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Blood Transfusion Practices in Major Orthopaedic Surgery

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1. Introduction

Blood forms a major component in the management of surgical patients in whom major blood loss is expected. In the past years, transfusion of allogeneic blood has been the mainstay of management of patients who have or are considered to be at risk of major bleeding, particularly in cardiac and orthopaedic surgery where blood loss can often be substantial. Studies have shown that in many countries across the world, over fifty per cent of red cells transfused were in surgical specialties (Cook 1991;Lenfant 1992;Regan 2002). For example, in Canada, 31% of all red cell transfusions were given in cardiac and orthopaedic surgery (Chiavetta 1996).

2. Blood loss in orthopaedic surgery

In primary hip surgery, the blood loss is estimated at 3.2 +/- 1.3 units(Toy 1992) and 4.07 +/- 1.74 grams of haemoglobin(Toy 1992). In revision hip surgery, the blood loss is about 4.0 +/- 2.1 units. In primary knee replacement, the blood loss ranges from 1000-1500mls and can average 3.85 +/- 1.4 grams of haemoglobin(Keating 1998;Mylod, Jr 1990) and may be higher in cementless knee replacements(Hays 1988). Transfusion rates of 2.0 +/- 1.8 units for primary THR and 2.9 +/- 2.3 units for revision THRs have been documented(Bae 2001). The rates for knee replacements are not well studied but are estimated at 1 – 2 units for primary surgery and can be up to 3-4 units for revision surgery(Callaghan 2000).

Other settings which present major blood loss scenarios in orthopaedic surgery include:

- Pelvic surgery
- Tumour surgery
- Bilateral primary joint replacement

3. Predictors of allogeneic blood transfusion

A series of studies covering a heterogeneous population of over 10,000 patients has attempted to define certain risk factors that may predict the need for allogeneic blood transfusion. All studies made an attempt to reduce confounding factors and risk factors

were shown to be consistent with high levels of statistical significance in their association with the risk of exposure to allogeneic blood.

Preoperative haemoglobin level is one of the main factors associated with risk of transfusion following total joint replacement(de, Jr 1996;Faris 1999) . In a study of 9,482 patients who underwent THR or TKR, Bierbaum *et al* demonstrated that the lower the baseline haemoglobin level, the more probable the transfusion of allogeneic blood(Bierbaum 1999) . Patients with a preoperative haemoglobin of less than 100g/L had a 90% chance of needing a transfusion, those with a level of 100-135g/L had a 15-25% chance of requiring allogeneic blood(Callaghan 2000).

Age over 65 years(Hatzidakis 1998;Hatzidakis 2000) has been shown to increase the risk of being transfused with patients less than 65 years with a haemoglobin of 135g/L or more having only a 3% chance of being transfused.

Other risk factors that have been closely associated with a likelihood of allogeneic transfusion include low weight, small height, female sex, estimated surgical blood loss, whether primary or revision surgery, type of surgery, anticoagulant use, thrombocytopaenia, other comorbidities and bilateral joint surgery(Bierbaum 1999; Borghi 1993; Churchill 1998; Hatzidakis 2000).

4. Risks of allogeneic blood transfusion

The association of allogeneic blood with numerous risks including transfusion transmitted infections (TTIs) has limited its utility in recent years(Klein 2000). Thus, there is now considerable interest in finding ways to avoid allogeneic blood.

1. Tranfusion transmitted infections (TTIs)

   The risks of transfusion transmitted infections have been considerably reduced in the developed world by measures to improve the detection and elimination of infected blood (Goodnough 1999a). The total TTI risk has been estimated at 1:100,000 to 1:1,000,000 in an American population (Kleinman 2000). However in developing countries, there is still a high prevalence of such infections and transfusion services are still inadequately equipped to conduct universal antibody screening (Lackritz 1998; McFarland 1997).

   a. Viral infections

      The risks of viral TTIs can be regarded as being very low in the developed world when compared to other life time risks (Glynn 2000;Regan 2000).

