellovac group, where a mean 216 mL (0 to 700) shed blood was retransfused, 28% (14 patients) required the allogeneic transfusion ($p=0.002$). When comparing Eprex with Bellovac in total hip replacement, the percentages were 7% (two of 30 patients) and 30% (nine of 30 patients) ($p=0.047$) respectively, whereas in total knee replacement, the percentages were 0% (0 of 20 patients) and 25% (five of 20 patients) respectively ($p=0.042$).

Preoperative epoetin injections are more effective but more costly in reducing the need for allogeneic blood transfusions in mildly anaemic patients than postoperative retransfusion of autologous blood.

INTRODUCTION

Operations for major joint replacement frequently require blood transfusion. The potential risks involved have stimulated the search for alternatives, such as preoperative injections of epoetin alpha¹⁻⁴ and postoperative cell saving.⁵⁻⁸ In spite of algorithms to reduce allogeneic blood transfusions,⁹ it is not known which intervention or combination of measures is most successful.

Preoperative injections of epoetin alpha have been shown to reduce the need for allogeneic blood transfusions by increasing the preoperative haemoglobin (Hb) level in patients whose baseline lay between 10.0 g/dL and 13.0 g/dL.^{2,4} One prospective randomised study⁴ showed that only 12% of patients treated with injections of epoetin alpha received at least one blood transfusion, compared with 46% in the control group. Postoperative retransfusions with autologous blood have been shown to reduce the requirements for allogeneic transfusion in patients who did not have preoperative anaemia. A prospective randomised study concluded that patients treated with a postoperative cell saving system had a significant reduction in transfusions of allogeneic blood compared with controls,⁷ as was evidenced by an absolute risk reduction from 19% to 6%. However, in that study, all patients had preoperative Hb levels between 13.0 g/dL and 14.5 g/dL.

After a Pubmed search¹⁰ (MeSH terms Blood Transfusion, Autologous, Erythropoietin, Recombinant) we found no randomised studies which compared preoperative injections of epoetin and postoperative cell saving. We therefore carried out a prospective randomised trial designed to evaluate the use of a relatively cheap postoperative retransfusion system in patients with preoperative Hb levels between 10.0 g/dL and 13.0 g/dL, compared with using expensive preoperative injections of epoetin alpha. Our aim was to compare the differences in the need for allogeneic blood transfusions in both groups.

PATIENTS AND METHODS

Between June 2006 and October 2007, all patients scheduled for elective total hip replacement (THR) or total knee replacement (TKR) for primary osteoarthritis (OA) with a preoperative Hb level between 10.0 g/dL and 13.0 g/dL were selected for the trial. Patients with haematological diseases, coagulation disorders, or with known malignancy or infection were excluded. Informed consent was obtained and the study was approved by the local hospital ethics committee.

A total of 100 patients were enrolled and all were randomly allocated to the Eprex or Bellovac groups by block randomisation and sealed envelopes which were labelled with a consecutive case number from 1 to 100. Patients in the Eprex group received 40,000 IU of epoetin alpha (Eprex, Janssen-Cilag BV, Tilburg, The Netherlands) in each injection. Four subcutaneous injections were given weekly, beginning three weeks before with final injection immediately after operation. The injections were supported by supplementary oral iron (ferrofumerate 200 mg three times daily), beginning three days before the first injection and finishing the day before operation.

To prevent bias, a retransfusion system (Bellovac ABT, AstraTech AB, Mölndal, Sweden) was employed in both groups, but only those in the Bellovac group had an autologous retransfusion. At the end of the operation a deep drain was connected to the retransfusion system after closure of the wound. This system comprises a suction bellows connected to a transfusion bag with a 40- μ m filter. The filtered blood was returned either when the bag was full (500mL) or six hours postoperatively. The amount of blood collected and retransfused was recorded.

Patients undergoing THR received an ABG-II system (Stryker Netherlands, Waardenburg, The Netherlands), cemented or uncemented depending on their age and bone quality. Those undergoing TKR received a cemented Vanguard prosthesis (Biomet, Dordrecht, The Netherlands). The operations were done by five different surgeons, all experienced in joint replacement. In TKR, a tourniquet was used and was released after wound closure.

Patients on anticoagulants (acenocoumarol or acetylsalicylate) stopped these five days before the operation. All patients received low molecular weight heparin for thromboembolic prophylaxis, starting after surgery and continuing for six weeks.

In order to evaluate the increase in Hb levels caused by injections of epoetin alpha, the Hb levels in the Eprex group were measured on the day of admission. As part of the routine preoperative investigations, Hb levels in the Bellovac group were also obtained on the day of admission. After operation the Hb levels were measured on the first and third days in both groups.

Allogeneic blood transfusions were administered according to hospital policy (Table 1). Postoperatively, the anaesthetist determined the Hb transfusion trigger, depending on the American Society of Anaesthesiologists (ASA) classification¹¹ and the course of the operation. The anaesthetist was independent but not blinded, as all prescribed medication, including epoetin alpha and ferrofumerat, were recorded. The preoperative Hb levels were different in the two groups, thereby making blinding difficult. All allogeneic

blood transfusions and complications were recorded according to the classification of Parvizi et al.¹² The rehabilitation programme conformed to a standard policy, with discharge from hospital planned for five days after operation. The length of follow-up varied from two to 18 months.

Before the study, a sample size calculation was performed based on retrospective data. A reduction of 10% in allogeneic blood transfusions by using a retransfusion system in patients with a preoperative Hb level between 10.0 g/dL and 13.0 g/dL, compared with controls from the past, was considered to be the smallest clinical difference. With the α level set to 0.05 and the power at 0.80, it was calculated that 50 patients were needed in each group. The results were analysed statistically using Fisher's exact test for testing the proportions of those receiving allogeneic blood transfusions. All other continuous variables were analysed with Student's t-test. A p-value <0.05 was considered significant. Patients were evaluated according to the intention-to-treat principle

Table 1. Transfusion triggers*

Haemoglobin level (g/dL)	ASA* score	Number of patients	
		Eprex group	Bellovac group
8.1	ASA 2, 1	25	17
8.9	ASA 3, 2 #	17	26
9.7	ASA 4, 3 ##	8	7

* ASA, American Society of Anesthesiologist; # = significant blood loss during surgery (>500 mL);
= minor complications during surgery for example, temporary deflections on electrocardiogram

RESULTS

Of the 50 patients in each group (Table 2), all were ASA grades 2 or 3 and there were no statistical differences between the groups in terms of age, gender, height, weight, preoperative Hb level, type of surgery or postoperative transfusion trigger.

There was one failure of inclusion in a patient randomly assigned to the Eprex group who received preoperative injections of epoetin alpha and then a postoperative retransfusion of 400 mL. One patient in the Eprex group suffered a thrombosis in the superior sagittal sinus with an Hb level of 15.6 g/dL after the second injection of epoetin alpha. No further epoetin injections were

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administered and the operation was postponed for six months until the patient had recovered completely. Both patients were evaluated according to the intention-to-treat principle.

Primary THR was performed in 60 patients and primary TKR in 40 patients. In most cases (84 patients, 84%) spinal anaesthesia was used. The remainder had general anaesthesia. The intra-operative blood loss was similar in both groups, being 395 mL in the Eprex and 381 mL in the Bellovac group ($p=0.75$).

