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AUSTRALASIAN ASSOCIATION FOR BLOOD CONSERVATION

To advance the practice of blood conservation in medicine and surgery for improved patient outcomes

Updates in
Blood Conservation and Transfusion Alternatives

Journal of the Australasian Association for Blood Conservation

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To advance the practice of blood conservation in medicine and surgery for improved patient outcomes.

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- Build an association that brings together specialists from all disciplines throughout Australasia with a common interest in improved blood management
- Encourage ongoing research to achieve optimal blood management and appropriate implementation of blood conservation and transfusion alternatives
- Create public and professional awareness of blood conservation
- Publish and distribute clinical and scientific information via newsletters, journals and the Internet
- Organise blood conservation clinical meetings and workshops
- Nurture co-operative links with similar organisations worldwide
- Establish acceptable standards of accreditation in Australasia for the practice of blood conservation

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Why Should Health Professionals be Concerned about Blood Management and Blood Conservation?

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Introduction

What may seem a simple question on deeper analysis turns out to be complex and multifactorial. There is no doubt that allogeneic blood transfusion has been one of the most significant medical advances during the 20th century. Massively bleeding patients survive, major surgical advances have been possible, haemophiliacs live longer and better lives and marrow failure from disease or myelosuppressive therapy can be survived. So what's the problem? Increasingly the view of many clinicians is that transfusion medicine has excessively focused on the blood component supply side of the system rather than from the demand/patient perspective. The terms "blood conservation" and "blood management" are examples of post-modernism ie their meaning is context dependent. The blood supply agency naturally wants to "conserve" a precious and altruistically donated resource that should be "managed" appropriately. On the other hand the clinician wants to conserve and manage a patient's blood appropriately. The later, in my opinion should be the accepted "true" meanings of "blood conservation" and "blood management" The clinical focus should be on "what is best for the patient?" not, "what is best for the blood supply?" This is not to deny the importance of the multiple issues and challenges facing the provision of an adequate and safe blood supply, but rather to ensure the horse is in front of the cart, willing and able to address the needs of patients, with the supply chain appropriately responding to clinical needs.

Clinical demand for blood components continues to increase, despite greater attention to the appropriateness of transfusion. How "legitimate" this increase in demand is, is currently difficult to assess. However, there is the increasing burden of chronic disease due to ageing of the population, a wider range of clinical indications for some blood components (eg IVIG) increasing severity of illness of ICU patients with better life-support technology available and newer blood-intensive surgical procedures are increasing.

Transfusion medicine consumes a substantial component of health budgets with bureaucrats becoming increasingly focused on the economics of blood supply and transfusion practices. The economic focus has generally been on the cost of blood and blood components rather than the total cost of transfusion medicine, starting with the patient and ending with the patient. The catch cry of the health bureaucrats continues to be "too much is being spent on blood components and they are being inappropriately used by the clinicians". There may be an element of truth in this stance, but we don't have good risk/benefit data for transfusion medicine not to mention a total deficiency in meaningful costing information. A "rubbery" assessment of the total cost of transfusion medicine in Australia is as much as three billion dollars. If these estimates can be substantiated with hard data one suspects that even the hardest nosed health bureaucrats may sit up and show an interest in blood management.

Background to the development of patient blood management

Allogeneic blood transfusion is supportive therapy and may be administered to control the effects of, or to prevent problems, associated with a haemopoietic deficiency. Allogeneic transfusion, particularly in the perioperative setting, should not be regarded as the first line of therapy for patients with haemopoietic defects. For most patients it is possible to minimise requirements for allogeneic blood components, or to correct or manage the effects of deficiencies in the haematopoietic system, without transfusing allogeneic blood components. Clearly, if allogeneic blood can be avoided the potential hazards need not be considered. For reasons which are not immediately apparent the transfusion of allogeneic blood has been regarded as the "default" decision when there is doubt about the possible benefits of allogeneic blood transfusion.

The benefits from transfusion have been assumed in most clinical circumstance and it is a sobering thought to consider that when there is no evidence to support the benefit of transfusion a patient is unnecessarily exposed to potentially major morbidity or even mortality. The decision-making process for blood component therapy can be difficult and much debate continues in relation to the indications for the use of

various allogeneic blood components. However, there are good common sense and scientific reasons to adopt a non-transfusion default position when there is no evidence for potential benefit.