      The following are estimated risks (Klein 1995;Klein 2000):

Human Immunodeficiency Virus (HIV)	1:1,000,000
Hepatitis B Virus (HBV)	1:100,000
Hepatitis C Virus (HCV)	1:500 to 1:5,000
Human T-Lymphocytic Virus 1 and 2 (HTLV)	1:200,000
Cytomegalovirus (CMV)	1:2,500

      A previous retrospective analysis of data from the United States, Australia and Europe found that in repeat donors, seroconversions were detected as follows (Muller-Breitkreutz 2000):

Anti-HIV screening	1:2,323,778
Anti-hepatitis C screening	1:620,754
Hepatitis B screening	1:398,499

Other viral infections such as Guillian-Barre virus C, human herpes virus and TT virus have not to date been shown to be relevant to transfusion practice (Allain 2000).

b. Bacterial infections
This risk is estimated at 1:400,000 transfusions (The SHOT Committee 2000).

c. Creutzfeld-Jacob disease
Universal leucodepletion of all blood prepared for transfusion, excluding previously transfused UK donors and excluding donor plasma from fractionation are precautionary measures instituted to prevent the transmission of CJD (Scottish Intercollegiate Guidelines Network 2001).

2. Direct immune injury
Mild haemolytic reactions range from 1:5,000 to severe haemolytic reactions and anaphylaxis in 1:600,000 (Callaghan 2000).

3. Immunomodulation
In vitro, allogeneic blood has been shown to have the capacity to depress immune function (Gafter 1992; Kaplan 1984), an effect mediated mainly by transfused white blood cells (Blajchman 1994; Bordin 1994). However, the clinical importance of this effect is poorly understood (Goodnough 1999a). The practice of leucodepletion of blood is now commonplace in developed countries. However, studies have not demonstrated a clear cut clinical benefit of this practice. Randomized control trials using both leucodepleted blood and autologous blood have not demonstrated an increase in either the risk of cancer or infection (Goodnough 2000; Jensen 1998). A meta-analysis of three randomized control trials and two cohort studies where control groups received either leucodepleted blood or autologous transfusion found no significant differences in cancer recurrence (McAlister 1998).

4. Procedural/clerical error
The blood transfusion process can be complex and crosses many disciplines and professions, with one study identifying over forty steps between the patient and their transfusion, all of which involve the potential for human error(Will 1996). Clerical error has been estimated at 1:25,000 (AuBuchon 1996). Serious complications including coagulopathy, renal failure, intravascular haemolysis, admission to ITU, persistent viral infection and death have been estimated at 1:67,000 (Scottish Intercollegiate Guidelines Network 2001; The SHOT Committee 2000). These risks can be controlled by using safe protocols for transfusion, for example those recommended by the British Committee for Standards in Haematology.

5. Risks of perioperative anaemia

Some studies have shown that surgical morbidity and mortality are inversely correlated with preoperative haemoglobin levels (Carson 1988;Spence 1998). The rate of fatal complications due to anaemia in sixteen reports of the surgical management of Jehovah's witnesses has been reported at 0.5-1.5% (Kearon 1997). A retrospective survey of a similar patient population indicated that when confounding factors were taken into account, mortality does not increase as haemoglobin falls to 80g/L (Carson 1996; Carson 1998a).

However, below this level, ninety per cent received transfusions and thus it is hard to comment on the effect of anaemia on mortality at haemoglobin below this level.

Substantial perioperative blood loss is common in major orthopaedic surgery and patients are often elderly with a high prevalence of ischaemic heart disease. Consequently, many who are undergoing major orthopaedic surgery will be at high risk of cardiovascular complications (Neill 2000). The incidence of anaemia increases with age (Ania 1997) and is four to six times greater than can be predicted by clinical symptoms in the over 65 year age group (Ania 1997).

Perioperative anaemia in the elderly is not without morbidity and includes fatigue, tachycardia, hypotension, dyspnoea and impaired level of consciousness (Spence 1998) and can be associated with decreased vigour, potentially prolonging the duration of hospital stay (Bierbaum 1999;Keating 1999) and affecting quality of life. Indeed a correlation between muscle strength and haematocrit levels suggests that haematocrit may be a valuable objective measure of vigour in patients undergoing major orthopaedic surgery (Keating 1999).

In patients with known cardiovascular comorbidity, severe preoperative anaemia can be associated with a massive increase in mortality. Carson *et al* (Carson 1996) reported that the 30-day mortality rate in patients with preoperative Hb levels of less than 60g/L was 33.3% compared with 1.3% for those with levels in excess of 120g/L.

Observational studies and consensus statements suggest that the elderly and those with a poor cardiovascular reserve or major cardiovascular comorbidity or peripheral vascular disease are less tolerant to perioperative anaemia and should therefore be transfused at a higher haemoglobin level(Carson 1998a).

6. Transfusion thresholds

In an attempt to provide optimal patient management balanced with patient safety, it is now common practice for clinicians to define transfusion thresholds of haemoglobin below which level the patient's haemoglobin should not fall during the perioperative period.

