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REVIEW

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Transfusion of post-operative shed blood: laboratory characteristics and clinical utility

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Abstract Increased awareness of the potential hazards of allogenic blood transfusion, such as incompatibility reactions, metabolic and immunologic disorders, or transmission of viral diseases, has led to an emphasis on allogeneic blood alternatives. For orthopaedic surgery, several autologous transfusion modalities have emerged as alternatives to allogeneic blood transfusion, avoiding its immunomodulatory effects. Among them, transfusion or return of post-operative salvaged shed blood has become popular in major orthopaedic procedures. However, although the effectiveness of this blood-saving method is well documented, several authors have questioned its safety and recommended the use of washed blood. Therefore, this review analyses the haematologic characteristics of unwashed filtered shed blood, including metabolic status and survival of red blood cells, the components of the haemostatic system, the content of fat particles, bacterial and tumour cells and the possibility of their removal, the content of inflammatory mediators, and the effects on the patient's immune system. From data reviewed in this paper, it can be concluded that post-operative salvage of blood seems to be an excellent source of functional and viable red cells without many of the transfusion-related risks and with some immuno-stimulatory effects. In addition, from our experience, post-operative re-infusion of unwashed shed blood after major spine procedures has proved to reduce post-operative homologous transfusion requirements and to complement pre-operative autologous blood donation, without any clinically relevant complication.

Keywords Post-operative salvaged blood · Spine surgery · Fat particles · Cytokines · Coagulation · Immune system · Effectiveness

Introduction

It is well known that the defence mechanisms provided by the immune system can be altered by traumatic injury, surgery and transfusions, and there is a growing interest for acquiring greater knowledge on the causes and mechanisms involved in the immunodepression induced by the anaesthetic-surgical procedure, since this increases the susceptibility to post-operative infection and tumour relapse after potentially curative surgery [15, 19, 62]. This interest further increases when it is seen that, in spite of current surgical techniques, of advances in anaesthetics and in the huge variety of anti-microbial agents, general and local infection continues to be one of the main causes of morbidity-mortality associated with traumatic injuries and surgery, increasing its incidence in those patients who have received allogeneic blood transfusions (ABT) [29, 61].

Patients undergoing orthopaedic surgery frequently receive ABT, and the results of two extensive studies including nearly 20,000 patients strongly suggest that peri-operative ABT in this surgery is associated with an increased risk of post-operative infection [5, 8]. The former was a retrospective study including 9,598 consecutive patients of over 60 years of age and having undergone surgery due to hip fracture. Fifty-eight percent of those patients received at least one ABT, and data analysis revealed that ABT was associated with a 35% increase in the risk of severe post-operative infection and a 52% increase in the risk of acquiring pneumonia. The increase was also dose-dependent [8].

In the later, 9,482 patients were studied who underwent elective orthopaedic surgery (EOS) of the knee or hip between September 1996 and June 1997. More than half of those patients (5,741) were included in a pre-operative autologous blood donation (PABD) program (average 1.7 U/patient), and of those, 9% (503) also received ABT, whilst 45% of the pre-deposited units were not used. The overall incidence of post-operative infections was 4.2%. However, when analysing the incidence of infections based on transfusions received, it can be seen that the patients who received ABT had 47% more post-operative infections than those not receiving them (7 compared to 3.68%, respectively; $p<0.001$), whilst there was no difference between those who received autologous blood and those that were not transfused (4 compared to 3%, respectively) [5].

This greater incidence of post-operative complications, in conjunction with other adverse effects both acute and chronic, have prompted the review of transfusion practice and the search for a series of alternative measures such as autologous transfusion, the final objective of which is to reduce to a minimum both the exposition to ABT and the ABT-associated risks [26, 34, 43, 59].