The ready availability of allogeneic blood components in Australia, at no direct cost to the patient or the clinical service provider, has resulted in minimal incentive for clinicians to be informed about the benefits and risks involved in the use of a limited and altruistically donated resource. Historically, there are two main factors that have driven a reassessment of this paradigm. In 1977 the pioneering cardiac surgeon, Denton Cooley and colleagues, published a landmark paper; *"Cardiovascular surgery in Jehovah's Witnesses. Report of 542 operations without blood transfusion*" (Ott DA, Cooley DA. JAMA. 1977 Sep 19;238(12):1256-8). In this paper they reported a 20-year experience with a consecutive series of 542 Jehovah's Witness patients ranging in age from 1 day to 89 years who underwent surgery. Mortality within 30 days after operation was 9.4%. In 362 patients requiring temporary cardiopulmonary bypass, early mortality was 10.7%. Mortality was 13.5% among 126 patients who had single- or double-valve replacement. The only deaths among patients who had aortic valve replacement or repair of a ventricular septal defect occurred in those who had some serious complication before operation. Preoperative or postoperative anaemia was a contributing factor in 12 deaths, and loss of blood was the direct cause of three deaths. These operations spanned a time when it was standard practice for patients undergoing cardiac bypass surgery to prime the pump with six units of whole blood and use an average of six further units during surgery. These provocative results on Jehovah's Witness patients should have "jolted" the medical community to question the excessive use of allogeneic blood transfusion in most surgical procedures. However, it was not until the mid 1980's, with the recognition that HIV/AIDS could be transmitted by allogeneic blood transfusion, that general concern questioning the benefits of allogeneic transfusion began to surface. Despite these two sentinel events that should have placed blood conservation high on the clinical agenda it has taken almost another two decades for medical practice to focus on appropriate alternatives to allogeneic blood transfusion and conservation techniques.

Most of these techniques have been available and used, to varying degrees, for nearly 30 years. However their benefits have not lived up to initial expectations. Research over recent years has demonstrated that there is marginal reduction in the use of allogeneic blood transfusion when these techniques are used, except in cases where large volumes of shed blood can be salvaged, washed and re-infused. In 1999 an AHMAC *Review of the Alternatives to Allogeneic Blood Donation* was published by the Australian Blood and Blood Products Committee and the Australian Health Ministers' Advisory Committee (http://www.nba.gov.au/pdf/allogeneic.pdf). This is an important document and relevant to the current issues under consideration regarding the alternatives that have been offered to the transfusion of allogeneic blood transfusion. In relation to methods for minimising allogeneic blood transfusion in the 1980's, autologous blood transfusion was regarded as a desirable and appropriate technique for achieving this end. Research during the 1990's produced evidence that benefits were minimal and cannot be justified on a cost benefit basis. Pre-operative blood deposit has several risks and there is a general view that risks significantly outweigh the marginal benefits. The AHMAC publication reviews this evidence and makes recommendations which would be found surprising in the 1980's context. It is now possible to state that in patients requiring larger volume blood transfusions (i.e. >750-1000 mls) preoperative autologous deposit of blood was not an effective option to avoid allogeneic blood transfusion and is associated with potential hazards, although the technique was recommended at the time.

Although autologous techniques have advanced in many respects, the focus in recent years has moved more towards the concept of blood management, combining autologous techniques with appropriate assessment for pre-empting blood loss and the application of techniques for minimising intraoperative blood loss. Preoperative autologous deposit can now be combined with recombinant erythropoietin and iron therapy, perioperative haemodilution with preparation of autologous plasma, platelet and fibrin gel/glue and intraoperative salvaging with better and more cost-effective technologies.

Acute haemorrhage as an example of why the focus should be on the patient's problem and blood management rather than blood transfusion

Blood transfusion has its origins and progressive development in the management of acute haemorrhage, particularly driven by demands during times of military conflict. There is no doubt that blood transfusion has been a major advance in the management of haemorrhagic shock and thousands of lives have been saved. However, in recent years there has been a major reassessment of the management of the acutely bleeding patient, especially in relation to trauma.

This reassessment has come about for several reasons:

1. Until recently there had been no significant improvements since the 1960's in the outcomes for acutely bleeding patients receiving massive blood transfusion. The reasons for this have been unclear, but presumed to be multifactorial, including, the nature of the underlying disorder,

delays in resuscitation, the quality of blood components, the inability to stop bleeding, irreversible shock and the multi-organ failure syndrome.