6.1 Preoperative thresholds

It is known that preoperative anaemia increases the likelihood of allogeneic transfusion (Spence 1990) and hence an attempt should be made to correct the haemoglobin level prior to a major orthopaedic operation where inevitably, a substantial amount of blood loss is expected or anticipated. When patients refuse a blood transfusion, for example due to religious convictions, the preoperative haemoglobin level becomes all so important as a determinant of operative outcome, particularly in the elderly and those with major cardiovascular comorbidity (Carson 1996;Spence 1990). Usually, a preoperative lower limit of 100g/L is taken prior to major orthopaedic surgery, in spite of there being little evidence for this arbitrary level (Scottish Intercollegiate Guidelines Network 2001).

6.2 Intraoperative thresholds

Accurate measurement of intraoperative blood loss is difficult. Rapid intraoperative measurement of haemoglobin levels using near-patient testing may improve safety margins

and avoid unnecessary transfusions (Loo 1997;Smetannikov 1996). However, intraoperative measurements must be interpreted in the context of a multifaceted clinical assessment of the patient in real time intraoperatively. This should include a clinical evaluation of blood volume status, on-going and anticipated postoperative bleeding (de Andrade Jr 1996, Welch 1992).

6.3 Postoperative thresholds

Experimental data from animal studies (Spahn 1992; Spahn 1994) indicate electrocardiographic changes occur between the haemoglobin levels of 50-70g/L and in one study in healthy humans during normovolaemic haemodilution, adequate oxygen delivery to tissues was sustained down to a haemoglobin level level of 50g/L (Weiskopf 1998).

A large randomized control trial performed over 800 patients admitted to intensive care (Hebert 1999) where patients were randomized to a haemoglobin level of 70-90g/L or 100-120g/L transfusion thresholds showed no significant differences in 30-60 day mortality or severe ventricular dysfunction between the two groups. However, caution is recommended in extrapolating these figures from the critical care setting to patients having routine elective orthopaedic surgery. Another large retrospective study of surgical patients found that, allowing for confounding factors, there was no definite difference in mortality using a lower threshold of either 80g/L or 100g/L as a transfusion threshold (Carson 1998a).

Guidelines and consensus statements have consistently expressed the transfusion threshold as a range between 70g/L and 100g/L, with clinical indicators further defining the need to transfuse in between these levels (Anon 1996; Simon 1998; Spence 1995).

A small randomized control trial involving elderly patients with fractured necks of femur found no difference in mortality in patients transfused when symptomatic or with a haemoglobin of less than 80g/L compared with the haemoglobin maintained at 10g/L(Carson 1998b). This study was limited by its inadequate analytical power to show significant differences in mortality and myocardial events(Scottish Intercollegiate Guidelines Network 2001). Most guidelines and consensus statements propose a higher transfusion threshold of 80-90g/L for those who are elderly, with cardiovascular comorbidity or peripheral vascular disease, rather than the lower level of 70-80g/L (Hebert 1999; Hill 2002).

7. Blood sparing strategies

Blood sparing strategies should be considered in every patient undergoing major blood loosing surgery in orthopaedics. In addition, special situations where these can be considered and may indeed be the only alternative include Jehovah's witnesses, those with multiple antibodies and those with serious anxieties about allogeneic blood transfusion.

Strategies include the following:

- Preoperative autologous blood donation (PABD)
- Acute normovolaemic haemodilution (ANH)
- Surgical technique
- Anaesthetic techniques
- Pharmacological therapies

- Increase RBC production – erythropoietin
- Reduce bleeding – antifibrinolytics, topical haemostatic agents, recombinant factor VII

- Cell salvage
  - Intraoperative
  - Postoperative

7.1 Surgical technique

Adherence to prescribed guidelines for maintaining haemostasis such as electrocautery and argon beam coagulation may reduce perioperative blood loss(Spence 1995).

7.2 Anaesthetic techniques

Specialist anaesthetic techniques such as hypotensive anaesthesia (Sharrock et al. 1993), regional anaesthesia (Carson 1998a; Dauphin 1997) and euthermia (Schmied 1996; Schmied 1998) may reduce surgical bleeding in arthroplasty surgery. For example, in one study, a difference in mean arterial pressure of 10mmHg significantly reduced mean intraoperative blood loss from 263mls to 179mls on average in patients undergoing primary THR (Sharrock 1993).