Auto-transfusion in orthopaedic surgery

PABD has been reputed as one of the most safe and effective transfusion therapies, being considered the "gold standard" in auto-transfusion. Thus, the analysis of the results obtained in 11 studies carried out in Spain and six studies carried out overseas with a total of 10,500 patients subjected to EOS of the knee, hip or spine has demonstrated that PABD has an average effectiveness, measured as the percentage of patients that avoid ABT, of 90%, although with an average yield, measured as the percentage of units donated that are transfused, of 62% [45]. Nevertheless, it should be taken into account that this over-collection of units is lower in Europe (10–15%) [53] than in the United States (40–50%) [26], being around 20% in Spain [45]. In addition, PABD may have problems of overtransfusion, is associated with higher rates of clerical errors, is not without infectious risks, and allogeneic transfusion may still be required (break-through transfusion) [5, 26, 45]. Moreover, because the possible role of blood storage on transfusion-induced immunomodulation [40], PABD might be accomplished as close to the operation date as possible, hence demanding a tight surgical program and limiting the number of units to be collected.

In regard to spine surgery, PABD can be safely used not only in adults but in adolescents as well [9, 42, 47, 51, 57]. In this clinical setting, adjuvant treatment with epoetin alpha (EPO) seems to facilitate the collection of the requested PABD units and results in higher peri-operative haematocrit levels [24, 41, 58].

Intra-operative cell salvage (ICS) and post-operative autologous transfusion (PAT) completely avoid the problem of blood storage. During surgery, the intra-operatively salvaged blood is processed to obtain a red cell concentrate ready for transfusion. This procedure has very few complications, the most normal being dilution coagulopathy when a large volume of processed blood is being transfused. However, in spine surgery, the effectiveness of ICS is controversial, and its selective use for operations with high intra-operative blood loss is recommended [1, 9, 10, 11]. Recently, a new automated, specifically designed device (OrthoPAT, Haemonetics), which recovers 80% of red cells from intra-operative blood loss, has been marketed, and both its clinical effectiveness and the quality of the yielded product are under evaluation by our group (unpublished data).

PAT consists of recuperation and re-infusion of shed blood from post-operative draining, total knee arthroplasty being the operation where it has been used the most. There are a number of devices for collecting post-operative shed blood, the principal differentiating characteristic being the existence or not of a washing process for the salvaged blood. When the ICS is not used, PAT is normally performed by using devices that recuperate and re-transfuse shed blood to the patient as unwashed filtered shed blood (USB).

With regard to clinical results, although there have been series published against the procedure, the re-infusion of USB has been shown to be effective in reducing the requirements for ABT [45]. In addition, a meta-analysis of the effectiveness of cell salvage in minimising peri-operative allogeneic transfusion concluded that, in orthopaedic surgery, devices producing either washed or unwashed cells decreased the frequency of exposures to allogeneic blood to a similar degree when compared with a control [30]. Regarding spine surgery, the addition of PAT can considerably reduce PABD requirements and/or complement ICS in both adult and adolescent patients undergoing instrumented spine fusion where the post-operative blood lost is substantial [4, 21, 52, 57, 56].

Controversy on the use of USB

Although the effectiveness of the return of USB after orthopaedic operations is well documented, several authors

Table 1 Some haematologic, metabolic, biochemical and immunological characteristics of post-operative shed blood in comparison with pre-operative venous blood in patients undergoing lumbar spinal surgery. Data are the mean ± SE of 20 determinations. *MCF* median corpuscular fragility, *f* fresh, *i* incubated, *ATP* adenosine triphosphate, *DPG* diphosphoglycerate, *PFHB* plasma-free haemoglobin, *GOT* glutamate-oxaloacetate aminotransferase, *GPT* glutamate-pyruvate aminotransferase, *LDH* lactate dehydrogenase, *CK* creatin kinase, *IL* interleukin, *TNF* tumour necrosis factor

	Pre-operative venous blood	Post-operative unwashed shed blood
Erythrocytes (10^6/μl)[a]	4.7±0.4	3.0±0.2**
MFC*f* (NaCl%)	0.406±0.01	0.422±0.01
MFC*i* (NaCl%)	0.498±0.01	0.486±0.01
ATP (μmol/g Hb)	3.5±0.8	4.3±0.7
DPG (μmol/g Hb)	16.1±2.6	11.5±2.6
D-glucose uptake (nmol/min g Hb)	6.53±0.55	12.10±0.11**
Haematocrit (%)	41.3±3.2	28.5±1.8**
Haemoglobin (g/dl)	14.2±0.3	9.6±0.8**
Leukocytes (10^3/μl)	6.8±1.6	6.7±0.6
Platelets (10^3/μL)	186±71	63±5
PFHB (mg/l)	49±8	2029±146**
Haptoglobin (mg/dl)	160±34	101±14
GOT (U/l)	26±3	1857±231**
GPT (U/L)	15±2	314±67**
LDH (U/l)	293±29	7452±662**
CK (U/l)	62±13	58791±2168**
IL-1β (pg/ml)	4.6±1.1	10.7±1.5*
IL-6 (pg/ml)	2.5±1.1	1335±49**
TNFα (pg/ml)	ND	ND