2. Advances in the retrieval of trauma patients, resuscitation protocols, techniques for rapid diagnosis, development of trauma teams and early "damage control" surgery have improved the management of acutely haemorrhaging patients.
3. Over the last decade experimental and clinical studies have identified blood transfusion *per se* as an independent risk factor for morbidity and mortality as well as increased admission rates to intensive care units, increased length of hospital stay and additional costs. Blood transfusion being implicated as part of the problem rather than optimal therapy has been a surprise to many clinicians, administrators and patients, as it has always been assumed that blood transfusion can only be beneficial for the bleeding patient, allowing time for effective resuscitation before definitive diagnosis and surgery. This long-standing belief is now being effectively challenged and currently the debate on the management of the acutely haemorrhaging patient has moved significantly from a paradigm with a focus on transfusion to one in which the urgent control of critical bleeding is the paramount priority, with avoidance and/or minimisation of blood transfusion. This has lead to a major reanalysis of guidelines for the management of acutely bleeding patients. The guidelines are no longer for the "management of massive blood transfusion" but rather for the "management of critical bleeding".
4. The reassessment of resuscitation of patients with acute haemorrhage is resulting in challenging of several long-standing dogmas.
   a. Greater tolerance of hypotension, until haemorrhage is controlled in order to reduce the volume of blood loss and likelihood of re-bleeding. By minimising the degree of blood loss many of the complications associated with large volume replacement and transfusion can be minimised.
   b. Tolerance of anaemia
5. More recently the development of recombinant activated factor VII (rVIIa) for the management of haemophilia patients with factor VIII inhibitors has not only been a major therapeutic advance, but has been the stimulus for a complete reassessment of long accepted models of how the haemostatic system works. The work of Dr Ulla Hedner in developing rVIIa has challenged long established views on the role of VII and VIIa in haemostasis. From being a lesser participant in the initiation, amplification and propagation of haemostasis and clot formation VIIa is now recognised as a central "player". It has taken nearly two decades for Dr Hedner's work to be accepted by mainstream haematology and transfusion medicine. The proposition that rVIIa could ultimately have a therapeutic role beyond the rare indication for inhibitors in haemophilia patients was viewed as unconventional, unlikely or potentially dangerous. Now that a cell-based model of haemostasis is widely accepted, coagulation factor VII/VIIa has been elevated to a pivotal role in the mechanisms of haemostasis and the control of bleeding. The acceptance that the old haemostatic paradigm was incorrect refocused attention on Dr Hedner's original postulations and recombinant VIIa has suddenly moved from "orphan" status for haemophilia patients to centre stage in the management of acute bleeding. To many experienced clinicians there was immediate realisation that *"this rVIIa is a real advance, and could this be a "penicillin" for the critically bleeding patient*". Over the years numerous pharmacological approaches have been and are used to control or minimise acute haemorrhage, but are generally of marginal benefit in the critically bleeding patient. Initial experience with rVIIa has been different and its rapid and unexpected move into mainstream medicine has been a challenge for all concerned. The accumulation of evidence for its efficacy has had a late start for the reasons outlined above and in many of the clinical settings in which it is used there have always been difficulties conducting clinical trials.

Critical bleeding is thus a good example of the modern approach to blood management. Blood transfusion is viewed as one of many potential interventions in the multi-pronged approach to a complex clinical problem, but has the potential to become part of the problem rather than an answer. Figure 1 outlines the thinking process in analysing whether blood transfusion has the potential to be part of the problem and reasons that the precautionary approach to transfusion should be adopted as it always has been in relationship to the safety of the blood supply.

Issues versus real issues

The increasing use of weasel words [1] in the bureaucratic and corporate worlds diverts attention away from important and central agendas. "Issues" versus "real issues" is such an example; what <u>is</u> the difference between an issue and a real issue? You won't find the answer in a dictionary, but regular interaction with the bureaucratic processes quickly enlightens you that the bureaucracy sees an issue as <u>your</u> problem and a real issue as <u>their</u> problem. Clinicians as advocates for their patients must concentrate on turning issues surrounding the delivery of appropriate and safe health care from issues into real issues. It is only then that the patient care agendas

Figure 1:

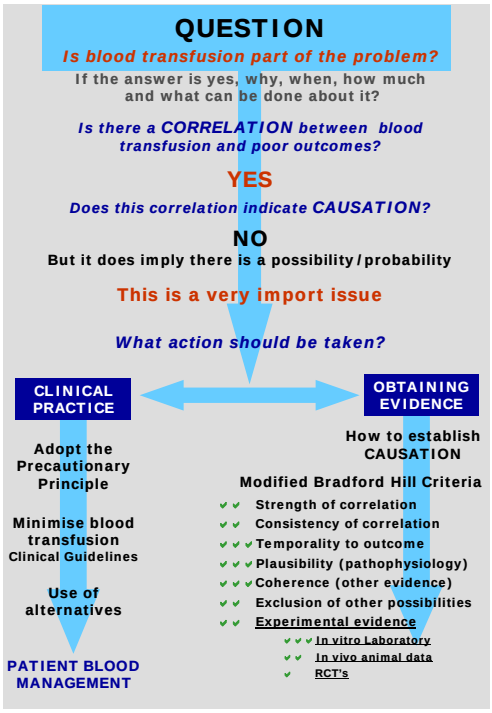
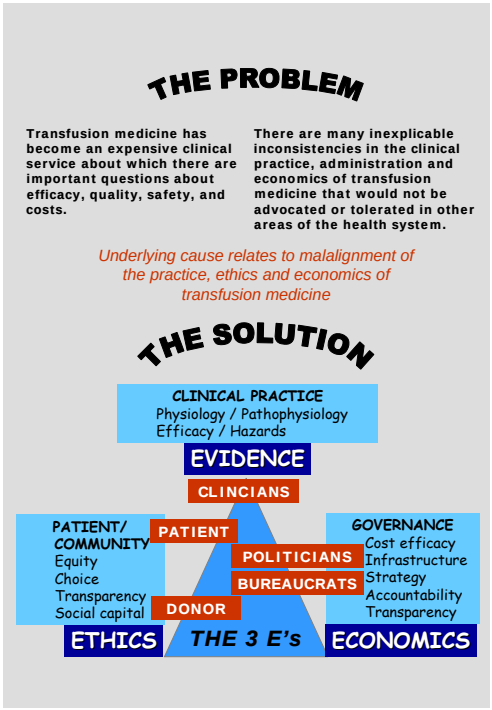