7.3 Preoperative autologous blood donation (PABD)

This entails the patient donating a unit of blood every week for 3-5 weeks preoperatively. This has been demonstrated to be safe and effective in the elective surgical setting and is widely practiced in a number of countries. 20 years ago, less than 5% participated in PABD before elective surgery in the United States and Canada. Today it ranges from 50-75% depending on the centre (Goodnough 1999b).

In orthopaedic surgery patients it has been used safely in elderly populations with diverse comorbidities (Kleinman 2000). However, it is recommended that patients should be stratified according to the risk of requiring a transfusion and should be considered if the likelihood of transfusion exceeds 50%.

The effectiveness of PABD in reducing patient exposure to allogeneic blood has been studied in a meta-analysis of six randomized control trials and nine well conducted cohort studies (Forgie 1998). Patients who pre-donated blood were less likely to receive allogeneic blood but autologous donors were statistically more likely to undergo any kind of transfusion, allogeneic or autologous. This is to say that PABD reduced allogeneic blood exposure albeit increasing the total number of transfusion episodes.

In another study, when the presenting haemoglobin was 110-145g/L in men and 130-145g/L in women, PABD was shown to reduce the expected number of patients exposed to allogeneic blood to less than 20% of the total (Hatzidakis 2000;Nuttall 2000).

Over collection of blood is a problem with PABD and often results in routine collection of more blood than is needed for the average patient(Keating 2002). When the presenting haemoglobin is between 110-145g/L (Voak 1994) PABD is unnecessary and limiting PABD to two units for joint replacement is usually sufficient to avoid most allogeneic blood

exposure(Bierbaum 1999;Churchill 1998). The magnitude and rate of patient response to compensatory erythropoiesis to replace lost red cells has also generally been overestimated(Goodnough 1999b) and can result in preoperative anaemia. A study of 225 patients estimated that compensatory erythropoiesis resulted in preoperative red cell production of 351mls compared with a mean loss of 522mls from weekly donated autologous blood (Kasper 1997). The degree of compensatory erythropoiesis is also dependant on initial iron stores (Goodnough 1995) and it may be necessary to supplement patients with iron.

Although its use has increased substantially over the past decade, it can be associated with risks such as ischaemic events and complications severe enough to require hospitalization (Popovsky 1995). Although rare, bacterial contamination of stored autologous units can rarely cause sepsis and death (Dodd 1992; Roth 2000) and is also subject to all the potential clerical/procedural errors as allogeneic blood albeit avoiding the hazards of TTIs and immunological hazards associated with allogeneic transfusion. It also requires a weekly commitment from the patient and involves a weekly appointment at the donation site, in addition to staffing, other practical issues and related costs of the PABD programme. There have been reports of potential reduction in the risk of postoperative deep vein thrombosis in TKR (Anders 1996) and THR (Bae 2001) but the current evidence is too weak to confirm this.

7.4 Acute normovolaemic haemodilution (ANH)

This is the removal of whole blood and the restoration of blood volume with acellular fluid shortly before anticipated significant surgical blood loss. Mathematical models indicate that ANH is only suitable for a minority of patients (Kick 1997). These include healthy adults in whom a relatively low target haemoglobin, both intraoperatively and postoperatively is acceptable, with an anticipated blood loss of greater than 50% and a relatively high starting haemoglobin (Goodnough 1998). The maximum volume of blood that can be withdrawn depends on the preoperative haemoglobin, the lowest acceptable intraoperative haemoglobin level and the estimated blood loss(Brecher 1997;Cohen 1995;Kick 1997).

The real evidence for the benefit of ANH is equivocal. A meta-analysis of ANH trials (Bryson 1998) found that allogeneic transfusion was reduced when more than 1000mls was withdrawn. There was a significant reduction in the average number of allogeneic units transfused, though not in the number of patients exposed to allogeneic blood. However, when trials without a transfusion protocol were excluded from the analysis, no significant benefit was identified in terms of reducing allogeneic transfusion.

7.4.1 ANH versus PABD

A randomized study comparing the above two blood sparing strategies found no differences in either calculated red cell savings or exposure to allogeneic transfusion, prompting the authors to suggest that ANH should be preferred to PABD on the basis of lower cost and less potential for transfusion errors (Monk 1998). However, issues of patient selection, theatre time, staff training and technical expertise and organisational issues that surround an effective ANH programme need to be factored into the equation.

ANH does have its advantages. In contrast to PABD, it does not require testing to screen for TTIs and is therefore less costly. There is virtually no risk of bacterial contamination or administrative error that could lead to blood group incompatibility and does not require additional time investment from patients to donate blood (Monk 1995).

