

# Transfusion Reduction in Orthopedic Surgery

Ruud H.G.P. van Erve and Alexander C. Wiekenkamp  
*Beter Lopen, Deventer  
The Netherlands*

## 1. Introduction

Clinical research has identified blood transfusion as an independent risk factor for immediate and long-term adverse outcomes, including an increased risk of death, myocardial infarction, stroke, renal failure, infection and malignancy (Rawn, 2008).

Blood transfusion is however widely used in orthopedic surgery although the performed surgery is mostly elective. Since the surgeries can, in the majority of cases, be planned ahead it is possible to reduce the use of blood and blood products by planning their use as well.

In the past few years substantial steps have been taken to reduce the need for blood transfusion. The reduction of blood transfusion can be accomplished by several methods, the most successful of which seems to be a combination of different methods available. (van Erve, 2008). It is best to speak of blood management, which is the philosophy to improve patient outcomes by integrating all available techniques to reduce or eliminate allogeneic blood transfusions (Seeber & Shander, 2007). It should be a patient-centered, multidisciplinary, multimodal, planned approach to patient care (Seeber & Shander, 2007).

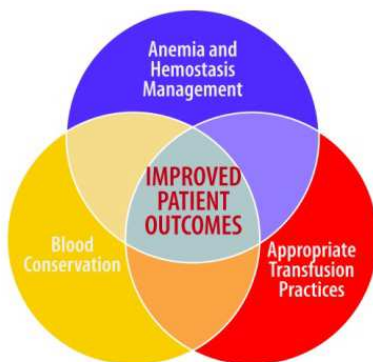
In order to reduce the use of blood in orthopedic surgery the following separate steps can be identified. First the patients can be optimized before surgery. Second, the use of blood conserving techniques during surgery is to be applied. These steps are considered as Anaemia and Hemostasis Management. Third, the transfusion triggers can be set as low as possible (Appropriate transfusion practices). Finally, the use of re-transfusion of drainage fluids from the surgical wound can be used (Blood conservation). All these measures should improve patient outcomes. Figure 1 illustrates the interconnection of the different parts of blood management.

In orthopedic surgery the above steps are relatively easy to carry out for there is sufficient time to organize them around the individual patient.

We will discuss all possible measures to be taken to reduce the use of allogeneic blood in orthopedic surgery.

## 2. Autologous transfusion

Patients can be encouraged to donate their own blood prior to surgery (pre-donation). The use of this technique is limited to surgery that can be planned ahead as it needs adequate planning and time to restore the hemoglobin level while the blood should not be taken too



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Fig. 1. Organogram as proposed by the Society for the Advancement of Blood Management (SABM)

early in order to have adequate red cell quality. The storage time of the patient's own red cells is the same as for allogeneic transfusions. Pre-donation should be done no more than 40 days before surgery because the storage time of red cells is limited and known to be of utmost importance to the quality of the cells. As most of the surgery done in orthopedics is elective, especially in adult reconstruction, this technique is highly suitable. In trauma surgery this technique is less feasible because of the lack of time to schedule it and the acute need for blood in most major trauma. In trauma surgery other techniques should be used to avoid the use of allogeneic blood. We will discuss these techniques later in this chapter.

Although pre-donated blood is safer than allogeneic blood it is not risk free and besides it is expensive (Domen, 1996). According to Domen the costs per saved quality adjusted life year may be as high as 1 million dollars. Vamvakas and Pineda found the cost effectiveness of pre-donation to be between 2,470 and 3,400,000 dollars per quality adjusted life year saved. The costs of predonation are high because the needs for collection, storage and avoidance of transfusion errors are expensive as well (Vamvakas & Pineda, 2000).

A specialized organization for the use of autologous blood is imperative for the blood has to be specially assigned to every patient individually. For each patient to be assigned his/her own blood an extensive security system is required to reduce the risk of interchanging blood between patients. This makes such a practice expensive. In order to avoid transfusion errors the safety measures for this type of autologous donation have to be the same as for allogeneic transfusion. Its use is therefore limited to hospitals with their own blood banks guaranteeing the safety of the blood harvested from the patients and used for their own re-transfusion when needed.

As the donated blood is not extensively tested for transferable diseases, nor typed and screened, the blood harvested from one patient cannot be used for other patients. Domen found in 1996 that only half of the autologous units collected are actually used. The amount actually needed might even be smaller because physicians in attendance may judge it a waste of good blood not to return the donated blood to the patient, thus giving more transfusions than strictly necessary using restrictive transfusion triggers (Domen, 1996).

Pre-donation includes the risks associated with blood donation in general. In fact all the signs of anemia can occur, dependent on the amount of blood donated and thus on the extent of the surgery planned. The pre-donation procedure introduces an acute iron deficiency anemia with all possible sign and symptoms. Especially in the elderly population, which in orthopedic surgery is the main target group, symptoms may occur. The expected symptoms are fatigue, headaches, faintness, breathlessness, angina, intermittent claudication and palpitations. The claudication will occur in a relative high percentage of the population for many of the orthopedic patients have vascular problems too. Because the pre-donation introduces an iron deficiency anemia it is to be accompanied by iron infusions or erythropoetin to enhance the production of erythrocytes in order to have the hemoglobin and the hematocrit at an appropriate level before surgery.

### 3. Pre-operative medication

The percentage of patients for major elective orthopedic surgery presenting with marked anemia is 10.5%, using the World Health Organisation (WHO) criteria (Bisbe et al., 2008), while Bierbaum et al found up to 35% hemoglobin levels of 13g/dl or less in patients in the USA (Bierbaum et al., 1999). According to several studies (Goodnough et al., 2011), the postoperative mortality and morbidity increase while the postoperative functional recovery and the quality of life is impaired in the presence of a preoperative anemia (Beattie et al., 2009; Conlon et al., 2008; Gruson et al., 2002).