Figure 2:



and the blood supply agendas will be talking the same language. Improved assessment of cost effectiveness, equity of access and clinical governance will only make progress if this paradigm shift occurs. What is medically appropriate for a patient should be based on sound evidence. The questions of affordability, cost effectiveness, equity, etc., clearly impact on the availability and delivery of appropriate therapy, but do not alter what is scientifically best for the patient. These are questions for the health sector and broader community to debate.

1. Are we making progress in transfusion medicine?
2. How beneficial is blood component therapy in specific clinical circumstances?
3. How should we cost transfusion medicine?
4. What are the "real" hazards of blood component therapy?
5. Is the quality of blood components adequate?

To answer these questions we need to be able to make appropriate measurements, but what should we be measuring? Do we have valid methods? Are we trying to measure better individual patient outcomes or overall improvements in transfusion practices within the health system? Are the questions and answers the same for different countries?

Focussing primarily on transfusion medicine using rising expenditure as a measure of progress can be equated to governments using Gross Domestic Product (GDP) as a measure of economic welfare and dare one say an indicator of happiness and satisfaction with life. Clearly, we must define our focus, what we are trying to measure and how it should be measured. A United States public policy organisation (Redefining Progress) has developed a more meaningful Genuine Progress Indicator (GPI). They illustrate the problem with using GDP that regards every expenditure as an improvement to the wellbeing of individuals and the community by stating:

By this reasoning, the nation's economic hero is the terminal cancer patient going through an expensive divorce, whose car is totalled in a twenty-car pile-up. The economic villain is the healthy person in a solid marriage who cooks at home, walks to work and doesn't smoke or gamble. The hero borrows and spends; the villain pays cash and saves for the kids' education. What economists call "growth", in other words, is not always the same as what most Americans would consider "good".

This analogy illustrates the point that focusing on blood transfusion and related costs is addressing the wrong question. We should be asking: Are we making progress in blood management and blood conservation? Are we better managing clinical conditions in which it has generally been assumed that

blood transfusion is necessary? What evidence do we have to support the proposition that blood transfusion is improving patient outcomes? Why don't we turn our focus more toward the clinical problem at hand and better identify the benefits of blood transfusion or the use of more economical and safer alternatives?

Conclusions

Patients think blood transfusion is special and beneficial, but have difficulty accepting small risks over which they have no control.

Blood Donors believe their contribution of blood is a gift to the community that will be used appropriately and safely to the benefit of those in need on an equitable non-profit basis.

Clinicians think blood is ordinary, take blood transfusion for granted, benefit is assumed and risks regarded as minimal.

Governments view blood as a commodity and transfusion medicine as an expensive support service which should be regulated and funded in a "McDonaldised" manner.[2]

These potentially disparate views on the same issue should be of concern to all health professionals and better alignment of the clinical, ethical and economic aspects of transfusion medicine are necessary (Figure 2). With the increased range of pharmacological agents, surgical and anaesthetic techniques and development of recombinant blood components the armamentarium for avoiding or minimising allogeneic blood transfusion is substantial. What is now needed is a broad clinical commitment to blood conservation techniques in conjunction with more realistic costing and accountability for allogeneic blood products, as well as recognition that allogeneic transfusion remains a potentially hazardous procedure for the patient and should only be undertaken if there is likely to be benefit and improvement in clinical outcomes. The blood supply in Australia is one of the safest in the World from the infectivity perspective, but remains a scarce and expensive resource given in trust that it will be managed appropriately. The main hazards of allogeneic transfusion are now at the clinical practice end of the blood chain, not at the supply end. Blood management is logical; evidence is accumulating that the benefits of transfusion have been overrated; there are limitations of blood supply as well as medicolegal pressures. Patients want greater input and choice in decisions about their clinical management.

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[1] Don Watson
[2] Ritzer: The McDonalisation of Society

The Use Of Autologous Blood In The Surgical Setting: Intraoperative Blood Salvage Should Be Used Where Possible.

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Abstract

Intraoperative blood salvage provides a safe and effective form of blood transfusion and complements the existing allogeneic blood transfusion services. Despite much evidence supporting the use of intraoperative blood salvage as best medical practice in many situations, it is underused in the surgical setting, relatively unknown to the public and is not financially supported by Government or Red Cross Blood Transfusion Services in Australia.