7.5 Erythropoietin (EPO)

The effect of EPO in minimizing exposure to allogeneic blood compared to placebo has been studied in patients undergoing orthopaedic (Faris 1998;Laupacis 1998), cardiac (Laupacis 1998) and colonic cancer surgery (Kettelhack 1998; Qvist 1999). In excess of 1000 patients were randomized and an overall significant reduction in allogeneic transfusion occurred in orthopaedic patients. Post-operative transfusion fell from between 40-60% in controls to 10-20% in EPO treated patients.

De Andrade *et al* (deAndrade, Jr. 1996) stratified 316 patients into those presenting with haemoglobins above and below 130g/L. In the EPO group a significant reduction (45-16%) in allogeneic transfusion rate was observed in those with a presenting haemoglobin of less than 130g/L as opposed to a non-significant reduction in patients with a haemoglobin of more than 130g/L. This finding has been confirmed by subgroup analysis in other studies (Anon 1993;Faris 1996).

In those with objections to allogeneic transfusion, for example Jehovah's witnesses, EPO may have a significant role in preparing these patients for surgery involving substantial blood loss (Gaudiani 1991).

Little evidence of side effects of EPO have been found(Faught 1998) and no trial or meta-analysis has been of sufficient power to detect important adverse effects at low incidence. In some studies concerns about increased risk of thrombosis were present in patients with a baseline haemoglobin of 130g/L but were similar to controls when the haemoglobin was 100-130g/L (de Andrade, Jr. 1996). Due to perceived thrombotic risk and the risk of uncontrolled hypertension, trials involving EPO have had very strict entry criteria. Despite this, studies have suggested no major increased thrombotic or hypertensive risk (Faught 1998). With a 50% rise in haematocrit during EPO treatment, some units recommend venesection.

7.5.1 PABD and erythropoietin

When PABD was used with EPO, a meta-analysis of 11 orthopaedic and cardiac randomized studies enrolling 825 patients found a statistically significant decrease in the proportion of patients transfused with allogeneic blood (Laupacis 1997). EPO-supported PABD individuals are also able to donate significantly more units than standard PABD (Mercuriali 1998;Price 1996;Rau 1998) and also had a higher day-of-surgery haemoglobin level (Cazenave 1997;de Andrade 1997). However, adequate iron status must be maintained through supplementation in patients receiving EPO (Adamson 1994).

7.6 Aprotinin

Aprotinin has been investigated for hip and knee replacements (D'Ambrosio 1999;Hayes 1996;Murkin 1995) and revisions (Murkin 1995), knee replacements (Thorpe 1994), spinal

surgery (Lentschener 1999) and tumour surgery (Capdevila 1998). A reduction in blood loss of between 25-60% was demonstrated. However, a Canadian study reported an increased risk of death in cardiac surgery patients treated with aprotinin compared with tranexamic acid and aminocaproic acid and this led to the market suspension of this drug(Fergusson 2008).

7.7 Antifibrinolytic drugs (Tranexamic acid and aminocaproic acid)

These inhibit fibrinolysis by binding to the lysine-binding sites of plasminogen to fibrin. They have been used in TKR patients who have had their operations under tourniquet control. In this situation, local fibrinolytic activity may be enhanced and may cause post-operative bleeding on release of the tourniquet (Murphy 1993; Petaja 1987). A reduction in blood loss of between 43-54% as well as a significant reduction in the total number of units transfused and the number of patients exposed to allogeneic blood has been demonstrated in a series of randomized control studies where the antifibrinolytic drug was given prior to tourniquet release (Benoni 1995; Benoni 1996; Hiippala 1995; Hiippala 1997; Jansen 1999; Zohar 1999). Concerns about the potential risks of thrombosis (Hiippala 1997; Howes 1996) have not been borne out by these studies, but studies have been small. In clinical practice, their use is usually reserved for those patients where other blood sparing techniques cannot be used and where major blood loss is anticipated.

7.8 Desmopressin (DDAVP)

This has been used to prevent bleeding in other types of surgery but has had no effect on reducing blood loss or allogeneic transfusion requirements in THR or TKR (Karnezis 1994; Schott 1995).

7.9 Topical haemostatic agents

Topically active agents that have been used include thrombin, collagen and fibrin glue. A gelatin matrix containing thrombin was shown to stop bleeding in cardiac surgery patients within 10 minutes in 94% of patients(Oz 2000). Fibrin glue made with highly concentrated human fibrinogen and clotting factors does not depend on platelet or clotting factor levels to be effective. The use of fibrin tissue adhesive has been shown to significantly reduce mean postoperative blood loss from 878-360mls in TKR (Levy 1999).