Table 2. Patient and surgical characteristics*

Characteristic	Eprex group (n=50)	Bellovac group (n=50)
Age (years)	73 (49-88)	75 (59-88)
Sex (male/female)	9 / 41	6 / 44
Height (cm)	164 (150-176)	163 (154-174)
Weight (kg)	71 (53-101)	76 (51-106)
Preoperative Hb at screening (g/dL)	12.4 (10.6-13.0)	12.4 (10.8-13.0)
Type of surgery (THR / TKR)	30 / 20	30 / 20
Type of hip replacement (uncemented / hybrid / cemented)	8 / 6 / 17	7 / 7 / 16
Type of anaesthesia (spinal / general)	43 / 7	41 / 9
Postoperative transfusion trigger (g/dL)	8.5 (8.1-9.7)	8.7 (8.1-9.7)

* Data are reported as mean (range). THR = total hip replacement; TKR = total knee replacement. There were no significant differences between both groups.

The mean transfusion triggers in the Eprex and Bellovac groups were 8.5 g/dL (8.1 to 9.7) and 8.7 g/dL (8.1 to 9.7) respectively (Table 2). A mean of 216 mL (0 to 700) were retransfused in the Bellovac group, 131 mL (0 to 500) in THR and 341 mL (0 to 700) in TKR. In one patient, retransfusion was not carried out as the quality of shed blood was considered dubious owing to premature disconnection of the drain to the collection bag. This patient was included according to the intention-to-treat principle.

In the Eprex group two patients (4%) received at least one allogeneic blood transfusion, compared with 14 (28%) in the Bellovac group ($p=0.002$). When comparing Eprex with Bellovac in THR, these results were 7% (2 of 30) and 30% (9 of 30), respectively ($p=0.047$), whereas in TKR they were 0% and 25% (5 of 20) ($p=0.042$). The number of units erythrocyte concentrates per transfused patient was 1.5 (3/2) in the Eprex group and 1.4 (20/14) in the Bellovac group. None of

RCT epoetin injections vs. retransfusion system

the patients randomly assigned to the Bellovac group with a postoperative transfusion trigger of 8.1 g/dL needed allogeneic blood. The costs of treatment in both groups and the costs of allogeneic transfusions are presented in table 3.

Table 3. Cost comparison in Euro's*

	Eprex Group	Bellovac Group
Epoetin alfa injections	1,831.68	None
Ferrofumerate tablets	302.22	None
Bellovac ABT retransfusion system	None	84.70
Allogeneic blood transfusion	12.04	80.24
Total costs per patient	2,145.94	164.94

* Data are reported as costs per patient in both groups. The costs of the used treatment were based on the recommended prices of the manufacturers. The cost of allogeneic blood per patient was based on the percentage of patients receiving allogeneic blood combined with the number of units erythrocyte concentrates transfused per patient. The cost of one erythrocyte concentrate was 200.60 Euro's.

The preoperative levels of Hb were a mean of 12.4 g/dL (10.6 to 13.0) in the Eprex group and 12.4 g/dL (10.8 to 13.0) in the Bellovac group (Fig. 1). The Hb level immediately before operation after the injections in the Eprex group increased by a mean of 2.5 g/dL to 14.9 g/dL (13.0 to 16.6). On the first day after operation the mean Hb level had decreased to 11.4 g/dL (9.0 to 13.8) in the Eprex group and to 9.7 g/dL (7.6 to 12.1) in the Bellovac group. By the third day the levels had decreased to 11.2 g/dL (8.4 to 13.7) in the Eprex group and to 9.5 g/dL (7.2 to 11.1) in the Bellovac group. These reductions were significantly different between the groups on the first ($p=0.011$) and third ($p=0.012$) days after operation.

The incidence of clinical complications was similar between the groups (Table 4). Four patients in the Eprex and five in the Bellovac had haematomas and prolonged wound discharge. In the latter group one patient with a superficial wound infection needed debridement without removal of the prosthesis.

DISCUSSION

Most hospitals use restrictive transfusion triggers because they are aware of the risks and complications of allogeneic blood.^{13,14} In addition, other interventions

to reduce the use of allogeneic blood are in use,¹⁻⁸ and it is not known which is the most successful. Postoperative cell saving using a retransfusion system is relatively inexpensive, whereas preoperative injections of epoetin alpha are approximately 15 times more expensive.⁵⁻⁸ Changing treatment from injections of epoetin to cell saving in patients with preoperative Hb levels between 10.0 g/dL and 13.0 g/dL would reduce the cost to the health system. Although its efficacy has already been demonstrated in patients without preoperative anaemia,⁶⁻⁸ the effectiveness of a retransfusion system in patients with mild anaemia before operation can be disputed. The analysis of the costs showed that in such patients the use of injections of epoetin supported by ferrofumerate tablets increased the cost per patients compared with the retransfusion system. Although this was only based on direct costs, an actual comparison of cost-effectiveness between the groups is hardly possible, as the indirect costs were not measured.

In this study, 28% of patients in the Bellovac group needed allogeneic blood, compared with 46% of the control group in the study of Weber et al.⁴

Figure 1. Perioperative Hb level*

* Data are reported as perioperative Hb level at various moments of measurements. Day -1 = day before surgery (i.e. in patients in only the Eprex group after epoetin alfa injections); Day 1 = first postoperative day; Day 3 = third postoperative day. Statistical significant differences between both groups are indicated by §.

Comparing these results, the absolute risk reduction would be 18%. Although some patients in the Bellovac group still needed allogeneic blood transfusions, their reduction of these was probably due to the retransfusion of shed blood. Our absolute risk reduction in allogeneic blood transfusion of injections of epoetin compared with postoperative cell saving is 24%. Thus, in every 4.2 patients treated with preoperative injections of epoetin alpha, one allogeneic blood transfusion was prevented compared with treatment with a retransfusion system.

The average amount of retransfused shed blood (216 mL) in the Bellovac group was small compared with published values.^{5,6,15} A possible confounding factor is the position of the drain. Some of our surgeons preferred the subfascial position in THR, which appeared to influence the amount of collectable blood compared with placement in the joint. Therefore, retransfusion of different amounts of shed blood may influence the increase in the systemic postoperative

Table 4. Clinical complications*

Complication	Eprex Group (n=50)	Bellovac Group (n=50)
Systemic major		
Cerebral thrombosis	1 (2)	
Perforated sigmoid colon		1 (2)
Systemic minor		
Nausea	1 (2)	1 (2)
Diabetes mellitus instability		1 (2)
Urinary retention	1 (2)	
Urinary track infection	1 (2)	
Local major		
Peri-prosthetic fracture		1 (2)
Local minor		
Haematoma	1 (2)	2 (4)
Prolonged wound discharge	3 (6)	3 (6)
Superficial wound infection		1 (2)
Total	8 (16)	10 (20)

* Data are reported as number (%) of patients with complications in both groups. The "Systemic major" complication includes a patient suffering a thrombosis in the superior sagittal sinus and a patient who developed a perforated sigmoid due to diverticulitis for what he needed an operation. The one patient in the Bellovac group with a "Local major" complication includes a patient with a periprosthetic fracture due to a fall one month after primary THR. A revision of the stem was performed. There were no significant differences between both groups.

Hb level and hence the need for allogeneic transfusion. More studies are needed in this respect.