Preoperative medication can be prescribed to enhance the amount of erythrocytes in the circulation. This can be combined with the previously described pre-donation but can be used separately as well. The trigger for the use of preoperative medication is set to 13.2 g/dl or lower (Goldberg MA et al., 1996). This threshold has to be taken into account to avoid introducing the risk of polycythaemia. If polycythaemia is introduced the risk for thrombosis, haemorrhage and cardiac failure increases. Although the increase of thrombotic or other complications has never been proven (De Andrade et al., 1996; Faris et al., 1996), the risk for thrombosis in orthopedic surgery is high enough without it being increased by medication, especially in hip and knee reconstructive surgery.

Mainly two types of drugs are used; iron and erythropoietin. We will describe these medications below.

#### 3.1 Iron

Intravenous iron can be used to boost the production of erythrocytes and is a component of autotransfusion practice. Especially in pre-donation it is extensively used. It is relatively safe and cheap medication though patients have to be admitted to hospital for the intravenous application. The adverse drug events have been studied by Johnson-Wimbley & Graham and Chertow et al. Some of the additional reported adverse events associated with iron preparations in their studies were hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting. These non life-threatening adverse reactions were more commonly associated with iron dextran and less so with iron sucrose or sodium ferric gluconate (50%, 36%, 35%, respectively) (Johnson-Wimbley & Graham, 2011). The absolute rates of life-threatening adverse drug events were 0.6, 0.9, 3.3 and 11.3 per million for iron sucrose, sodium ferric gluconate complex, lower molecular weight iron dextran and higher molecular weight iron dextran, respectively (Chertow et al., 2006).

In an elaborate review Chritchley & Yenel found adverse events to be rare with slightly higher numbers in high molecular weight iron dextran than in low molecular weight iron dextran (Critchley & Yenel, 2007).

The use of oral iron and of intravenous iron is being intensely studied at the moment. The Society for the Advancement of Blood Management publishes weekly articles of interest in his field at its website ([www.SABM.org](http://www.SABM.org))

The efficacy of preoperative iron supplementation is mounting. A study of 569 patients undergoing colorectal cancer surgery found that among the 116 patients who were anemic, intraoperative transfusion was needed in a significantly lower proportion of those who received 2 weeks of preoperative oral iron supplementation (200 mg) compared with those who received no iron therapy (9.4% vs 27.4%;  $P < .05$ ) (Okuyama et al, 2005).

According to Serrano-Trenas et al. intra-operatively iron infusion can be administered as successfully as preoperative iron infusions. They compared iron sucrose in hip fracture patients with no iron suppletion and found reduced transfusion requirements in patients with intra-capsular fractures and in those with hemoglobin levels of 12g/dl or more if given 600 mg intravenous iron during the operation (Serrano-Trenas et al., 2011). They found no difference in mortality, morbidity or length of hospital stay, however (Serrano-Trenas et al., 2011).

### 3.2 Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone normally produced in the kidney. The renocortical interstitial cells secrete it in response to reduced oxygen tension in the blood. Erythropoietin functions in the recruitment and differentiation of erythroid progenitor cells, aids in their maintenance and survival, and stimulates the synthesis of Hb (Ersley, 1991). The synthetic Epoetin alfa, the most used administered form of EPO available, is identical to endogenous erythropoietin in its amino acid sequence and biologic activity (Figure 2).

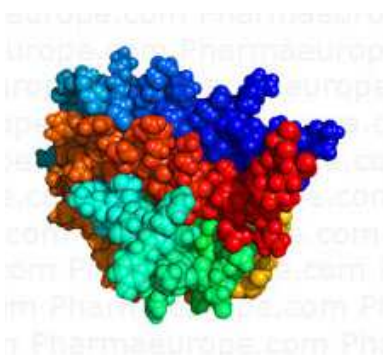


Fig. 2. Eprex molecule, a synthetic erythropoietin alpha ([pharmaeurope.com](http://pharmaeurope.com))

Like endogenous erythropoietin, epoetin alfa effectively and safely stimulates synthesis of Hb. The medication can best be administered subcutaneously with 4 injections during the 3 weeks prior to surgery with the last injection given in the operating theater. The subcutaneous method is better than the intravenous administration because the slow release from the depot provides a more sustained plasma level (Ersley, 1991). The amount

of erythropoietin given should be 300 IU/kg/day for 15 days peri-operatively or 600 IU/kg in 4 weekly doses beginning 3 weeks prior to surgery (Figure 3).

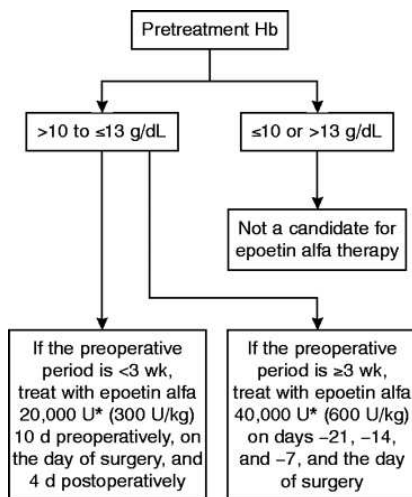


Fig. 3. Treatment algorithm for the use of Epoetin alpha in anemic patients scheduled for elective non-cardiac, non-vascular surgery at high risk for transfusion because of anticipated blood loss (Keating & Meding, 2002).