7.10 Recombinant factor VIIa

Recombinant factor VII is produced from a line of baby hamster kidney cells with an amino acid sequence identical to that of endogenous factor VII (Thim 1988) and becomes active after forming a complex with tissue factor. Following this factors IX and X are activated and a thrombin burst is induced, leading to a quicker formation of a fibrin clot at the site of vascular injury (Rizoli 2006), and also binds to the surface of thrombin-activated platelets, activating factor X directly independent of tissue factor (Monroe 1997).

In Europe, recombinant factor VII (rVIIa) has been licensed for the treatment of and for the prevention of further bleeding episodes in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX, patients with congenital haemophilia who are

expected to have a high anamnestic response to factor VIII or IX administration, patients with acquired haemophilia, patients with congenital factor VII deficiency and some patients with Glanzman's thromboaesthenia with past/present resistance to platelet transfusions (Rodriguez-Merchan 2004). Although life expectancy in haemophiliac patients is now getting closer to that of the normal population (Darby 2007), the significant burden of joint disease does have an impact on their quality of life (Scalone 2006), with problems such as joint instability, muscle atrophy and flexion contractures (Gringeri 2003). One study showed that 24% of males with haemophilia aged 14-35years were reliant on a wheelchair (Morfini 2007).

Data from an international series of 108 patients of elective orthopaedic surgery performed in seven countries revealed that 19% were involved in hip and knee arthroplasty. 80% had good results with a further 5% having fair results reported (Rodriguez-Merchan 2004). Another study of patients given an initial bolus dose followed by a continuous infusion revealed an overall good final outcome in all cases (Ludlam 2003). The optimal dose and whether bolus or infusions are better still remains to be established (Obergfell 2008). The outcome of 10 major orthopaedic operations in five comprehensive care centres in the United Kingdom and Ireland in haemophilia patients has shown good results with bolus doses (Giangrande 2009). Intraoperative haemostasis was found to be satisfactory in all 10 operations. Two cases had postoperative bleeding episodes one of which was managed with an increased bolus dose of rVIIa and the other with an addition of tranexamic acid and the final results were reported as excellent or extremely satisfactory in all cases (Giangrande 2009).

Elective major orthopaedic surgery in patients with haemophilia should be undertaken in comprehensive care centres that have the multidisciplinary expertise and facilities according to the consensus protocols (Giangrande 2009). Management in these centres have demonstrated a survival benefit compared to non-specialist centres (Soucie 2000). Topical application of fibrin sealant during the intraoperative period to minimize capillary ooze and the use of vasoconstrictors and antifibrinolytics can be used to enhance the effect of rVIIa and improve haemostasis (Schulman 1998). Activated prothrombin complex concentrate (aPCC) has also been used to cover surgical procedures in haemophilia patients with inhibitors (Dimichele 2006;Goudemand 2004;Hvid 2002;Negrier 1997;Tjonnfjord 2004) and data suggests similar efficacy to rVIIa, albeit having the risk of an anamnestic rise in antibody titre (Schulman 1998), a risk not present with rVIIa. Current guidelines give equal merit to rVIIa and aPCC in managing bleeding in haemophilia (Hay 2006). Costs to cover this type of surgery can be prohibitive although they may be recovered in the long term through abolition of bleeding episodes. One pharmacokinetic study calculating the break-even time (time after surgery when cost is completely offset by savings resulting from avoiding bleeding episodes) ranging from 5-9 years (Lyseng-Williamson 2007).

Recombinant factor VII has also been used to treat coagulopathic trauma patients. rVIIa functions by triggering an enhanced coagulation response dependant on multiple agents in the clotting cascade. Thus, to increase its efficacy, the mechanisms that lead to coagulopathy in trauma patients need to be corrected before its administration, including administering FFP and maintaining fibrinogen levels at >0.1mg/dL using cryoprecipitate and platelet transfusions to maintain platelet count > 50,000/mm^3, correcting hypothermia and acidosis (Gunter, Jr 2008; Holcomb 2008; Meng 2003; Sperry 2008). In two parallel randomized placebo- controlled blinded studies of 301 patients experiencing blunt or penetrating