*p<0.05
**p<0.01
[a]All data taken from references 27 and 33
ND: not detected

have questioned the safety of this blood-salvaging method, because USB is diluted and may be contaminated with fat particles, bone fragments, free haemoglobin, activated coagulation factors, fibrin degradation products or inflammatory mediators, and programs set an upper limit on the volume of USB to be reinfused [3, 6]. In the following paragraphs, we will discuss these points of controversy in relation, where possible, to the USB salvaged after elective spinal surgery (ESS).

Haematologic and biochemical characteristics of USB

The haematologic characteristics of USB, recuperated in the first 6 post-operative hours of ESS using the ConstaVac CBC II (Stryker, USA) blood collection canister, were studied in 28 consecutive patients undergoing instrumented spinal fusion (SF), comprising 2–4 levels with or without decompression of the neurologic elements by microsurgery [56]. As shown in Table 1, USB samples contained lower erythrocyte and platelet counts, haemoglobin and haematocrit than blood drawn from the patient in the pre-operative period, with similar figures being reported previously [6, 52]. However, their erythrocytes showed no significant morphological abnormalities, presented a normal osmotic fragility and maintained a normal energy metabolism. In this regard, intra-cellular concentrations of adenosine triphosphate (ATP) and diphosphoglycerate (DPG) in USB erythrocytes were found to be higher than those of banked blood erythrocytes [44]. Taken together, these results seem to show that these red cells are not significantly damaged, keep all their functionality, and have a viability comparable to those from pre-operative and intra-operative blood collection [14, 50].

Measurement of PFHB has been used as an index of haemolysis and, certainly, its levels in USB were above the normal limits (Table 1). However, it has been previously reported that if USB is reinfused up to 15% of the total blood volume [6] or 1,000 ml [3], there seems to be enough circulating haptoglobin to bind PFHB, avoiding possible renal damage [4]. The increased serum concentrations of K^+, glutamate-oxaloacetate aminotransferase (GOT) and lactate dehydrogenase (LDH) in USB also suggest a degree of haemolysis, whilst increased levels of glutamate-pyruvate aminotransferase (GPT) and creatin kinase (CK), as well as partially those of LDH, are most probably due to enzyme release from muscle during surgery [56]. High levels of these enzymes were measured during the first post-operative week in patients undergoing SF, with a similar but more pronounced pattern being observed in patients receiving USB [56]. Therefore, caution should be taken when the serum levels of these enzymes are used for diagnosis at this time.

Fat particle content of USB

From a micro-rheological point of view, both the total blood and the erythrocytes of USB show a greater filterability through 5 μm polycarbonate membranes (which would be

equivalent of passing through a capillary bed) than the patient venous blood, which could be attributed to the practical absence of fibrinogen and a reduction in the number of leukocytes in USB [12, 13]. On the other hand, blood stored in a bank or processed with a cell saver shows a far less filterability than the blood from the patient [36]. Nevertheless, USB plasma shows less filterability than venous blood [13], which is attributable to contamination with several types of particles, among which are fat.

Return of fat probably increases the risk of fat embolism syndrome, which is mostly associated with acute lung injury. Thus, an effective, reliable, low-cost method of monitoring fat particle content in USB would be useful in ensuring that shed blood that is returned to the patient is not contaminated with fat. Usually, fat content in shed blood was measured in Nile red-stained samples with flow cytometry or fluorescence microscopy, which is an expensive and complex methodology [6, 28]. On the other hand, fat particle removal has been accomplished by either filtration [28, 35] or the use of cell salvage devices that wash and concentrate autologous RBCs [7, 35].