Erythropoietin should be used in combination with oral or intravenous iron administration to boost the erythrocyte production (García et al., 2009). If erythropoietin is used allogeneic transfusions are markedly reduced. In a prospective observational study of low Hb patients to whom 600 IU/kg EPO in 4 doses was administered, a transfusion percentage of 3.6% was found, while in the low Hb group who did not receive EPO the percentage was 45.2%, and in the normal Hb group 11.9% (Lafosse et al., 2010). The reduction of allogeneic transfusions reached with the administration of EPO was therefore 92% (Lafosse et al., 2010).

Epoetin alfa is expensive but very effective in increasing the Hemoglobin level of the patients by 4g/dl in 4 weeks (if administered 600 IU in 4 subcutaneous injections) which is equivalent to 5 units Red Blood Cells. The Canadian Coordinating Office for Health Technology Assessment performed an economic evaluation of erythropoietin use in surgery in 1998. In their report they state the costs of EPO to be less than 100,000 dollars per gained life year. Assuming 10% of all hip arthroplasty and cardiac bypass surgery patients need EPO they calculated the total costs for the Canadian health care to be 5.9 million dollars annually. These costs were to be made in order to have a potential benefit of 0.12 life years gained for the total population (Otten, 1998). If, however, the use of EPO and autologous transfusion are compared to pre-donation, EPO has better results in the increase of Hb and decrease of allogeneic transfusions (Deutsch, 2006).

#### 4. Peroperative measures

In orthopaedic surgery multiple options are available to help reduce the intra-operative need for allogeneic blood transfusion. Although some methods are very commonly used

worldwide, other methods are used less frequently. In this section we will discuss a selection of the major methods in the current orthopedic practice, divided into surgical and anaesthesiological techniques, autologous blood transfusion and anti-fibrinolytic drugs.

#### 4.1 Surgical and anaesthesiological techniques

During operation surgical haemostasis should be performed as thoroughly as possible. In orthopedic surgery electrocautery is the most widely used technique. Operations can be performed using a tourniquet and exsanguination to reduce the amount of shed blood. If, and wherever possible, the use of endoscopic techniques can help to reduce the amount of shed blood. The use of anaesthesiological techniques such as controlled hypotension, maintenance of normothermia and acute normovolemic dilution can reduce the loss of blood as well.

The usage of tourniquets in total knee arthroplasties is often used to help reduce the intra-operative blood loss (Matziolis et al., 2011; Smith & Hing, 2010; Zhang et al., 2010). Matziolis et al. found this to be an effective method to reduce intra-operative blood loss (Matziolis et al., 2011). A study by Zhang et al. found a decrease in intra-operative blood loss, but also a significant increase in post-operative blood loss (Zhang et al., 2010). A systematic review and meta-analysis by Smith and Hing found a significantly reduced level of intra-operative blood loss in patient groups where tourniquets were used, compared to non-tourniquet control groups. They state however, that there was no difference found in total blood loss and complications were more frequent in the tourniquet groups (Smith & Hing, 2010). The usage of tourniquets seems to reduce the amount of blood loss intra-operatively, but it increases the amount of post-operative blood loss. It is therefore useful to take proper post-operative measures, e.g. the use of post-operative autologous reinfusion systems or tranexamic acid. These methods will be discussed later in this chapter.

When using acute normovolemic dilution, patient's blood is withdrawn intra-operatively or shortly before the operation. The withdrawn blood is replaced by an equal volume of crystalloid or colloid solution. In normal circumstances 0,5-1,5 liters of blood are withdrawn from the patients circulation. This makes the blood lost contain less erythrocytes, making the loss of blood less important. The withdrawn blood is always re-transfused as autologous transfusion. Davies et al. compared different studies and concluded that acute normovolemic dilution may be a cost effective method to decrease the need for allogeneic blood transfusion (Davies et al., 2006). Goodnough et al. compared the methods of pre-operative autologous blood donation and acute normovolemic hemodilution in patients undergoing total hip arthroplasties. They found acute normovolemic hemodilution to be safe. No differences were found regarding the need for allogeneic blood transfusion in both groups. However, acute normovolemic hemodilution turned out to be significantly more cost effective than pre-operative autologous blood donation (Goodnough et al., 2000).

#### 4.2 Autologous transfusion

The option of intra-operative autologous transfusion is interesting because of the theoretical possibility for re-infusion of infinite amounts of blood. The use of autologous transfusion in orthopedic surgery is useful in large surgeries, i.e. spine and revision surgery, though not in infections and tumor surgeries. Autologous transfusion in smaller surgeries is not practical and expensive.

#### 4.2.1 Washed autologous transfusion

For over 30 years the method of washed autologous transfusion has been used successfully in multiple medical disciplines, especially in surgeries with expected major blood loss. The use of cell saving techniques is warranted to accomplish this. Herein the shed red cells are collected, washed, concentrated and re-infused into the patient. As stated before, the potency of re-infusing large amounts of blood is a great advantage of the cell savers. In orthopedic surgery however, the loss of blood intra- and post-operatively rarely approaches the huge amounts of blood loss in, for instance, cardiac or trauma surgery. In other words, the role of cell saving in orthopedic surgery is limited.

Carless et. al. conclude in their systemic review that cell salvage is an effective tool to reduce the need for allogeneic blood transfusion in both cardiac and orthopaedic surgery. They state however that many studies may have been biased and are therefore difficult to interpret (Carless et al., 2010). It is stated that intra-operative cell salvage is beneficial in surgery when blood loss exceeds 1,000 ml (Lemaire, 2008; Sculco, 1995). Davies et. al. find that cell salvage may be cost effective (Davies et al., 2006). However, it should again be noted that many studies may not be reliable due to biasing.

In their study, Benli IT et al. found higher hematocrit level in patient's blood when cell salvage was used intra-operatively compared to a control group (Benli et al., 1999). Usage of intra-operative cell salvage also provides advantages regarding post-operative wound infections and the healing process of the wound (Duffy & Neal, 1996; Steinitz et al., 2001; Weber et al., 2005).