Both options for allogeneic transfusion involved complications. In the Eprex group a patient with an Hb level of 15.6 g/dL after the second injection of epoetin suffered thrombosis of the superior sagittal sinus. This serious event raised the question whether epoetin was related to thromboembolic complications, in line with suggestions that such problems might arise from an additional influence on coagulation activation.^{16,17} However, other studies, including large randomised clinical trials, observed no differences in adverse events between epoetin and controls.^{2,4,18,19} Hence, the thromboembolic complication in our patient, although recognised in the literature, could not be proven to be related.

Patients with preoperative Hb levels >14.5 g/dL have less chance of receiving allogeneic blood than do mildly anaemic patients with a preoperative Hb <13.0 g/dL.²⁰ Treating these patients enhances the level of Hb. In our study, the average increase in Hb was 2.5 g/dL to an absolute of 14.9 g/dL, agreeing with earlier reports.^{2,4} After primary THR and TKR the mean total blood loss to the third postoperative day causes a fall in Hb of approximately 3.0 g/dL.²¹

The average reduction in Hb in patients in our Eprex group was 3.5 g/dL on day 1 and 3.7 g/dL on day 3, compared with the preoperative level. Severe blood loss was needed before an allogeneic blood transfusion was given. Conversely, in the Bellovac group, the average reduction in Hb was 2.7 g/dL and 2.9 g/dL, respectively. Because the postoperative levels of Hb were significantly lower, less blood loss was needed before allogeneic blood was given to these patients. Our finding that none of the Bellovac patients with a postoperative transfusion trigger of 8.1 g/dL needed allogeneic transfusion may imply that, being even more restrictive, fewer patients in the Bellovac group would need allogeneic blood. Therefore, further randomised trials on this topic are justified.

In conclusion, preoperative injections of epoetin are more effective in reducing the need for allogeneic blood transfusions in mildly anaemic patients with preoperative Hb levels of 10.0 g/dL to 13.0 g/dL compared with postoperative retransfusion of autologous shed blood in major joint arthroplasty, but are more expensive.

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CHAPTER 9

Retransfusion of filtered shed blood in everyday orthopaedic practice

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ABSTRACT

The efficiency of postoperative cell saving after major joint arthroplasty has been demonstrated in prospective studies focusing on blood management. In everyday practice, however, it is likely that transfusion policy is followed less rigorously due to a slackening in attention to blood management, with a reduced efficiency of postoperative cell saving. The primary research question of this retrospective study was whether the number of allogeneic blood transfusions administered to patients treated with a retransfusion system was similar to the results found in a preceding prospective study.

A total of 438 patients treated with the Bellovac ABT retransfusion system were analysed in which the majority was operated on a total hip (THA) and total knee arthroplasty (TKA). The amount of retransfused shed blood, the perioperative Hb levels and the number of allogeneic blood transfusions were registered.

The average amount of retransfusion was 152 mL in THA and 410 mL in TKA whereas the allogeneic blood transfusion rate was 8.4% and 5.1% in both groups, respectively. The average percentage of allogeneic blood transfusions administered in this study (i.e. 7%) proved to be marginally higher than the percentage found in a preceding prospective study (i.e. 6%) because of slackening of attention for transfusion policy in everyday practice. Limited bone resection procedures such as resurfacing THA or unicompartmental knee arthroplasty was associated with very limited shed blood and low risk of allogeneic blood transfusion, indicating the doubtful cost efficiency of using a retransfusion system in these patients.

It can be concluded that the efficiency of the retransfusion system in everyday practice was similar to the efficiency shown in a preceding prospective study focusing on blood management. However, continual training of the clinical team is crucial.

INTRODUCTION

Prosthetic orthopaedic surgery is associated with considerable blood loss and blood transfusions are frequently necessary. However, allogeneic blood transfusions have more downsides than originally thought. Although the chances of contracting a transmittable disease, such as HIV or hepatitis, are slim, immune reactions and a decrease in the body's immune system play a negative role in blood transfusion.¹ As a consequence, transfusion policy has attracted increased attention over the past few years. Besides sharpening the postoperative transfusion trigger, alternatives to allogeneic blood transfusions are used more frequently. One of these alternatives is postoperative cell saving using a retransfusion system. Filtered wound blood is collected and returned to the patient. The efficiency of such a retransfusion system has been demonstrated in a number of studies including our preceding study that reported a transfusion rate of 6%.²⁻⁵ These were mainly prospective studies focusing on blood management and in which the need for allogeneic blood transfusion was low because the transfusion triggers were followed meticulously. However, as attention to transfusion policy slackens, the number of allogeneic blood transfusions increases.⁶ It is likely that attention is suboptimal in everyday practice. The efficiency of a retransfusion system reported in prospective studies focusing on blood management is therefore not necessarily equal to the efficiency for patients in everyday practice who are not taking part in blood management studies.

The purpose of this retrospective study was to follow up a prospective randomised study, evaluating the efficacy of a retransfusion system in everyday orthopaedic practice. The primary research question was whether the number of allogeneic blood transfusions found in the retrospective study was similar to that found in the preceding prospective study. In addition, the study examined which variables influence the amount of shed blood and the number of allogeneic blood transfusions.

MATERIALS AND METHODS

This retrospective study enrolled all patients who received a retransfusion system in the period from July 2006 until August 2007. The Bellovac ABT retransfusion system (AstraTech AB, Mölndal, Sweden) was used as a standard for patients undergoing elective total hip (THA) and total knee arthroplasty (TKA). Additionally, the system was used for patients undergoing primary unicompartmental knee arthroplasty (UKA).

In the period studied, 602 patients were treated with the retransfusion system. Patients who were participating in a prospective blood management study that was being run simultaneously, were excluded. Likewise, we also excluded patients undergoing revision surgery as well as those undergoing surgery for a femoral neck fracture because the perioperative blood loss in these procedures was considered to be variable and unpredictable.

The retransfusion system was used in accordance with the directions of the manufacturer. All patients received one deep wound drain just before wound closure. The position of this drain in THA was either intra-articular or subfascial, depending on the preference of the surgeon, but always intra-articular in TKA and UKA. The drain was then connected to the retransfusion system. This system contains a suction bellow with an intermittent suction pressure of 0 to -90 mmHg. For all patients who were operated on without a tourniquet (i.e. THA) the vacuum pressure was applied immediately after surgery; for procedures with a tourniquet (i.e. TKA and UKA) the suction bag was opened in the recovery room, 15 minutes after wound closure.

During the first six hours following surgery, the wound blood was collected in an autotransfusion bag, after which it was returned to the patient. A minimum of 100 mL of shed blood was set as a critical threshold for starting a retransfusion. During this retransfusion, the shed blood passed a macro and micro filter with a minimum pore size of 40 microns. When the first autotransfusion bag filled up within six hours (500 mL) a second bag was connected up until six hours after surgery, and then used for retransfusion. From six hours after the surgery onwards, the wound blood was collected in a regular collection bag using the system for low-vacuum wound drainage. The wound drain was removed in all patients on the first day after surgery.

All surgery was performed under the supervision of five experienced surgeons. A standard THA was performed by all surgeons, whereas the other types of procedures were performed by one or more (Table 1). TKA and UKA were cemented in all cases, as was performed in the femoral component of a resurfacing THA. The use of cement in a standard THA depended on the age of the patient.