Very recently, we have validated a new method, far more simple and faster than the flow cytometry, based on the use of the different hematologic cytometers, that allows for detecting fat particles in USB and verifying their elimination by the use of several leukocyte filters (Pall RC100, PureCell, LeukoGuard, Sepacell, BioR, Imugard IIRC) [46, 49]. Also, there is data that supports the efficiency of these filters in the elimination of tumour cells and bacteria [16, 48], although other authors recommend washing and irradiating the blood [27].

Haemostatic alterations induced by re-infusion of USB

USB contains certain activated coagulation factors as well as degrading products of the fibrinogen so that its reinfusion could lead to a coagulopathy. In fact, compared to blood drawn from patients before the surgery, USB shows high levels of fibrinogen degradation products, tissue factor antigen, plasmin/antiplasmin complexes and D-Dimers, which indicates a certain degree of fibrinolysis, and low levels of alpha2-antiplasmin, antithrombin-III, Factor V, Factor VIII, Protein C and plasminogen [6, 20, 38, 39, 52]. Nevertheless, when analysing the evolution of the levels of these proteins in samples obtained from the patients at 1 and 24 h after re-infusion, a trend to normalisation was seen, except for the fibrinogen [6, 20], and no alterations were detected in standard coagulation times [52, 56]. For this reason, it was not surprising that in 13 studies with nearly 700 patients undergoing TKA, THA or SF, those who received a re-infusion of an average of 560 ml of USB did not experience clinically significant coagulopathy or increase in post-operative bleeding [44].

Inflammatory mediators in USB

With regard to the presence of inflammatory mediators, in several studies, an increase in serum levels was found of interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor (TNF-α) and anaphylatoxins in USB [45]. The use of a leukocyte filter between the wound and the drain blood container reduces IL-8 and TNF-α in drain blood, but at the same time triggers complement activation [2]. Nevertheless, in spite of the high concentration of certain proinflammatory cytokines in USB that produce a temporary increase in their circulatory levels after the infusion, 12–18 h later, no differences existed in the levels observed in the reinfused patients relative to the non-reinfused patients [56]. It should be remembered that these cytokines, which are also present in stored blood [33], induce the expression of adhesion molecules (ICAM-1, VCAM-1 and P-selectin) by the endothelial cells. These adhesion molecules specifically interact with the circulating leucocytes, facilitating adhesion to the endothelium and migration to the site of injury where they exert phagocytic and bactericidal (respiratory burst) effects [60]. Also, the leukocytes can strengthen platelet aggregation by means of the interactions between leukocyte P-selectin and platelet PSGL-1 [18]. On the other hand, the exposition of endothelial cells to an inflammatory stimulus also promotes the adhesion of circulating erythrocytes to endothelin [17]. All of this can give rise to alterations in micro-circulation, in conjunction with those that can directly induce anaphylotoxins [37], and we are conducting experiments to ascertain whether the temporary increase in cytokine levels that occurs after USB re-infusion induces changes in the expression of adhesion molecules by endothelium beyond that induced by cytokines released during surgery.

Reinfusion of USB and the immune system

Finally, with regard to cellular immunity, the ABT, even after being de-leucocyted, induces a depression of immunity measured by T cells, while these alterations have not been detected in patients receiving PABD [23, 31]. On the contrary, the influence of USB re-infusion is largely unknown. However, data from two recent reports seem to indicate a positive effect of USB on cellular immunity; namely, a significant increase in the production of reactive oxygen species by neutrophils [32] and in natural killer cell precursor frequency [25] in patients who received USB. This findings may support the hypothesis that this treatment may be another way of reducing post-operative infections after orthopaedic surgery. These results also support the previous clinical studies where infection rates after autologous transfusion were lower than after conventional treatment.