The use of allogeneic blood transfusion comes with an increased risk of post-operative wound infections as is shown in two studies (Duffy & Neal, 1996; Steinitz et al., 2001). Duffy finds a decrease in post-operative wound infections when autologous blood is used for transfusion instead of allogeneic blood (Duffy & Neal, 1996). Also, the post-operative wound healing may be positively influenced by using cell salvage, as Weber et. al. find a longer healing process after usage of allogeneic blood transfusion, compared to a control group in which patients did not receive allogeneic blood transfusion (Weber et al., 2005).

The normal way to collect shed blood is using a vacuum suction device. Many studies have been done to identify the best ways of collecting, especially regarding vacuum suction pressure and blood-air contact. Gregoretti found in his study that a vacuum pressure of up to 300 mmHg could be used safely, considering that the levels of potassium, hematocrit and red blood cells did not change significantly when higher pressures than normal (above 150 mmHg) were used (Gregoretti, 1996). He did find however substantial influence of the air-blood contact on the level of hemolysis. A study by Waters et. al. showed that hemolysis increased when a higher vacuum pressure was used in the suction device. Furthermore, they found that suction from flat surfaces also increased the level of hemolysis, when compared to suctioning from a cavity (Waters et al., 2007). They advise diluting the blood with normal saline while it is collected, using minimal vacuum pressure and minimizing the contact between the collected blood and air, both in the suction tube as well as in the collecting device, for this too will increase the amount of hemolysis, thus reducing the quality of the blood. In another study Yazer et al. also conclude that a higher level of air-blood contact increases the level of hemolysis. They also found that hemolysis was decreased by using a vacuum suction device with variable pressure (Yazer et al., 2008).

Another interesting point of debate in cell salvage is the use of it in revision of metal on metal (MoM) hip prosthesis revisions which is increasingly problematic at present in orthopedic surgery. The MoM prostheses, which gained in popularity the past years, have lately proven to shed a lot of metal ions which induce increased levels of mainly Cobalt and Chromium ions in the plasma and full blood of patients and local pseudotumors consisting of large amounts of metal ions in granulomatous tissue surrounding the prostheses causing loosening. If those prostheses are to be revised the metal ions are likely to be sucked into the cell saver with the blood and the plasma components. The metal ions are mostly solved in plasma and incorporated in the leucocytes and thus reintroduced into the patient with the red cells and the leucocytes at retransfusion. Since these ions are known to be carcinogenic and tend to accumulate in the liver, the spleen, the kidneys and the lymphatic system the extra amount of these metal ions introduced in the patients circulation at re-transfusion of the salvaged blood during operation might increase the risk for serious long term complications. The effects of these metals have not been investigated properly since they have not been used in large quantities for long enough to induce carcinomas but the extra load of the ions which is potentially introduced during revision surgery has, potentially, such hazardous consequences that we think we should advise against using cell salvage in the presence of MoM prostheses. More research on this subject is desired.

#### **4.2.2 Non-washed autologous transfusion**

Using non-washed blood is a relatively new way to achieve reduction of allogeneic blood transfusion. In this method, shed blood is collected intra-operatively and is to be re-infused into the patients circulation after a filtration process. One has to consider that unwashed intra-operative autologous transfusion differs from the post-operative autologous transfusion, the method we will discuss in the next subsection of this chapter. While collecting the shed blood intra-operatively, large amounts of lipids and bone marrow will also be aspirated into the collecting device. This collateral catch may obstruct the filters of the device, ultimately blocking the system.

The lipids, if not properly filtered, can potentially increase the risk of fatty embolism if introduced in the circulation. The risks of these fatty embolisms have been described extensively in the literature concerning cemented hip prostheses as they are widespread during the preparation of the bone for the prosthesis.

Then there is the theoretical possibility to be considered of tiny bone fragments collected from the surgical wound to rupture the filter in the device or even cause vessel ruptures after being re-infused into the patient's circulation. However, the latter has never been described so far and is very difficult to prove.

The use of non-washed blood from the wound is still under investigation and debate. In three different studies, blood samples are tested after being filtered and considered to be safe when reinfused, regarding potassium, sodium, plasma haemoglobin and systemic haemoglobin levels (Bengtsson et al., 2008; Kvarnström et al., 2008; Stachura et al., 2008). Wiekenkamp et. al. however question the safety of this particular device as they found high levels of plasma haemoglobin (>0.64 g/dl) in their blood samples after filtration (Wiekenkamp et al., 2010). These levels are comparable with levels found by Kvarnström et. al. and Bengtsson et. al., 1.15 g/dl and 1.63 g/dl respectively. Wiekenkamp et. al. continue



with an example by stating: a normal person is physically capable to bind 0.03-0.2 g/dl of plasma haemoglobine to haptoglobine. Considering one has the capability to bind 0.2 g/dl and a circulating blood volume of six liters, a maximum of 12.0 g of plasma haemoglobin can be bound. Higher plasma haemoglobin levels will result in saturation of haptoglobine and the risk of binding of plasma haemoglobin to nitric oxide, which will result in dangerous reactive oxide radicals. In this case the maximum level of plasma haemoglobin to safely re-infuse 500 ml of filtered blood, is 2.4 g/dl. Considering that many patients have less binding capabilities, the risk of saturating haptoglobine and therefore endangering the patient with reactive oxide radicals is very real (Wiekenkamp et al., 2010).