Allogeneic blood transfusions were administered according to hospital policy if the haemoglobin (Hb) levels reached the postoperative transfusion trigger. This trigger was determined by the anaesthesiologist and was based on the co-morbidity of the patient according to the classification according to the American Society of Anaesthesiologist.

All clinical charts of the patients were studied retrospectively for patient records such as gender, age, diagnosis, type of surgery, surgeon, method of

Table 1. Characteristics of different types of surgery

	Number (n (%))	Gender (n (male / female))	Age (yr)	Surgeons* (n)	Transfusion trigger (g/dL)
THA, uncemented	83 (19)	37 / 46	63	5	8.4
THA, hybrid	60 (13)	20 / 40	65	5	8.4
THA, cemented	82 (19)	25 / 57	75	5	8.6
THA, resurfacing	12 (3)	8 / 4	56	1	8.1
TKA	175 (40)	55 / 120	69	4	8.5
UKA	26 (6)	14 / 12	61	2	8.3

*Number of surgeons that performed the surgery in question.

anaesthesia, drain position, amount of autologous retransfusion, Hb levels (preoperative, day 1 and day 3, postoperative), transfusion trigger and allogeneic blood transfusions. Patients were excluded if it was not possible from these data to determine the amount of retransfused shed wound blood.

The correlation between different patient records and the amount of shed blood retransfusion, or the necessity of allogeneic blood transfusion, was assessed using a logistic regression analysis. Further analysis was carried out using Student's t-test. A p-value less than 0.05 was considered a significant difference.

RESULTS

In total, 602 patients enrolled in this retrospective study. Ninety-six patients (16%) were excluded because of participating in a prospective blood management study and 45 patients (7%) because of revision surgery as well as surgery for femoral neck fracture. Additionally, 23 patients (4%) were excluded because of incomplete data regarding the amount of shed blood retransfusion. Consequently, a total of 438 patients were included for analysis. For the majority of these, a THA (54%) or a TKA (40%) was performed. The subdivision by type of surgery is shown in table 1. The total number of female patients was significantly higher than the number of male patients. In the resurfacing THA and UKA the patients' age was lower, the preoperative Hb level higher and the postoperative transfusion trigger lower compared to the other patient groups. Although enough wound blood was collected, in four patients a retransfusion was not started because of doubts about sterility, as the autotransfusion bag had come loose. However, these patients were included in the analysis.

The amount of retransfused shed blood six hours after surgery in all patients was on average 240 ± 259 mL (SD; range 0-1200). For patients who

had undergone a standard THA this was 152 ± 175 mL (SD; range 0-800) whereas in TKA 410 ± 284 mL (SD; range 0-1200) was retransfused. The amount of retransfused shed blood in the UKA group was limited; with an average return of 63 ± 104 mL (SD; range 0-300). One possible transfusion reaction was observed in a TKA patient, who registered a temporary hypotension after retransfusing 100 mL of the total amount of 550 mL. This reaction was reported to the Dutch national haemovigilance office 'Transfusion Reactions In Patients' (TRIP). Retransfusion was cancelled after which the blood pressure of the patient recovered.

In a THA, the amount of retransfusion differed significantly depending on the technique used, as shown in figure 1. All patients who had undergone resurfacing THA had less than 100 mL of shed blood in the autotransfusion bag; not a single autologous retransfusion was performed in this group. The only surgeon who performed this surgery placed the wound drain subfascial, based on personal preference. In addition, different amounts of collected wound blood were found between different drain positions in other procedures.

Figure 1. Relation between retransfusion and type of surgery*

* Data shown as the average amount of shed blood retransfusion with standard deviation in different types of surgeries. THA = total hip arthroplasty (standard uncemented (-), standard hybrid (-/+), standard cemented (+), resurfacing (rsf)), TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty. § = significant difference from THA- ($p=0.001$), §§ = significant difference from THA- ($p<0.0001$).

Although this difference was not significant, the results did show a trend for increasing collected amount in patients whose drain was placed intra-articular.

The number of patients with allogeneic blood transfusions was 8.4% in standard THA (19/225) and 5.1% in TKA (9/175). None of the patients in the resurfacing THA or UKA group were given an allogeneic blood transfusion. The average Hb levels of the different groups are shown in figure 2. No correlation was found between the amount of retransfused shed blood and postoperative Hb levels, or the number of allogeneic blood transfusions.

Figure 2. Perioperative Hb level*

*Data shown as average Hb levels in different types of surgeries at the perioperative measuring points (preoperative, day 1 and day 3 postoperative). THA = total hip arthroplasty (standard uncemented (-), standard hybrid (-/+), standard cemented (+), resurfacing (rsf)), TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty.

DISCUSSION

This retrospective study was set up to evaluate the efficiency of a retransfusion system in hip and knee arthroplasty surgeries in everyday orthopaedic practice compared to the efficiency showed in a preceding prospective study focusing on blood management. The efficiency was highlighted by the low percentage of allogeneic blood transfusions after standard THA (8.4%) and TKA (5.1%) resulting in a mean percentage of 7% after these procedures. Although marginally higher, this percentage was similar to that of a preceding prospective randomised study focusing on blood management in the same institution; that

is 6%.⁴ The patient characteristics of both studies, including gender, age, type of surgery, method of anaesthesia and transfusion trigger were similar. However, the preoperative Hb levels of both studies were slightly different, namely 14.5 g/dL in this retrospective study versus 14.0 g/dL in the prospective study. As such, the percentage of allogeneic blood transfusions in our retrospective study was higher than what would be expected, as it was previously shown that higher preoperative Hb levels decreases allogeneic blood transfusions after surgery.⁷ One explanation may be the slackening of attention to transfusion policy in everyday practice. Continual training programmes and a persisting awareness among the medical staff and nurses are crucial for preventing such slackening of attention, as has been shown previously.⁶

Analysis of variables influencing the amount of shed blood found the type of surgery to be relevant because procedures with limited resection of the bone, such as resurfacing THA and UKA, lost less wound blood. As a result, for these operations, only a very limited number of patients shed a volume of blood exceeding the critical threshold of 100 mL indicating doubtful cost efficiency for a retransfusion system in these patients. The more so as their risk of receiving an allogeneic blood transfusion was reduced because of their higher preoperative Hb levels. In addition, these patients are usually younger with less co-morbidity resulting in a lower postoperative transfusion trigger. This further reduces the chance of receiving allogeneic blood.

Focusing on blood loss in THA, it was shown that cemented THA surgeries produced significantly less wound blood compared with non-cemented procedures. Furthermore, the position of the drain also affected the amount of retransfused wound blood. A subfascial drain position in THA yielded a lower amount of shed blood compared with an intra-articular drain position. This again brings into question the cost efficiency of a retransfusion system in these patients because a large number of patients did not exceed the critical threshold of 100 mL after which retransfusion was started. No published studies were found that examined the relation between the position of the wound drain and the amount of collected wound blood with eventual transfusion need. A prospective randomised study is currently evaluating this possible confounding effect of the drain position in THA.

Finally, we examined a possible relation between the amount of retransfused blood and the need for allogeneic blood. It was expected that the more shed blood was retransfused, the lower the number of allogeneic blood transfusions would be. However, this relation was not confirmed by regression analysis. The tamponading effect of a forming haematoma after surgery was possibly counteracted by the wound drain itself since the drain was used for

prolonged low-vacuum drainage. This may indicate a beneficial effect of earlier drain removal. This issue would be further clarified by a prospective randomised clinical trial addressing the question of the need for allogeneic blood in patients treated without a drain versus patients treated with the retransfusion system in which the drain is removed six hours after surgery, when retransfusion is started.