Table 2 Patient characteristics

	Group A[a]	Group B[a]	Group C
No. patients	31	28	64
Age (years)	48±2	52±3	51±2
Gender (M/F)	12/19	14/14	31/33
Haemoglobin (g/dl)			
Pre-operative	13.5±0.3	14.2±0.3	13.0±0.2
Post-operative	10.7±0.3	10.5±0.3	10.1±0.2
Operation length (h)	5.3±0.4	5.3±0.1	5.2±0.1
Hospitalisation (days)	9.6±1.4	8.4±0.5	9.1±0.5
Complications	4 (12.9%)	3 (10.3%)	4 (6.3%)*

All data are expressed as the mean ± SE (*n*)
*p<0.05
**p<0.01
[a]Data taken from reference 27

Table 3 Blood lost and blood units transfused. For data comparison, 1 U of pre-operative autologous blood donation (PABD) was consider to be equal to one allogeneic red cell concentrate, and the number of unwashed shed blood (USB) units were calculated according to the expression: Shed blood volume (ml) × shed blood haematocrit (%) / 400 (ml) × pre-operative haematocrit (%)

	Group A[a] (*n*=31)	Group B[a] (*n*=28)	Group C (*n*=64)
Blood lost (ml)			
Intra-operative	670±46	852±55*	959±50**
Post-operative	480±40	542±41	631±32*
Allogeneic blood (U/pt)			
Intra-operative	1.35±0.13	1.22±0.11	0
Post-operative	0.64±0.50	0.25±0.19*	0.28±0.08*[b]
Autologous blood (U/pt)			
PABD[c]	0	0	2.03±0.06**
USB	0	0.65±0.05**	0.77±0.03**
Overall transfusion (U/pt)	1.90 ± 0.22	2.13±0.19	2.98±0.11**

All data are expressed as the mean ± SE (*n*)
*p<0.05
**p<0.01
[a]Data taken from reference 27
[b]Eighteen units of RBC concentrate were administered to 12 patients
[c]Seven patients donated 3 U

Our experience in the use of post-operative USB reinfusion

Based in our previous experience with reinfusion of post-operatively salvaged USB in cardiac surgery [54] and after the evaluation of the quality of intra- and post-operatively salvaged USB in different types of orthopaedic surgery [44, 61], we decided to initiate a blood saving program in spine surgery introducing the use of USB recovered after the operation with the ConstaVac CBCII (Stryker). In this initial study, we included 28 consecutive patients undergoing lumbar spinal fusion in which post-operative shed blood was collected and reinfused (Group B). In comparison with a previous series of 31 patients (Group A), this procedure reduced allogenic blood requirements by almost 30% ($p<0.05$) without any increase in post-operative complications [56] (Tables 2 and 3). Despite these good results, it became evident that the exclusive use of post-operative USB was not enough to avoid ABT, and we decided to complement it with a short-time protocol of PABD. Eligible patients (Hb >12 g/dl) were asked to donate 2 U of autologous blood, the first one being donated 7–10 days before surgery (real PABD). The second unit was drawn the day before surgery, and the donated blood volume was replaced with saline (delayed normovolemic haemodilution).

Between 1999 and 2000, 64 patients undergoing instrumented lumbar spinal fusion were included in this new protocol (Group C). Despite a higher peri-operative blood loss due to an increase proportion of revision surgery, with this blood saving strategy, 80% of the patients avoided exposure to ABT (Table 3), and post-operative complications were reduced by 50% (Table 2). The use of erythropoietin in patients with Hb <13 g/dl might possibly prevent the decrease in Hb levels after PABD and reduce further the exposure to ABT. On the other hand, 96% of PABD units were transfused, and overall transfusion rate was higher than in group A, suggesting a tendency to a more liberal transfusion criteria when autologous blood is available [22].

Conclusions

The development of complex surgical procedures for the treatment of orthopaedic diseases have raised the demand for allogenic blood to a level that often exceeds supply. In addition, increased awareness of the potential hazards of allogeneic blood transfusion, such as incompatibility reactions, metabolic, and immunological disorders or transmission of viral diseases, has led to an emphasis on blood-saving techniques. Among them, reinfusion of salvaged shed blood has become popular in major orthopaedic procedures, including spine surgery, but this blood-saving technique is still controversial. However, in our experience, post-operative reinfusion of USB after major spine procedures has proven to reduce post-operative homologous transfusion requirements [56] and to complement PABD without any clinically relevant complication. Moreover, from data reviewed in this paper, it can be concluded that post-operative blood salvage seems to be an excellent source of functional and viable red cells without many of the transfusion-related risks and with some immuno-stimulatory effects.

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