### 4.3 Anti-fibronolytic drugs

The use of medical agents, like tranexamic acid, can be a useful tool to reduce blood loss preoperatively (Erstad 2001a; Erstad 2001b; Henry et al., 2011; Keating, 1999; Lemaire, 2008; Sepah et al., 2011). Anti-fibronolytic drugs are to be given pre-, intra- or post-operatively, depending on the kind of drug that is used. Purpose of using these anti-fibrinolytic agents is decreasing the volume of intra- and post-operative blood loss. Because of the relatively low costs and their successful use in many disciplines, e.g. gynaecology and cardiac surgery, the anti-fibrinolytic drugs are an interesting option in orthopedic surgery.

Henry et. al. found a decrease in blood loss and a lower need for allogeneic red cell transfusion when anti-fibrinolytic drugs were used. Aprotinin showed slightly better results than tranexamic acid or epsilon aminocaproic acid in comparative studies, but also a higher risk of death. No serious adverse effects were found while using tranexamic acid or epsilon aminocaproic acid (Henry et al., 2011). In a retrospective study comparing a group of patients who received tranexamic acid pre- or post-operatively to a group of patients who did not receive tranexamic acid, Sepah et. al. found a significant effect of tranexamic acid. Both the value of the mean Hb-loss and the mean volume of post-operative wound drainage had substantially decreased in the group of patients who received tranexamic acid (Sepah et al., 2011). Den Hartog et. al. compared a group of patients who did receive tranexamic acid intra-operatively with a control group in both total knee and in total hip surgery. In the total knee surgery a 55.6% decrease of blood loss was found post-operatively. In total hip surgery they found a decrease of 20.4% (den Hartog & Roorda, 2011).

In three studies no increased incidence of deep vein thrombosis was found when tranexamic acid is given to patients during total knee replacements (Nielsen & Husted, 2002; Orpen et al., 2006; Zhang et al., 2007). According to Nielsen, the optimal effect is reached by starting with a bolus of 10-15 mg/kg. There seems to be less effect in every dose given on top of the initial dose (Nielsen & Husted, 2002). The three afore mentioned studies conclude that the use of tranexamic acid in total knee replacements is an effective way to reduce post-operative blood loss. Camarasa et. al. find the decrease in blood loss reflected in a reduced requirement for allogeneic blood transfusions (Camarasa et al., 2006). In a study by Good et. al. a decrease in total blood loss was also found when using tranexamic acid in total knee replacements. They state however that the concealed blood loss was not that much influenced when tranexamic acid was used (Good et al., 2003).

In a meta-analysis and systemic review by Sukeik et. al., use of tranexamic acid in patients undergoing total hip replacements was studied. According to Sukeik the use of tranexamic

acid reduces the requirement for allogeneic blood transfusion. Furthermore, no significant differences were found between control groups and groups in which tranexamic acid was given, concerning adverse events, such as infection rates or deep vein thrombosis (Sukeik et al., 2011).

Ortega-Andreu et. al. compared a group of patients who received tranexamic acid intra-operatively to a control group, consisting of historical patients who had not received tranexamic acid. The tranexamic acid group showed a decrease in allogeneic transfusion rate, lower visible blood loss and proved to be more cost effective than the control group (Ortega-Andreu et al., 2011).

Given the relatively low costs, the effectiveness and the slight chance of adverse events, it can be stated that usage of tranexamic acid is a safe and reliable way of decreasing the need for allogeneic blood transfusion.

## 5. Postoperative techniques

Postoperatively it still is possible to reduce further allogeneic transfusion.

### 5.1 Re-transfusion of wound drain fluids

In orthopedic surgery, especially adult reconstruction surgery, such as hip and knee replacements, most patients lose about 1-1.5 liters of blood during surgery if it is not performed using a tourniquet. Especially in knee surgery the tourniquet can, as previously described, reduce the preoperative bloodloss substantially. If a tourniquet has been used, the patient will still lose some 1-1.5 liter blood from the wound but using postoperative collection techniques this blood can be returned to the patient and thus reduce further allogeneic blood transfusion. In hip surgery the use of a tourniquet is, of course, not possible so the amount of blood, shed during surgery, is higher and the use of drainage fluids to return to the patients is more arguable.

At the end of the operation wound drains may be left behind in the wound to reduce swelling and hematoma formation. The fluid from these drains can be collected and, after filtration, be re-infused to the patient (Hendriks et al., 2009). We conducted several studies concerning the use of these drains and their safety. If such a system is to be used the first choice to be made is the type of system one wants to use. Several types of systems are marketed. The main difference between them is the application of continuous vacuum or intermittent vacuum using a bellow system. A second difference between systems is the filter used to reduce the amount of leucocytes and thrombi. Most systems use standard Sangopur® filters which is a gradual screen filter with pore size of 80 and 40 microns. Some systems use a Pall Lipiguard® Filter, which is a depth filter consisting of polyester screen media with variable pore size with the smallest size being 40 microns. A third difference is the vacuum pressure reached. In the bellow systems the maximum vacuum pressure reached is 90 mmHg, whereas in the continuous vacuum systems the vacuum pressure can be as high as 150 mmHg.

The numerous differences between the systems make comparison difficult and give rise to continuous debate.

### 5.1.1 Vacuum type and pressure

The vacuum type and especially the vacuum pressure has been the subject of debate between producers. It has not been proven one or the other is better. The erythrocytes seem to be able to survive equally well in 90 as in 150 mmHg vacuum. If the vacuum were a problem at higher values the erythrocytes would burst and thus the plasma hemoglobin would be raised in comparison to low vacuum systems. This seems not to be the case if blood is suctioned from containers (Waters et al., 2007). If suctioned from a flat surface the vacuum pressure does make a difference though it is very small (Yazer et al., 2008). 'Although the variable-pressure device produced a significant reduction in hemolysis during one-pass blood collection, the clinical significance of this reduction is not clear. In relative terms, the variable-pressure device would recover an extra 10 ml of RBCs for every liter of salvaged RBCs, which is negligible compared to the blood loss in major surgery.' The drains used in wound drainage, however, do not suck the blood from a flat surface, but from a cavity, more like the cups used in Water's study previously mentioned. Since the vacuum pressure does not seem to matter if the blood is taken from a cavity the activity of the vacuum on the wound healing as such might be taken into account.