In conclusion, the efficiency of the retransfusion system in everyday orthopaedic practice was shown to be similar to the efficiency in prospective studies focusing on blood management. However, to prevent slackening of compliance with the departmental transfusion policy, continual training and reminders to the clinical team are crucial.

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CHAPTER 10

General discussion

A.F.C.M. Moonen

INTRODUCTION

Postoperative cell saving with shed blood is common practice in transfusion medicine. The aim of this thesis was to establish the role of postoperative cell saving in orthopaedic practice using an autologous retransfusion system for filtered shed blood in patients after total hip (THA) or total knee arthroplasty (TKA), to elucidate when and how this retransfusion system should be used, and to suggest improvements to optimize the method for further use. As such, this thesis seeks to answer a number of research questions as set forth in **Chapter 1**. The answers to these specific research questions will be addressed in this general discussion alongside with recommendations for future research and policy.

- **How safe is the retransfusion system?**

Retransfusion remains controversial. While a number of studies have stated that it is a safe method, others have reported disadvantages and risks.¹⁻⁷

Before implementing the retransfusion system, a pilot study was undertaken to examine the quality of shed blood by evaluating the amount of haemolysis in the transfusion bag (**Chapter 4**). Haemolysis can be caused by several factors, such as suction pressure, contact with synthetic materials, and stasis of blood out of the body in the collection bag. Haemolysis leads to increased levels of free Hb which eventually cause kidney damage after retransfusion. In our study all samples from the collection bag showed a free-Hb level below the critical level of 0.6 g/dL. Although equipped with a different filter haemolysis was absent with the use of either the Bellovac ABT system as the Donor system (**Chapter 5**). Considering the absence of haemolysis, the quality of the cells in the collected bag can be assessed as good.

Many questions concerning the role of leukocytes remain. Although the allogeneic erythrocyte concentrates are all leukocyte depleted, the effect of leukocytes in autologous blood retransfusion is still under debate. Even though positive effects of retransfusion have been noted⁸, the clinical effects of the retransfusion of activated leukocytes are still unknown.⁹ A few studies have been published in which the authors conclude that retransfusion of autologous shed blood alters the activity of the polymorphonuclear leukocytes and activates systemic immunity after joint replacement.^{10,11} These results suggest a reversal of the immunosuppression associated with surgical trauma and blood loss.^{10,11} As the removal of leukocytes from autologous shed blood might take away this benefit, this implies that there is no need for leukocyte depletion in

autologous blood retransfusion. In addition, retransfusion of autologous blood was accompanied by a significant decrease in postoperative infections.^{8,12}

In our study, filtering shed blood with the filter of the Donor system caused a significant decrease in the amount of leukocytes by 56 percent, whereas filtering with the filter of the Bellovac ABT system did not (Chapter 5). Although this suggests superior conditions when patients are treated with the Bellovac ABT system, larger, sufficiently powered studies are needed to evaluate both systems with respect to postoperative infections.

It is known that surgical trauma increases the local production of interleukins and complement factors in patients undergoing TKA.¹³ Accordingly, higher concentrations of pro-inflammatory interleukins and complement split products were found in shed blood compared to control blood.^{14,15} Shed blood collected starting from 6 hours after surgery up to 12 hours after surgery revealed even higher concentrations of interleukins.¹⁶ Concerns have been raised that return of these compounds may induce hypotension, hyperthermia and febrile reactions.^{4,5,17} None of the studies presented in this thesis focused on interleukins or complement factors. In one of the studies only one patient showed a possible transfusion reaction: hypotension was observed during the retransfusion of 100 mL shed blood (Chapter 9). However, in evaluating this effect, no causal correlation with the retransfusion could be proven. Regarding febrile reactions, our results showed no relationship between retransfusion and postoperative febrile reactions (Chapter 7). In addition, retransfusion of more than 500 mL of filtered shed blood did not increase the percentage of patients showing febrile reactions. These results are in accordance with the results presented in the literature.^{1,9,18}

As such, the absence of adverse events in all of our studies reported in this thesis indicates that postoperative autologous retransfusion of shed blood is safe for use. Nevertheless, improved haemo-vigilance in regard to autologous retransfusions is important, as the lack of serious adverse events from the retransfusion of shed blood may simply be the result of a lack of observation and auditing. Continued research will be needed to optimize the safety of this alternative for allogeneic blood transfusions.

- **What are the differences between retransfusion systems with respect to the filtering performance?**

Several retransfusion systems for autologous shed blood are in use in The Netherlands. Although all systems are based on the same principle, they differ slightly in suction pressure, the type of incorporated filter and handling procedures.

Currently, the Bellovac ABT system is used most often in our country, but the Donor system is gaining popularity.

The Bellovac ABT system used in all studies has an intermittent vacuum pressure between 0 and –90 mmHg. The Donor retransfusion system that was used for comparison has a continuous vacuum pressure of –150 mmHg (Chapter 5). Our results show a trend towards collecting more shed volume in the retransfusion system with the highest suction pressure. Although the American Association of Blood Banks (AABB) recommends a suction pressure not exceeding 100 mmHg (at higher values red blood cells might be lysed¹⁹), no indications of haemolysis were found in either system as the free Hb level remained below the critical level of 0.6 g/dL.

Our pilot study also examined the effect of the filter integrated in both systems with retransfusion after TKA (Chapter 5). While the filters are supposed to reduce the amount of potential emboli sources by reducing emulsified fat, cell-aggregates, and debris, their main function is to recover blood. Shed blood filtered in the Donor system showed a significant decrease in the amount of leukocytes by 56 percent this did not occur with the Bellovac ABT system. While the leukocyte depletion in the Donor system was expected, the reduction of erythrocytes in that system was surprising since the average size of erythrocytes is almost 8 μm .²⁰ As a result, the filtering rates for Hb level (defined as the Hb level before filtering minus the Hb level after filtering) for the Donor System and the Bellovac system were significantly different. These results suggest that the function of blood recovery is hampered in the Donor system, but is preserved in the Bellovac ABT system. However, conclusions concerning differences in systemic Hb level after retransfusion in both systems cannot be made due to the small sample size. Larger, sufficiently powered studies are needed to confirm our findings regarding presumed differences in shed volumes, systemic Hb level after retransfusion and accompanying differences in the need for allogeneic blood transfusions.

- What is the effect of drain position when using the retransfusion system?

As the clinical efficiency of the retransfusion system after total joint arthroplasty was evaluated, several studies reported various amounts of retransfused shed blood.^{8,21-23} Similar variations occurred in our department of orthopaedic surgery. After TKA the retransfused shed blood volume was approximately 400 mL (Chapters 5, 7, and 9). The average retransfused volumes showed similarity in all studies since the drain was placed intra-articular in all patients. However, after THA striking differences in the volumes

of collected and retransfused blood were found, ranging from 0 to 1000 mL (Chapters 6, 7, 8, and 9). A possible confounder could be the drain position of the retransfusion system. Some surgeons prefer the intra-articular drain position in THA while others prefer the subfascial position based on the surgeons own assumption regarding infection risks.