Introduction

Australians boast that the provision of blood is 'safe and free'. However, the safe form of blood transfusion, 'intraoperative blood salvage' (IBS) remains relatively unknown to the public.[1] IBS is a form of autotransfusion by which blood from the patient collected during or after an operation, is processed and reinfused - a form of processed blood recycling.[2-4] Even though the quality of the red blood cells using IBS is superior to allogeneic and stored blood, IBS is not supported with funding by the government or Red Cross Blood transfusion services, unlike allogeneic blood, and is not free.[3] The provision of IBS as an alternate blood replacement option would help reduce the strain on stored blood resources as well as nullify any risk of disease transmission as the patient is receiving their own blood, rather than a donor's.[3,5] These factors would suggest that best medical practice would include the use of IBS in situations where patients are undergoing surgery during which blood loss is inevitable and cell salvage possible.

i). Allogeneic blood transfusion

Allogeneic (donor) blood has historically been the most utilised method of blood transfusion in Australia. The provision of donor blood became readily available by the late 1930s with the introduction of better means of blood typing and storing.[6] Donor blood will continue to provide the backbone of the blood transfusion services essential for non-surgical conditions, emergency situations and for those with malignant or infective contamination until synthetic haemoglobin is available.[2]

The Australian Red Cross provides a highly effective service in which the quality of donor blood is recognised as being of high standard as evidenced by the low levels of Human Immunodeficiency Virus (HIV) and hepatitis infection rates.[7] The development of effective testing procedures for transmissible diseases and use of leuko-depleted blood has substantially improved the safety of donor blood. A survey by Whyte and Savioa showed that the risks of blood screened by the Australian Red Cross Service being infective for HIV, hepatitis B or hepatitis C were 0.79, 2.71 and 4.27 (respectively) per million donations.[7] Despite this massive reduction in disease transmission, the risk has never been eliminated.[2,5,8] This risk was highlighted by the transmission of the HIV virus in a 14 year old girl in Victoria in 1999.

On the 28th July 1999 "The Age" informed the Australian public that a Melbourne schoolgirl had contracted the Human Immunodeficiency Virus due to the use of infected blood during surgery.[9] This is the first case of transfusion-related HIV in Australia in 14 years. Although the likelihood of contracting HIV via anonymous donor blood transfusion is rare, there is no doubt that this Melbourne family believes that it is no longer rare enough. HIV is only one of a multitude of other viruses that can be transmitted by allogeneic blood transfusion.

Table 1: Processed salvaged blood has greater advantages and fewer disadvantages over stored and unprocessed salvaged blood.[3,7]

	Stored (Unprocessed)		*Salvaged (Unprocessed)*		*Salvaged (Processed)*	
White cell components	Adv's	Disadv's	Adv's	Disadv's	Adv's	Disadv's
Fibrin degradation products	Normal		Increased			Normal
Complement	Decreases			Increases	Removed	
Lysolecithin	Decreases			Increases	Removed	
Leukotrine	Low			Increases	Low	
Plasminogen		Increases		Increases		Increased
Inhibitor activity		Increases		Increases		Increased
C3a		Increases				
Serotonin		Increases		Increases	Lower than stored	
Phospholipase		Increases		Increases		
Lysoplatelet activity factor		Increases		Increases		
Elastase		Increases		Increases	Removed	

Table 2: Year to date statistics of average packed cells returned per operative procedure at Royal Perth Hospital using cell salvage. For most cardiac surgery blood is salvaged and recycled through the perfusion pump. The cell salvage process is used for procedures "off-pump" and post-pump bleeding.

Procedure	Number of cases	Average packed cells returned (mls)	Equivalent units
Orthopaedics	160	600	2.5
Cardiothoracic	4	1100	4.5
Vascular	36	800	3.3
	Average	833	3.5

Costs estimate:
Equivalent costs for 700 (200 cases x 3.5 units) of bank units = $210,000.00
Running cost to Royal Perth Hospital $300.00 per operation = $60,000.00
Cost saving to tax payer = $150,000.00

Additional problems that are associated with the use of donor blood include incompatibility, and sensitisation to donor blood owing to previous transfusions or pregnancy. This can result in a wide array of immune reactions, some of which can, under some circumstances, be fatal.[5,10] The transmission of other blood borne diseases, some of which are not subject to screening tests, such as Creutzfeldt-Jakob disease (mad cow) and hepatitis C, because of prohibitive costs must also be taken into consideration when using donor blood.[11,12] The non red-cell elements, particularly the contents of the white cells, which include elastase, are released with the death of the cells within three days and have detrimental and cumulative effects with increased volume and age of the blood.[9] There is an effect on coagulation: plasminogen activator remains active in stored blood, while plasminogen activator inhibitor denatures.[8] There is an argument for the provision of red cells with white cell filtration at collection, and it has been recommended that allogeneic blood used in conjunction with a cell saver, should also be washed prior to transfusion when large volumes of blood are transfused.

ii). Autologous blood transfusion methods

The realisation of disease transmission and the fatal nature of HIV in the early 1980s produced a resurgence in interest and use of autologous techniques: predonation, predilution and IBS.