The type of vacuum used has proven differences if the effects on wound healing are compared. Berman et al. proved that 80% of the total drainage is collected within 6 hours post-operatively with a constant suction device, whereas with intermittent suction this is spread over days (Berman et al, 1990). Furthermore they state that a clear advantage to using a continuous vacuum suction device over an intermittent spring-loaded device is seen with respect to hematoma evacuation, wound drainage, wound healing, and possible complications.

There are no proper studies addressing the differences between continuous and intermittent suction in re-transfusion drain models.

### 5.1.2 Filter type

One point that needs addressing if we speak about filter type is whether or not leucocytes from the wound are to be re-transfused into the patient. Especially in cardiac surgery patients who need more than three blood transfusions, leukocyte depletion by filtration of the allogeneic blood, results in a significant reduction of the postoperative mortality. This effect can only partially be explained by the higher incidence of postoperative infections in those receiving packed cells without buffy coat (van de Watering et al., 1998). Some researchers believe the activated leucocytes do no harm, might even improve wound healing by triggering the body to a generalized activated state of inflammation, thus reducing the amount of infections (Innerhofer et al., 2005). The leucocytes activated in the study of Innerhofer, however, were activated by contact with foreign surfaces, not by the wound itself for he used pre-donated autologous blood and compared that to allogeneic blood. Others believe thus activated leucocytes induce a generalized activation of the immune system which reduces lung function and increases the inflammatory response of the body (Gu et al., 1996). Especially in cardiac surgery the effects of extracorporeal circulation have been extensively investigated. Contact of blood with foreign surfaces, as in the containers of the retransfusion systems, activates complement and leucocytes (Kirklin, 1991), as does the suction of the blood from the surgical wound (Bengtsson &

Lisander, 1990; Sieunarine et al., 1991). Washing the blood, which is done in intra-operative cell salvage, does reduce the complement complexes but in the postoperative systems in which the blood is not washed but only filtered, these activated complement complexes pass some of the filters used. Moonen et al described that filters do have an influence on the quality of retransfused blood. The Pall® filter reduced the amount of leucocytes and thrombocytes more adequate then the Sangopur® filter with the latter allowing more erythrocytes to pass (Moonen et al., 2008). The thrombocytes found in the transfused blood using the Sangopur filter® are, since they are not found with use of the Pall® filter and both filters are 40 microns large, likely to be thrombi and not loose thrombocytes. This might mean that the activated complement complexes, being incorporated in the thrombi, pass the Sangopur® filter, thus activating the body's inflammatory response. Some studies investigating the general reactions of the body to retransfused blood found no transfusion reactions nor fevers when transfused with unwashed, filtered autologous blood. Some chills were found, though (up to 3,1%), with use of a non-leucocyte depleting filter (Athanasoulis et al., 2007; Horstmann et al., 2010). Duchow et al found high levels of factor XIIa, thrombin and fibrin generation markers, and markers of fibrinolysis in the shed blood. After re-transfusion increased levels of these markers together with decreased values for factor XIII and plasminogen were found in the circulation indicative of renewed clot formation and fibrinolysis. These changes were highly significant compared to pre-re-transfusion values of the patient's blood. The unwashed drainage blood contained high levels of pro-coagulation material and induced an activation of the plasma coagulation pathway with renewed clot formation and fibrinolysis in the patients (Duchow et al., 2001). De Jong et al found similar results as they found markedly increased activation of leucocytes and platelets and a distinctive decrease in platelet count of the recipient after infusion, thus potentially favoring thrombosis (de Jong, 2007).