Our prospective randomised clinical trial evaluated the effect of these drain positions (Chapter 6). The intra-articular drain position collected more shed blood compared to the subfascial drain position. Consequently, more blood was retransfused in these patients. However, there was no relationship between increased volume of shed blood retransfused and reduced need for allogeneic blood transfusion, raising the question whether the tamponading effect of post-surgical haematoma is counteracted by low-vacuum wound drainage when the drains were removed 24 hours after surgery. A possible explanation could be the additional blood loss in the period from 6 hours after surgery until drain removal, as the absolute amounts are higher in that particular period in the intra-articular group than they are in the subfascial group. By this, the reason for prolonged drainage of the wound after retransfusion starting at 6 hours after surgery can be discussed. To illustrate, in a large meta-analysis incorporating 18 studies and 3495 patients it was suggested that drainage in TKA and THA enhances blood loss since active drainage up to 2 days was associated with a greater need for allogeneic blood transfusions compared to treatment without drain.²⁴ It has been suggested that the negative pressure gradient generated by these devices enhances blood loss. This assumption seems valid since a trend towards collecting more shed volume was shown in the retransfusion system with the highest suction pressure (Chapter 5).

Nevertheless, the conclusion of the meta-analysis that routine use of wound drainage may be more harmful than beneficial has to be interpreted with caution since the included studies showed an overall transfusion requirement of 40 percent in patients treated with a drain indicating a liberal transfusion policy. Nowadays transfusion policies are more restrictive. In addition, contrary to the drainage system used in the patients included in the meta-analysis, the system used in our studies was a retransfusion system in which shed blood is not only collected, but also retransfused after TKA and THA. And as shown by our results, retransfusion of shed blood significantly reduced the need for allogeneic blood transfusions compared to standard wound drainage (Chapter 7).

In the literature we found only one retrospective study presenting the effectiveness of a retransfusion system in comparison with treatment without a drain.²⁵ The results showed a trend towards slightly less allogeneic blood

transfusions in the drain group compared to the no-drain group. Since this difference was not statistically significant, the authors concluded that the retransfusion system used did not appear to be beneficial in regard to allogeneic blood transfusions. However, this conclusion might be disputed on the basis of the moderate study design.

Reconsidering the results of our study in the light of the findings cited above, it makes sense to consider earlier drain removal than 24 hours after surgery as is common practice. This issue would be further clarified by a prospective randomised clinical trial addressing the question of the need for allogeneic blood in patients treated without a drain versus patients treated with a retransfusion system in which the drain is removed 6 hours after surgery, when retransfusion is started.

- **What is the efficiency of the retransfusion system compared to standard therapy?**

The clinical efficiency of the retransfusion system has been evaluated in a prospective randomised clinical trial (**Chapter 7**). Patients in the study group were treated with the Bellovac ABT retransfusion system, while patients in the control group were treated with a standard drain for low-vacuum drainage. Our results showed that 19 percent of the control patients received allogeneic blood transfusions as opposed to only 6 percent of the transfusion group. These results confirmed the efficiency of the retransfusion system shown in previous studies. A meta-analysis incorporating 16 studies, determined that postoperative cell saving is effective in reducing allogeneic blood transfusion.²⁶

The efficiency of low-volume retransfusion can be disputed as the average Hb level in shed blood measured was on average only 9.3 and 11.0 g/dL (**Chapters 4 and 5**). This level corresponded to approximately half the Hb level found in erythrocyte concentrates as presented in our pilot study (**Chapter 4**). This means that one volume of erythrocyte concentrate corresponded with double the volume of shed blood regarding total Hb retransfused. As such, collecting high volumes results in higher red blood cell return. The highest average volumes were recorded after TKA (**Chapters 5, 7, and 9**). The average volumes after THA varied (**Chapters 6, 7, 8, and 9**), apparently dependent on drain position (**Chapter 6**) and use of bone cement (**Chapter 9**). In addition, the type of surgery performed also influenced the volumes, since the average volumes after UKA and resurfacing THA appeared to be less than the applied level of 100 mL in which retransfusion was started (**Chapter 9**). Therefore, the efficiency of the method after these procedures is disputable.

On the other hand, allogeneic blood transfusion of 28-day stored red blood cells in erythrocyte concentrates resulted in significantly malperfused and underoxygenated microvasculature.²⁷ This maldistribution of microvascular pO_2 suggested the potential development of focal ischaemia. Transfusion of these stored red blood cells in rats failed to immediately improve tissue oxygenation in comparison to fresh red blood cells.^{28,29} Cell deformability is thought to be an important determinant of adequate red blood cell function, because the adjustment of the red blood cell shape to very small diameters is required for passage through the microcirculation. During storage, red blood cell deformability is reduced, which can induce haemodynamic changes after administration.³⁰⁻³²

It is well documented that stored red blood cells lead to a left-shift in the oxygen dissociation curve due to the decay of 2,3-DPG and ATP concentration over time, which will gradually return to normal levels from 7 up to 24 hours after transfusion.^{33,34} As such, they are able upon transfusion to load oxygen in the lungs, but will be less able to deliver oxygen to tissue. Contrary to allogeneic blood, the 2,3-DPG concentration in autologous shed blood was found to be increased in the collection bag 6 hours after surgery.³⁵ Owing to this enhanced ability of autologous shed blood to deliver oxygen to tissue, retransfusion of autologous shed blood 6 hours after surgery seems superior to a transfusion with stored erythrocyte concentrates. In addition, high concentrations of ATP were found in shed blood as signs of excellent energy exchange.³⁵ Additionally, the erythrocyte viability in retransfused autologous shed blood was presented as good.³⁶

Therefore, any retransfusion of autologous shed blood seems advantageous to the patient. Even a retransfusion with low volumes can be deemed useful due to the advantages in red cell metabolism and function compared to allogeneic blood. We applied an arbitrary level of 100 mL since the efficiency of volumes below that level seems questionable. Further studies evaluating the additional effect of retransfusion of autologous shed blood on oxygen delivery to the human cells are justified.

- **Which patients would benefit from treatment with the retransfusion system compared to other alternatives?**

The most frequently used alternatives to diminish the use of allogeneic blood transfusions are restrictive transfusion triggers, preoperative epoetin injections, preoperative autologous blood donation, and postoperative cell saving. Although algorithms for reducing allogeneic blood transfusions have already

been published^{37,38}, it is still unclear which intervention or combination is the most successful. The several studies in the literature that claim a better effectiveness of one of these alternatives must be interpreted with caution, since they often compare patients with retrospective data from an era of more liberal transfusion policies. Therefore, more prospective randomised studies are needed to compare the various alternatives with each other.

In a prospective randomised clinical trial, the effect of preoperative epoetin injections was compared with the effect of postoperative retransfusion of shed blood after THA or TKA in patients with mild anaemia (**Chapter 8**). Treatment with epoetin injections in the perioperative period has many potential benefits. However, there are still concerns about the cost of this treatment. The results of our study showed that preoperative epoetin injections were superior to postoperative cell saving in reducing the need for allogeneic blood transfusions in mildly anaemic patients with preoperative Hb levels between 10.0 and 13.0 g/dL at screening. As a result of the epoetin injections, the preoperative Hb level increased to a higher level and in this way reduced the chance of receiving any allogeneic blood transfusion. Remarkably, the average amount of retransfused shed blood in the retransfusion group was relatively small. As discussed in our study, a possible confounder was the position of the drain. This assumption seems valid as the position of the drain affects the amount of collected and retransfused shed blood (**Chapter 6**).