trauma, patients with blunt trauma who were managed with rVIIa required fewer PRBC transfusions than patients randomized to placebo. The need for massive transfusion was also significantly reduced in these patients (Boffard 2005). Two other trials have also demonstrated a decreased mortality in trauma patients who received rVIIa. In the combat setting, 30 day mortality in patients requiring massive transfusion was reduced from 51% to 31% (Spinella 2008). A mortality benefit has also been demonstrated in the civilian major trauma setting in patients requiring massive transfusion secondary to trauma (Rizoli 2006). In the military setting, some of the proposed criteria for the use of factor rVIIa are haemorrhage induced hypotension, base deficit of >6mEq/L, difficult to control bleeding associated with hypothermia, clinically coagulopathic bleeding or INR > 1.5, the need for damage control measures, the need for fresh whole blood, anticipated or actual PRBC transfusion of > 4 units or significant surgical haemorrhage (Nessen 2008) and some of these may well be indications for rVIIa in the civilian setting as well (Holcomb 2007).

Complications of rVIIa in the trauma setting have also been studied with 9.4% experiencing thrombotic complications (Boffard 2005). This contraindicates it in patients with symptomatic vaso-occlusive disease (angina, claudication, deep venous thrombosis, pulmonary embolism, cerebral or myocardial infarction) within 30 days prior to traumatic injury.

8. Cell salvage

Cell salvage has been shown to have some benefit in reducing the exposure to allogeneic blood. Seven orthopaedic trials with a total of 427 patients between them reported on data for volume of allogeneic blood transfused. For the patients that were randomized to cell salvage, there was an average saving of 0.82 units of red blood cells per patient (Carless 2010).

The Cochrane Collaboration review which included 67 cell salvage trials in both cardiac and orthopaedic surgery with a total of 6025 patients, indicated that overall, the use of cell salvage reduced the rate of allogeneic blood transfusion by a relative 38%, although heterogeneity between studies was significant (Carless 2010). Of the trials included in the Cochrane review, 32 involved orthopaedic surgery, demonstrating a larger reduction in orthopaedic trials than any other trials with regards to the number of patients exposed to red blood cell transfusion (Carless 2010). When cell salvage was used in orthopaedic surgery, the risk of exposure to allogeneic transfusion was reduced by 54% compared to only 22% in cardiac surgery.

8.1 Intra-operative cell salvage

This is intra-operative collection of cells that are washed prior to retransfusion. Larger volumes can be transfused in comparison to post-operative blood salvage (Goodnough 1999b;Paravicini 1983) with cell washing devices being able to provide the equivalent of 10 units of blood per hour. This can be used in patients with substantial blood loss in major orthopaedic surgery, providing less costly, immediately available blood (Goodnough 1999b).

However, there is a considerable capital cost of the basic equipment and it is estimated that at least two units need to be recovered per patient for it to be cost effective to run(Goodnough 1999b). The recommendation is to use it in patients where intra-operative blood loss of 1000-1500mls is anticipated (Gargaro 1991;Schmied 1998;Slagis 1991;Wilson 1989). It can be used in

pelvic surgery and revision arthroplasty where infection has been ruled out and should not be used in bacterial contamination or tumour surgery (Napier 1997).

8.2 Post-operative cell salvage

This involves collecting blood from surgical drains followed by retransfusion. The blood is filtered to eliminate larger aggregates but not bacteria (Gannon 1991; Kristensen 1992; Martin 1992). Complications of unwashed blood have included hypertension, hypothermia, upper airway oedema and coagulopathy (Southern 1995). Because the recovered blood is diluted, defibrinated and partially haemolysed and contains cytokines, there is generally a threshold of blood that can be transfused by this method. This is usually not more than 1500mls. The risk of bacterial contamination/infective colonization increases with time and it is generally recommended that recovered blood should not be transfused later than six hours after collection. The safety and efficacy of post-operative cell salvage also remains somewhat controversial (Faris 1991;Ritter 1994) and due to high cost and questionable benefit, some have recommended its use to be limited to cases in which a large post-operative blood loss is anticipated.

However, studies have shown that it can reduce exposure to allogeneic blood if no autologous pre-donated blood is available (Ayers 1995;Knight 1998;Newman 1997) and may further reduce allogeneic exposure when autologous blood is available (Xenakis 1997). Forty six trials in the Cochrane review reported the use of post-operative cell salvage and included 4361 patients. 2209 were randomized to post-operative cell salvage. The risk of allogeneic blood exposure was reduced on average by 37% in those patients treated with post-operative cell salvage compared to controls. However, significant heterogeneity was present amongst the studies included.

8.3 Washed versus unwashed blood

27 trials in the Cochrane review studied washed cell salvage while 40 investigated unwashed cell salvage. Overall when cell salvage was conducted with devices that washed the blood, the relative risk of exposure to red cell transfusion was only marginally lower than that with unwashed blood salvage and for orthopaedic trials, this difference was insignificant (Carless 2010). Again these results must be interpreted with caution due to significant heterogeneity between studies.