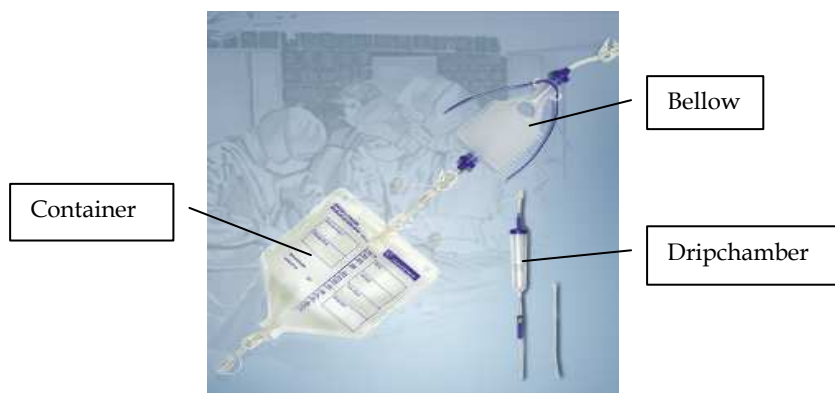


Fig. 4. The Sarstedt retransfusion system

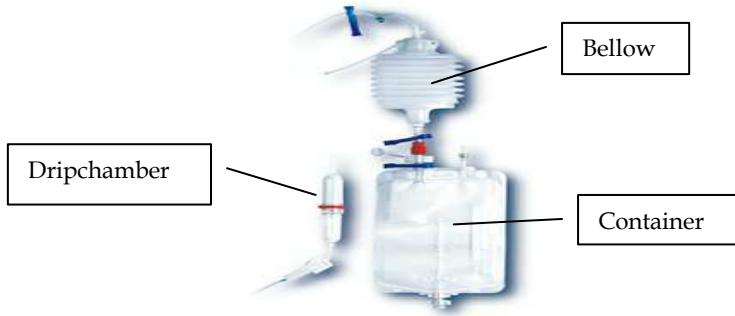


Fig. 5. The Bellovac ABT system

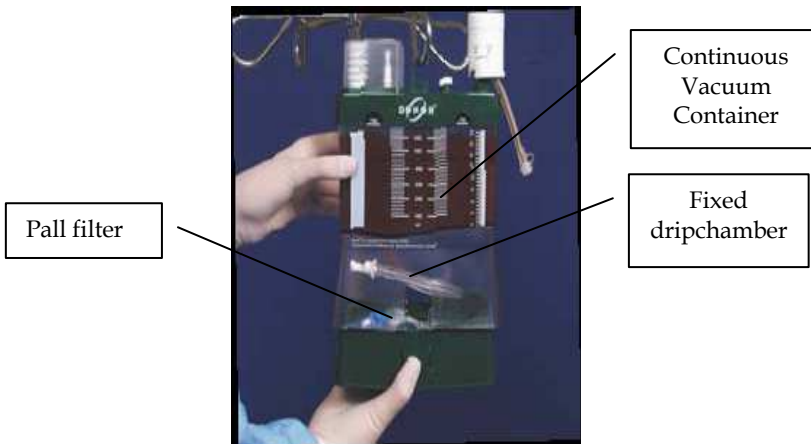


Fig. 6. The Donor system

**5.1.3 Total system comparison**

No published studies have been done comparing different draining systems for re-transfusion of drain fluids. In a study comparing three systems in a total of 80 patients with 52 hip and 28 knee arthroplasties, a system sold by Sarstedt® (28 patients), which is a bellow system using a stepwise filter of 120 to 10 microns, one from Astra Tech (Bellovac ABT®)(24 patients), which uses a bellow system and a Sangopur® filter and one from van Straten Medical (Donor®)(28 patients) with a Pall Lipiguard® filter, we tested the Hb, leucocytes, complement C5 and antithrombin 3 (AT3). In the final samples, just before infusing the blood into the patients the measurements were done. Patient characteristics were comparable, and a mean of 484 ml (150-1300 ml) drain fluid was collected. No differences between the systems regarding the amount of drain fluids collected were found. Table 1 shows our findings.

|                                  | Sarstedt | Bellovac | Donor |
|----------------------------------|----------|----------|-------|
| Hb (g/dl)                        | 8.86     | 11.28    | 11.44 |
| Leucocytes (x10 <sup>9</sup> /l) | 3.8      | 3.4      | 0.5*  |
| C5 (IE/ml)                       | 78.7     | 87.7     | 80.6  |
| AT3 (% of normal)                | 31.8*    | 41       | 37.5  |

Table 1. Blood component concentrations in the retransfusible blood in the different systems. (\*p<0.05)

As the table shows the levels of AT 3 are substantially lower than normal in blood (0.12 mg/ml), while the levels of C5 are normal and the Hb levels are low. The leucocytes are adequately filtered by the Pall® filter. AT 3 is known to be low after major surgery. Obviously the complement has not been used to activate clotting, not even in the Donor® system which is the only system without heparin coating in the container (van den Boom & van Erve, non published data). The quality of the blood collected in the three systems seems to be comparable although the systems do have different collection mechanisms, (two bellows and one continuous vacuum), different suction pressures (Sarstedt® 70 mmHg, Bellovac ABT® 90 mmHg and Donor® 150 mmHg) and also different filter systems, as previously described.

The choice of system seems to be led by the wish of the physician in attendance to donate the leucocytes and the thrombi back into the patient. Since that is not adequately proven to be good or bad, as mentioned earlier, it remains the choice of the orthopedic surgeon.

#### 5.1.4 Effects of the introduction of re-transfusion of drainage fluid in orthopedic surgery

To determine whether or not the introduction of re-tansfusion of drainage fluid is worthwhile we did a prospective observational study (Hendriks et al., 2009). We compared 195 patients before introduction of the re-transfusion system in our hospital to 175 patients after the introduction of the device. We used the Donor® type drain as described earlier. A restrictive transfusion trigger was used for all patients and patients with a preoperative Hb lower than 13.2 g/dl received EPO (4 doses of 600 IU each). All patients were treated with Acenocoumarol to prevent thrombosis starting the day of surgery (INR targetlevel: 2.5-3.4). Hip and knee arthroplasty patients were evenly distributed between groups as were the other patient characteristics (Table 2). The use of re-transfusion of drainage fluid reduces the use of allogeneic transfusions by 70-98% depending on the type of surgery and the system used.

|   | Total hip arthroplasty |                 |         | Total knee arthroplasty |                 |         |
|---|------------------------|-----------------|---------|-------------------------|-----------------|---------|
|   | No autotransfusion     | Autotransfusion | p value | No autotransfusion      | autotransfusion | p value |
| Nr of patients                            | 128                    | 100             |         | 67                      | 68              |         |
| Male (n/%)                                | 37 (29)                | 34 (34)         | 0.41    | 17 (25)                 | 15 (22)         | 0.65    |
| Mean age (range)                          | 70.5 (39-95)           | 69 (46-90)      | 0.20    | 71.5 (38-91)            | 73.7 (53-93)    | 0.16    |
| Mean nr RBC's (range)                     | 0.4 (0-4)              | 0.06 (0-2)      | <0.01   | 0.8 (0-6)               | 0.02 (0-1)      | <0.01   |
| Mean volume autotransfusion in ml (range) |                        | 409 (0-750)     |         |                         | 505(0-1000)     |         |

Table 2. patient characteristics and results of a study into the effects of introductions of an autotransfusion system on the need for allogeneic transfusions in hip and knee arthroplasty patients. (RBC = unit allogeneic blood, p is calculated using  $\chi^2$  or t-test)

In a logistic regression analysis in this study the only factor of interest proved to be the use of autologous transfusion.