Predonation

Predonation is a process whereby the patient undergoing surgery donates blood several weeks before the time of surgery to provide for any blood needed for transfusion during the operation.[3] This method of autologous blood transfusion has the obvious benefit of removing disease transmission and incompatibility risks.[5,13] Predonated blood, carries all blood storage lesions, labelling and handling errors which also characterise allogeneic blood.[4,6,13] Predonated blood also contains a high quantity of degraded white cell components which can cause clotting and autoimmune reactions when reinfused.[6,13] In addition, the collection of blood from an ill person

may result in reinfusion of unhealthy red blood cells. This technique is labour intensive, inefficient, incurs a Medicare rebate cost and may carry some risk in patients with co-morbid conditions. As such, this technique may only be of assistance in a limited number of situations.

Predilution

Predilution is similar to predonation: the patient donates up to 20% of their blood in the anaesthetic room immediately prior to surgery. The volume lost is then replaced with colloid fluid.[3,14] Any blood lost during surgery has a diluted red blood cell content which can then be boosted and concentrated by the red blood cells collected prior to surgery.[14]. The transmission of blood diseases and the problems associated with incompatibility are, as with predonation, overcome by using this technique.[5] However, the predilution method of autologous transfusion suffers from the disadvantage of being limited by quantity; the amount of blood that is available to be extracted from the patient prior to surgery is restricted to 20% of the total blood volume. This method also has some potential detrimental effects on the patient because of the induced anaemia and, as such, is of strictly limited value.

Intraoperative Blood Salvage

Unprocessed salvaged blood was originally utilised in the 19th century, in particular, associated with ruptured ectopic pregnancies and penetrating abdominal or chest wounds.[13,15] Despite the elementary nature of the initial intraoperative autotransfusion devices the associated complication and death rates were less than those of allogeneic transfusion.[15] The early devices were improved to control the reinfusion rate and reduce haemolysis by replacing vacuum suction with roller pumps.[16] This reveals that although the benefit of intraoperative autotransfusion was recognised by the 1970s, if not the 1940s, the use of allogeneic blood remained the most popular method of transfusion until the 1980s.[17]

The Vietnam war provided the stimulus for a dramatic increase in the use of autologous, (filtered but unwashed) blood transfusion owing to a shortage of allogeneic blood.[6] However, as with all forms of blood transfusion this method is not without risk. Direct re-infusion of unwashed salvaged blood, only filtered of foreign materials, can result in a higher risk of blood coagulopathy within the body as well as autoimmune reactions.[2,3,13,18] These occur when white cell components react to contact with collecting materials outside the body.[6] Re-infusion of these white cell components can have devastating effects. These effects are also apparent with the use of unprocessed bank blood, especially as storage time increases.[4,6,8,13,19] Washed salvaged blood does not provide coagulation factors and is free of plasminogen activator.[8]

The detrimental effects of IBS, however, can be virtually eliminated by washing the blood in saline prior to reinfusion. This purges the unwanted white cell matter (Table 1) and enables the reinfusion of concentrated red blood cells which are important for transporting oxygen in the body.[6,8,13,18] Washed salvaged blood reduces micro-organism contamination and is not recommended when there is obvious risk of bacterial contamination where the infective dose will be high.[2] Thus, not only does this technique provide the re-infusion, once processed, of high quality red blood cells, it overcomes incompatibility, immune and disease transmission and storage risks associated with donors and predonated transfusions. In addition, IBS may be useful in assisting with the availability of blood for people with rare blood types, as well as provide a more acceptable method of blood transfusion for certain religious groups.[3,13,18] Although limitations of IBS include that it is not recommended in operations for malignant disease and where there is overt infection or bacterial contamination, it may be the only form of blood transfusion required in many situations. It is always complementary with allogeneic blood, and when the machine is being used to salvage blood, any allogeneic blood needed should also be washed by the same process before re-infusion.

IBS is an under-utilised resource in our community with a developed technology to support it.[20] In a society in which the transmission of fatal diseases via transfusion can still occur, the availability of a technique such as IBS would complement existing services, for those undergoing elective surgery where blood transfusion is expected. An important feature of IBS is that surgeons and anaesthetists carry out the blood salvage process: no handling, testing or storage of blood is required outside the operating room, in contrast to conventional Red Cross allogeneic blood donation procedures. As such, IBS is clearly a distinct process, which is quite separate from the traditional blood transfusion service.

Should Intraoperative Blood Salvage be funded by Medicare?