8.4 Volume of blood transfused

32 trials reported on the volume of allogeneic blood transfused and included 2321 orthopaedic and cardiac patients. 1172 patients were randomized to cell salvage. Although overall, the use of cell salvage reduced the volume of red cells transfused by 0.68 units, greater reductions than this were observed in trials involving orthopaedic surgery compared to cardiac surgery (Carless 2010).

8.5 Other complications

It has been thought that post-operative cell salvage may increase the rate of infection and wound complications in orthopaedic surgery. This has not been borne out in the 16 trials

involving 1462 patients of whom 1011 were randomized to cell salvage (Carless 2010). Likewise, the relative risk of developing any thrombus including deep vein thrombosis, stroke and non-fatal myocardial infarction in patients treated with cell salvage was not significantly different compared to controls (Carless 2010).

Principle findings from the systematic review appear to suggest that the efficacy of cell salvage in reducing the need for allogeneic transfusion appear to be greatest in the setting of orthopaedic surgery where the risk of exposure to allogeneic transfusion was reduced by 54% compared to 23% in cardiac surgery. However, these results should be interpreted with caution as most of the trials were un-blinded leading to a potential source of bias in favour of cell salvage, in addition to heterogeneity between the studies considered (Carless 2010).

8.6 Cost considerations

A recent cost effectiveness analysis indicated that cell salvage was cost effective compared to all other transfusion strategies except ANH (Davies 2006). The study indicated that the net benefit of cell salvage was between £112 and £359 per person, compared with the allogeneic blood transfusion strategy, PABD, PABD and EPO, Fibrin sealants, antifibrinolytics and EPO. It also estimated a blood saving of between 6,500 and 320,000 units of allogeneic blood per year (Davies 2006). The economic viability of cell salvage has been suggested by other studies as well (Mirza 2007). However, cost analysis should also be interpreted with caution as in many instances, neither the cost of the technology/manpower needed to execute this activity have been taken into account, nor have the capital cost of the cell saver devices.

9. Conclusions

Orthopaedic surgery often involves a substantial volume of blood loss. Blood is a scarce resource and developing a rational approach to transfusion in orthopaedic surgery involves the following:

- Individual assessment of patient risk for transfusion
- Estimating anticipated blood loss
- Pre-operative haemoglobin assessment
- Determining patient-specific transfusion triggers according to age, risk factors and comorbidities
- Optimizing operative and anaesthetic techniques
- Developing transfusion practice standards and institutional guidelines
- Determining the most appropriate blood conservation technique or option according to individual patient characteristics, operation and circumstances and local protocols and resources

The true value of avoiding allogeneic blood transfusion remains debateable. However, concerns over the safety of allogeneic transfusion have led to the development of new techniques of blood conservation. Preoperative assessment of estimated blood loss and transfusion risk and consideration of alternatives to allogeneic blood are now key to optimizing blood management. The growing evidence on the efficacy of transfusion triggers means that a more conservative approach to transfusion is recommended in patients with cardiovascular risk factors (Carson 1998b;Carson 2002). However, surgeons must be

discriminating in the method of blood sparing strategy used by carefully considering individual patient condition, specific surgical practices and potential for adverse events. The choice of intervention that best minimizes patient exposure to allogeneic blood transfusion is not clear cut with the current evidence. The evidence and safety of ANH and PABD is generally regarded as being of indifferent quality due to lack of blinding outcomes and heterogeneity between studies. However, they have been shown to have blood sparing effects. Cell salvage appears to be justified in orthopaedic surgery although again there is significant heterogeneity between existing studies. Surgeon preference, availability and cost primarily determine what alternative to allogeneic blood transfusion is used. Large multicentre randomized studies are needed to answer questions about the safety and efficacy of the various alternatives to allogeneic blood transfusion.

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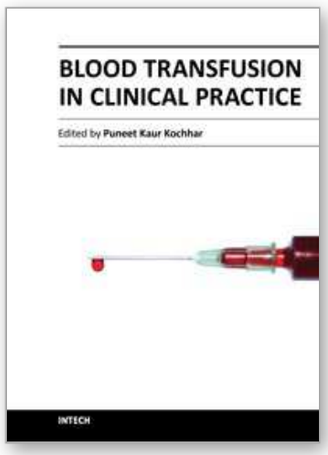

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Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group 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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