## 5.2 Use of a restrictive transfusion trigger

Another important measure to be taken after the operation is the use of a restrictive transfusion trigger. This means that the patient should not be given blood unless the oxygen transport capacity is proven to be lower than the tolerable threshold. The University of Groningen together with the CBO (Centraal Begeleidings Orgaan, Dutch for Central Counseling Bureau) developed a guideline for transfusion which is widely used throughout The Netherlands. It is called 4-5-6 rule (the Hb is expressed in mmol/l in The Netherlands) the international formulation would be: 6.5-8-9.7 rule. The rule is adopted by the national Bloodbank, Sanquin®, and put forward in their transfusion manual (van Rhenen et al., 2011).

This rule uses the ASA class (system developed by the American Society of Anesthesiologists) as a guideline to the patient's general health. The ASA class defines the general condition of the patient's health and is used by anesthesiologists worldwide to assess in easy terms the preoperative condition of the patient.

Consider transfusion if the Hb < 6.5 g/dl (Ht: 0,20) and if there is :  
acute blood loss in healthy individuals (ASA-class I) < 60 years old with normovolemia and blood loss in 1 location  
chronic asymptomatic anemia.

Consider transfusion if the Hb < 8 g/dl (Ht: 0,25) and if there is:  
acute blood loss in healthy individuals (ASA-klasse I) ≥ 60 years old with normovolemia and blood loss in 1 location  
acute blood loss in healthy individuals < 60 years old with normovolemia and blood loss at more than 1 location (polytraumapatienten)  
expected blood loss > 500 ml in a patient < 60 years old who will be operated upon  
fever  
uncomplicated post-operative period after open heart surgery  
uncomplicated ASA-class II en III

Consider transfusion if the Hb < 9.7 g/dl (Ht: 0,30) and if there is:  
ASA-class IV  
Inability to increase heart minute volume to compensate for haemodilution  
sepsis or toxinemia  
serious lung disease  
symptomatic cerebrovascular disease

Formulated by: University Medical Centre Groningen.

Source: [www.cbo.nl/product/richtlijnen/folder20021023121843/bloedkaart.pdf](http://www.cbo.nl/product/richtlijnen/folder20021023121843/bloedkaart.pdf)

**ASA-Classes:**

- I: healthy individuals;
- II: patients with a mild systemic defect, without functional impairment;
- III: patients with a seriously impairing systemic defect;
- IV: patients with a systemic defect that poses a constant threat for life;
- V: patients who are moribund and who will, with or without operation, probably die within 24 hours.

The 4-5-6 rule is an easy to use guide to whether or not transfuse patients based on their capacity to cope with anemia. Several studies showed that postoperative anemia is generally well tolerated as it is in the critically ill. Post-operative anemia after cardiac operations, with hemoglobin levels of 8 to 10 g/dl is well tolerated in patients who have not received a transfusion and induces only a transient impairment of exercise tolerance (Ranucci et al., 2011). Moreover, in critically ill patients a restrictive transfusion trigger is well tolerated (Nichol, 2008) as it is in critically ill children (Lacroix, 2007). The rule of thumb as formulated by the University of Groningen and accepted by the Dutch National Bloodbank and the counseling bureau has proven right in even the critically ill.

For the international community one could consider to change the lower limits from 6.5, 8 and 9.7 to 7, 8 and 10 to make it easier to remember, which is one of the prerequisites for a good rule while still being safe. The limits are thus a little higher than needed, but are comprehensive, easy to remember, easy to use and proven safe. It saves a little less blood than with the limits set more restrictive but the easy application makes the rules more widely acceptable and introducible.

## 6. Conclusion

In orthopedic surgery, as in other surgeries and in the critically ill, the use of allogeneic blood can be reduced using a wide variety of methods and techniques. All those different methods individually have proven to contribute to the reduction of the use of bank blood. Few if any studies have been done to find out what the combined effect of the introduction of the different methods is. Generally it is assumed the methods and techniques reinforce each other. The additive effect of the used methods is, however, not clear.

The costs of the combination of blood saving methods may, in the end, outweigh the costs of allogeneic blood. It is, however, very difficult to determine the costs of allogeneic blood. In addition to that, the costs are different for every country because of the difference in blood bank systems, salaries and overhead costs.

The effect of hospital admission time has been made clear by Weber et al. who described an increase of hospital admission time of 2.7 days (+/- 0.5 days) per transfused unit of red blood cells in total hip arthroplasty patients (Weber et al., 2005). In a study we performed in 1,422 patients who received a total hip arthroplasty, we found the administration of allogeneic blood to be one of the independent variables in a stepwise regression analysis, for



hospital admission time, increasing admission time by 1.78 days per unit Packed cells (p<0.000) (van Erve et al., 2010).

All in all it seems appropriate for all of the above-mentioned measures to be combined to reach the goal set, which is to reduce the administration of allogeneic blood to the minimum.

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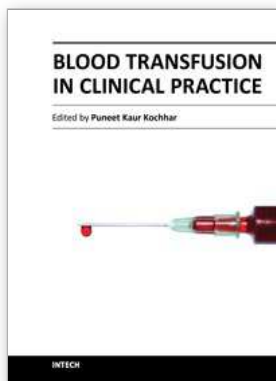
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Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group system in blood transfusion. The second section discusses the use of transfusion in various clinical settings including orthopedics, obstetrics, cardiac surgery, etc. The third section covers transfusion transmitted infections, while section four describes alternative strategies to allogenic blood transfusion. The last section speculates over immunomodulatory effects of blood transfusion.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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