It is difficult to estimate the cost of one unit of blood because of the number of products obtained from one unit of allogeneic blood despite the known cost of testing, collection storage, handling and administration. It is estimated that IBS becomes cheaper than allogeneic blood if two units or more are transfused.[20] The costs of IBS are fixed and do not rise with increased salvage (Table 2). IBS is already routinely utilised by many hospitals, including teaching and private institutions. The provision and operation for IBS equipment is funded by the public hospitals themselves from general revenue and as such, this procedure is under constant threat of budget cuts. The lack of rebate provision by public and private health funds, as demonstrated in Table 3, has also had an impact by further exacerbating the under-utilisation of the technique. There are studies which suggest that IBS does not reduce the use of allogeneic blood.[21,22] Poor training of operating room personnel results in

much wastage. The continued use of a floor or wall sucker in tandem with a cell saver and the use of 'pack mopping' are the two most common causes of wastage. An independent audit by the Department of Haematology at Royal Perth Hospital (1991, Perth, Western Australia) showed that the transfusion rate declined from 80% of patients undergoing aortic aneurysm surgery to 20% when all suckers were connected to the cell saver.

Table 3: Rebates provided by public and private health insurance companies for the intraoperative blood salvage service.

Health Fund	Rebate
Medibank	Nil
National Mutual	Nil
Health Insurance Fund (includes Goldfields, St Lukes and Geelong)	Nil
Health Benefits Fund	$200
Medical Benefits Fund	75% of total cost APP 3

Table 4: Blood loss and packed red cells returned during vascular surgery from a private cell salvage operator (Mount Private Hospital, WA). Vascular surgery constitutes 10% of all cell salvage cases by this operator. One packed red cell unit is equivalent to approximately 240mls. Please note the volumes in the last column.

Date	Surgery	Blood loss (mls)	Packed cells returned (mls)
15/07/98	AAA	1100	450
22/07/98	AAA	2575	900
30/07/98	AAA	2500	1080
5/08/98	AAA	2800	1510
18/09/98	AAA	880	375
23/09/98	AAA	3000	1140
28/09/98	AAA	3000	1010
23/01/98	Liver resect	1350	450
29/10/98	AAA	1670	670
11/11/98	AAA	2300	1015
25/11/98	AF Bypass	520	240
29/11/98	Liver resect	2600	1000
10/12/98	AAA	1200	500
6/01/99	AAA	1100	400
14/01/99	AAA	2600	950
20/01/99	AAA	3455	1600
28/01/99	AAA	2400	1050
10/02/99	AAA	2200	1015
11/02/99	AAA	3350	1400
11/02/99	AAA	960	475
17/03/99	AAA	2000	900
15/04/99	AAA	600	235
21/04/99	AAA	1400	430
5/05/99	AAA	2250	675
	TOTAL	47820	19470

The average cost of cell salvage in Mount Private Hospital is $500 ($200 for a private contractor to run and supply the machine in addition to $300 for disposables).

Cost estimate:
Estimated cost for 81 units of bank blood = $24,300
Total costs to patients = $12,000 ($500 per patient)

Minimally invasive surgery, bloodless surgery and the acceptance of lower post-operative haemoglobin levels have done much to reduce allogeneic transfusion. It has been questioned therefore whether it is worth making the equipment and consumables for IBS available when allogeneic blood has to be available anyway.[21,22] Furthermore, despite the Medicare rebate for the administration of allogeneic blood and only the altruistic incentive for the administration of salvaged blood, the practice continues because it is patient driven.

Obviously, hospitals prefer to utilise the 'free' donor blood service, which is ultimately government funded. Clearly, there is a need for government assistance and recognition for IBS separate from that of the current government funding of bank blood. Tables 2 and 4 provide examples of the costs at a teaching hospital where the cell salvage machine is operated by existing operating room staff versus a private hospital that hires a machine and technician from an external source. Some private hospitals do have their own machine and therefore the costs are usually between the two extremes provided here. In both cases, the use of autologous blood salvage results in a cost saving. It needs to be emphasised if bank blood had been used, the cost would be equivalent to the cost of the number of blood bank units. There is an approximate cost saving of half, even before you consider the benefit to the patient and the medico-legal costs of an adverse event with the known risks of allogeneic blood.