Reconsidering the results, this could indicate that the superiority of epoetin injections may be challenged when all patients are treated with an intra-articular drain position and possible earlier drain removal than in this study. Therefore, further studies on this topic are needed to examine which patients would benefit the most from treatment with retransfusion of shed blood, compared to the various alternatives used in blood management. Presently, a large randomised multi-centre study (TOMaat study) in the Netherlands is comparing three different interventions (preoperative epoetin injections, intra- and postoperative cell saving) with a restrictive transfusion group as control in THA and TKA.³⁹ Hopefully, the results of this study will provide more evidence-based data on the effectiveness of the various alternatives used in orthopaedic surgery in the field of blood management.

- **What is the efficiency of the retransfusion system in everyday orthopaedic practice?**

Slacking compliance to blood management policy causes an increase in allogeneic blood transfusions (**Chapter 2**). It has been suggested that this

slacking compliance is due to a relapse of attention regarding blood transfusions in everyday practice. In addition, the introduction of the retransfusion system in everyday practice is not straightforward.⁴⁰ The efficiency of the retransfusion system in everyday practice has been evaluated in our retrospective cohort study (Chapter 9). Of the 438 patients analysed in the study, most had a THA or TKA, and an average of 7% of patients needed allogeneic blood, marginally higher than the 6% of patients in the preceding prospective study in the same institution (Chapter 7). Limited bone resection procedures such as resurfacing THA or unicompartmental knee arthroplasty (UKA) was associated with very limited shed blood and low risk of allogeneic blood transfusion, indicating the doubtful cost efficiency of using a retransfusion in these patients. Therefore, our results showed that the retransfusion system is only indicated after THA en TKA. However, in order to prevent slackening of compliance with the departmental transfusion policy, continual training and reminders to the clinical team is of paramount importance (Chapters 3 and 9). By this, everyday use of the retransfusion system can be incorporated in good clinical practice.

CONCLUSION

Great strides have been made towards the realisation of the concept of “bloodless surgery”. The initial problem of making the orthopaedic surgeon aware of the risks of allogeneic blood transfusion is currently being solved through better education. Besides restrictive transfusion policies, various additional treatment alternatives are available to reduce allogeneic blood transfusions. A frequently used alternative is postoperative cell saving by using a retransfusion system for filtered shed blood.

This thesis established the role of postoperative cell saving in orthopaedic practice. The question of when and how to use this retransfusion system was discussed in detail following our research questions. Possible adjustments to optimize the efficiency of the retransfusion system were stated. Additionally, recommendations for the future were presented.

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CHAPTER 11

Summary

&

Samenvatting

A.F.C.M. Moonen

SUMMARY

In **Chapter 1**, this thesis starts out by outlining the history of blood transfusion and transfusion medicine in orthopaedic surgery. Nowadays, postoperative cell saving using an autologous retransfusion system for shed blood is widely used in patients after total hip (THA) or total knee arthroplasty (TKA). The aim of this thesis is to establish the role of postoperative cell saving in orthopaedic practice. Research questions are formulated in this chapter that are addressed in the subsequent chapters.

Chapter 2 presents a critical review of the literature on perioperative blood management in elective orthopaedic surgery. Several techniques to reduce the need for allogeneic blood transfusions are discussed. The implementation process of blood management in our orthopaedic surgery department is presented in **Chapter 3**. Besides putting a restrictive transfusion policy into practice, education and awareness of the issue are important factors in blood management.

In **Chapter 4** the amount of haemolysis in shed blood is evaluated in a pilot study in which eighteen patients were treated with the Bellovac ABT retransfusion system after THA or TKA. Considering the absence of haemolysis in the transfusion bag, the quality of cells in collected blood can be assessed as good. As such, it seems safe to return shed blood to the patient.

Another study, presented in **Chapter 5**, evaluates whether the different filters integrated in postoperative retransfusion systems affect the amount of blood cells retransfused after TKA. Twenty-two patients received either the Donor retransfusion system or the Bellovac ABT retransfusion system. Using both systems, blood with different amounts of blood cells was retransfused to the patient. The haemoglobin level of retransfused blood from the Donor system showed significantly lower levels than the blood from the Bellovac ABT system. It was concluded that the type of filter integrated in retransfusion systems significantly affects the amount of blood cells retransfused.

Chapter 6 presents a prospective randomised clinical trial elucidating the effect of the drain position after THA. One hundred patients were randomly assigned to the intra-articular group or the subfascial group. The intra-articular drain position resulted in a higher amount of shed blood than the subfascial position at 6 hours after surgery as well as the total amount of shed blood when the drain was removed 24 hours after surgery. However, there was no relationship between increased volume of shed blood retransfused and reduced need for allogeneic blood transfusion, raising the question whether the tamponading effect of post-surgical haematoma is counteracted by wound

drainage when drains were removed at twenty-four hours after surgery.

Chapter 7 evaluates the clinical efficiency of retransfusion systems in a prospective randomised clinical trial. A total of 160 THA and TKA patients were assigned to receive either a retransfusion system or a regular low-vacuum drain as control. In the control group 19% of patients received at least one allogeneic blood transfusion, as opposed to 6% in the retransfusion group – a significant difference. It was concluded that postoperative retransfusion of shed blood is effective in decreasing allogeneic blood transfusion. In addition, no relationship between retransfusion of shed blood and postoperative febrile reactions was found.

A prospective randomised clinical trial performed in patients with the highest risk of receiving allogeneic blood transfusions is presented in Chapter 8. One hundred patients with preoperative mild anaemia, scheduled for TKA or THA, were assigned to either the Eprex group (preoperative epoetin injections) or the Bellovac ABT group (postoperative cell saving). In the epoetin group 4% of patients received at least one allogeneic blood transfusion whereas in the cell saving group this was 28%. It was concluded that treatment with preoperative epoetin injections is superior in reducing the need for allogeneic blood transfusions in preoperative mildly anaemic patients.

In Chapter 9 the use of a retransfusion system in everyday orthopaedic practice is evaluated. It was hypothesised that the effectiveness of the retransfusion system in everyday practice is reduced by the expected relapse in attention to transfusion policy. In total, 438 patients were analysed in this retrospective study. The results showed that the effectiveness is in accordance with results presented in the prospective study in the same institution. However, in order to prevent slackening of compliance with the departmental transfusion policy, continual training of the clinical team is an important factor in blood management.

This thesis ends with a general discussion in Chapter 10. The answers to the specific research questions formulated in the first chapter are discussed in relation to the results of all performed studies. The role of postoperative cell saving in orthopaedic surgery is discussed in detail in this final chapter. In addition, recommendations for future research are made.

SAMENVATTING

In **Hoofdstuk 1** begint dit proefschrift met het schetsen van de geschiedenis van bloedtransfusies en transfusiegeneskunde binnen de orthopaedische chirurgie. Tegenwoordig wordt postoperatieve “cell saving” door middel van het gebruik van een autoloog retransfusiesysteem voor opvangen wondbloed, veel gebruikt bij patiënten na het plaatsen van een totale heup (THP) of totale knie prothese (TKP). Het doel van dit proefschrift is om de rol vast te stellen van postoperatieve “cell saving” in de orthopaedische praktijk. Onderzoeksvragen worden geformuleerd in dit hoofdstuk en aangepakt in de hierop volgende hoofdstukken.

Hoofdstuk 2 geeft een “critical review” van de literatuur betreffende perioperatief bloedmanagement bij electieve orthopaedische chirurgie. Diverse technieken ter vermindering van de behoefte aan allogene bloedtransfusies worden besproken. Het implementatieproces betreffende bloedmanagement op onze orthopaedisch chirurgische afdeling wordt gepresenteerd in **Hoofdstuk 3**. Naast het in de praktijk brengen van een restrictief transfusiebeleid zijn scholing en bewustwording van het probleem, belangrijke factoren in het bloedmanagement.

In **Hoofdstuk 4** wordt de mate van hemolyse in opvangen wondbloed geëvalueerd in een “pilot study” waarbij achttien patiënten behandeld werden met het Bellovac ABT retransfusiesysteem na het plaatsen van een THP of TKP. Gezien de afwezigheid van hemolyse in de transfusiezak werd de kwaliteit van de cellen in het opvangen wondbloed als goed beoordeeld. Op grond hiervan, is het veilig om wondbloed terug te geven aan de patiënt.

Een andere studie gepresenteerd in **Hoofdstuk 5**, evalueert of verschillende filters zoals geïntegreerd in postoperatieve retransfusiesystemen, effect hadden op de hoeveelheid bloedcellen geretransfundeerd na het plaatsen van een TKP. Twee en twintig patiënten ontvingen ofwel het Donor retransfusiesysteem ofwel het Bellovac ABT retransfusiesysteem. Door gebruik van beide systemen werd bloed met verschillende hoeveelheden bloedcellen geretransfundeerd aan de patiënt. Dientengevolge vertoonde het hemoglobine gehalte van geretransfundeerd bloed van het Donor systeem significant lagere waarden dan van het Bellovac ABT systeem. Geconcludeerd werd dat het type filter zoals geïntegreerd in retransfusiesystemen, de hoeveelheid bloedcellen geretransfundeerd significant beïnvloedde.

Hoofdstuk 6 presenteert een prospectieve “randomised clinical trial” waarin het effect van de drainpositie na het plaatsen van een THP werd toegelicht. Honderd patiënten werden door het toeval toegewezen tot de intra-

articulaire groep of de subfasciale groep. De intra-articulaire drainpositie resulteerde in een toename in de hoeveelheid opgevangen wondbloed vergeleken met de subfasciale positie op 6 uur na de operatie alsook bij de totale hoeveelheid opgevangen wondbloed bij het verwijderen van de drain 24 uur na de operatie. Een relatie tussen een toename in hoeveelheid gere transfundeerd wondbloed en een afname in de behoefte aan allogene bloedtransfusies werd niet aangetoond. Hierdoor rijst de vraag of het tamponerende effect van een postoperatieve hematoom wordt tenietgedaan door wonddrainage bij drain verwijdering 24 uur na de operatie.

Hoofdstuk 7 evalueert de klinische effectiviteit van het retransfusiesysteem in een prospectieve “randomised clinical trial”. In totaal werden 160 patiënten toegewezen tot het ontvangen van ofwel een retransfusie systeem ofwel een regulier laagvacuüm drain als controle. In de controlegroep ontvingen 19% van de patiënten op zijn minst één allogene bloedtransfusie, tegenover 6% in de retransfusie groep, wat significant verschillend is. Geconcludeerd werd dat postoperatieve retransfusie van opgevangen wondbloed effectief is in het verminderen van allogene bloedtransfusies. Daarnaast werd geen relatie tussen retransfusie van wondbloed en postoperatieve koortsreacties gevonden.

Een prospectieve “randomised clinical trial” uitgevoerd bij patiënten met het hoogste risico op het ontvangen van allogene bloedtransfusies wordt gepresenteerd in **Hoofdstuk 8**. Honderd patiënten met preoperatieve milde anemie ingepland voor het plaatsen van een THP of TKP, werden toegewezen tot de Eprex groep (preoperatieve epoëtine injecties) of de Bellovac ABT groep (postoperatieve “cell saving”). In de epoëtine groep ontving 4% van de patiënten op zijn minst één allogene bloedtransfusie terwijl dit 28% was in de cell saving groep. Geconcludeerd werd dat de behandeling met preoperatieve epoëtine injecties superieur is in het verminderen van de behoefte voor allogene bloedtransfusies bij patiënten met preoperatief een milde anemie.

In **Hoofdstuk 9** wordt het dagelijkse gebruik van het retransfusiesysteem in de orthopedische praktijk geëvalueerd. Er werd verondersteld dat de effectiviteit van het retransfusiesysteem in het dagelijkse gebruik minder is door verwachte terugval in de aandacht betreffende transfusiebeleid. In totaal worden 438 patiënten geanalyseerd in deze retrospectieve studie. De resultaten toonden dat de effectiviteit in overeenstemming was met resultaten gepresenteerd in de prospectieve studie in hetzelfde ziekenhuis. Echter, om verslapping van het transfusiebeleid te voorkomen is continue scholing van het medische team een belangrijke factor in het bloedmanagement.

Dit proefschrift besluit met een algemene beschouwing in **Hoofdstuk 10**. De antwoorden op de specifieke onderzoeksvragen zoals geformuleerd in het

eerste hoofdstuk, worden besproken in relatie tot de resultaten van alle uitgevoerde studies. De rol van postoperatieve “cell saving” in de orthopaedische chirurgie wordt tot in detail behandeld in dit laatste hoofdstuk. Bovendien worden aanbevelingen voor toekomstig onderzoek gedaan.

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Curriculum Vitae

CURRICULUM VITAE

Adrianus F.C.M. (Sjors) Moonen was born on October 23rd, 1975 in Udenhout, the Netherlands. He spent a happy childhood in Biezenmortel, a little village in the province of Noord-Brabant, with his brother and parents. In 1994 he graduated from high school (Atheneum) at the Maurick College in Vught and entered medical school at the University of Maastricht. At the time, he was a semi-professional soccer player for Willem II and MVV. His interest in sports injuries resulted in an enthusiasm for orthopaedic surgery. This intensified during an internship in "surgery and orthopaedics" in Eldoret, Kenya. After successfully graduating from medical school in 2001 (cum laude and clear pass) he went on a trip around the world with his best friends.

In 2002, he started working as a resident at the orthopaedic department of the Maasland Hospital in Sittard (headed by dr. A.D. Verburg). As part of his orthopaedic training, he completed a two-year residency in general surgery at the Isala Clinics, location Sophia in Zwolle (headed by dr. J.E. deVries) in 2004. From 2005 onwards he worked at the orthopaedic department of the Maasland Hospital again; in 2006 he started working as a resident at the Atrium MC in Heerlen (headed by dr. I.C. Heyligers). His orthopaedic training will be completed by the end of 2008 after a one-year period at the Academic Hospital Maastricht (headed by prof. dr. G.H.I.M. Walenkamp). In this final year, he recently performed a travelling fellowship in arthroscopy in several hospitals in Belgium.

During his orthopaedic training, he has worked on several studies examining the role of autologous blood retransfusion of filtered shed blood in orthopaedic practice. These studies resulted in this PhD thesis. In addition, he is working as a voluntary doctor in a medical team that assists at several sports events, such as the 2008 Olympic Games in Beijing, China.

In the year 2009, he wants to spread his wings and start working as an orthopaedic surgeon in the Netherlands.