Commonwealth Review of Blood Banking and Plasma Product Sector

The Commonwealth Review of Australian Blood Banking and Plasma Product Sector released in 2001 provided an important opportunity to discuss the merits of autologous blood, particularly IBS, at a systems level.[23] It was disappointing that cell salvage was not discussed and autologous blood usage was deemed to be outside the terms of reference of the Review. This was despite submissions being made to the Review from experts in the field of vascular and emergency medicine. By deliberately excluding cell salvage, the Review has not served the Australian public well. It has not fulfilled its mission to focus on issues of quality and safety, the identification of impediments to best practice, the supply of blood and plasma products, and to recommend improvements to the system-wide decision making processes. It has ignored international moves to increase the use of cell salvage to complement donor blood reserves and has deprived the Australian public of the safest and highest quality blood available. It has also ignored the fact the intraoperative cell salvage has been shown to be more cost-effective than the use of donor blood, with costs expected to double in the UK due to the increased cost of screening blood for infectious agents such as Creutzfeldt-Jakob disease (mad cow) and

hepatitis C.[11] In addition, there is international concern about dwindling reserves of donor blood.[12]

Once again the authors contend that there is a need for Government assistance and recognition of IBS separate from that of the current government funding of the blood bank. Blood transfusion services do not see IBS as part of their brief which provides a need for those specialties, and specialist Colleges, which might use blood salvage to become more vocal in pushing the case for IBS. Best medical practice should include the use of IBS, particularly in situations where patients are undergoing surgery during which blood loss is inevitable and cell salvage possible. The public does need to be reassured their best interests are being served.

It is only with appropriate funding that the full potential of IBS will be realised and thus, allow Australia to meet the claim of providing 'safe and free' blood transfusion services. Facilitating and encouraging the use of IBS, combined with the other current successful surgical measures to reduce blood loss, will reduce the strain on blood banking. Even before you consider the benefit to the patient and the medico-legal costs of an adverse event with the known risks of allogeneic blood,[24] there is a case in Australia for the provision of equivalent funding for a unit of blood derived using IBS in theatre, and its administration, as there is for allogenic blood - at least equivalent to that provided for allogeneic and predonated blood transfusions.

Conclusion

There is currently no special provision of rebate for the administration of salvaged blood and the lack of a Medicare rebate removes the responsibility of the health funds to support the practice with gap provision, as demonstrated by Table 1. There are, if anything, disincentives for the use of IBS. Good arguments exist to encourage the use of blood salvage as a support to allogeneic blood and provision of autotransfusion with all its advantages. Many believe it should be used for this purpose whenever available.[16,25]

Blood transfusion is an emotive public issue which impacts on the blood transfusion practices of clinicians. Cell salvage has, to date, been driven by the patient's desire for his or her own blood, and operating room staff commitment. The benefit of the inclusion of IBS as a safe and effective blood transfusion modality will increase public confidence in the provision of the blood transfusion services.

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Optimisation of Perioperative Autotransfusion

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Abstract

Cell salvage involves a number of processing steps which include collection, filtration, concentration and washing of shed surgical blood. The efficiency of cell salvage, or how much shed blood is returned to the patient, can be altered or influenced by each of these stages. This article addresses each of these steps and describes how the autotransfusionist might optimise the efficiency of this process.

Introduction

There has been a developing interest in blood conservation in recent years due to an allogeneic blood shortage [1] rising costs of blood products, immunosuppressive effects of allogeneic transfusion, and the potential transfusion risk of variant Creutzfeldt-Jakob disease.[2] Multiple strategies can be applied to avoid allogeneic transfusion. The primary strategies involve preoperative erythropoietin and iron supplementation, preoperative autologous donation, acute normovolemic hemodilution, and the application of cell salvage (CS) systems. In our institution, CS offers the greatest ability to avoid allogeneic transfusion.

Mathematical modelling of cell salvage has revealed that small changes in red cell processing efficiency can make large differences in the maximum allowable blood loss that a patient can sustain prior to allogeneic transfusion therapy.[3] These models suggest that a 70 kg patient with a starting hematocrit of 45% can sustain a blood loss of 9,600 ml if a transfusion trigger of 21% is used and cell salvage captures 60% of lost red blood cells. The sustainable blood loss rises to 13,750 ml if 70% red cell recovery is achieved. This small change in red cell recovery with a large change in the ability of a patient to avoid a blood transfusion highlights the importance of optimizing the cell salvage system.

Optimizing cell salvage can occur at multiple points in the processing. In this article, each processing step will be addressed and a discussion will be attempted of how each step can be optimized. Figure 1 schematically details each of these steps. Many aspects of cell salvage technique is unstudied. For this reason, much of what will be discussed is anecdote and based on the experience gained at the Cleveland Clinic Foundation. In areas where research has been performed, every effort has been made to reference this work.

Patient Factors

Rheologic characteristics of a patient's red cell membrane may make them more or less prone to hemolysis during cell salvage. More hemolysis means less red cells to return to the patient. Many factors such as ABO typing have not been studied but some work exists which suggests that drug therapy may be used to increase a red cell's ability to sustain haemolytic stress. It is well known that the physical properties of a red cell such as cell shape, hypotonic lysis resistance, permeability or cell aggregation, can be altered by the intercalation of amphiphilic molecules into the red cell membrane lipid bilayer.[4] Amphiphilic drugs encompass a variety of therapeutic classes of medications including antiarrhythmics, antidepressants, neuroleptics, beta-adrenoceptor blocking agents, antihistamines, antimalarial drugs, and anaesthetic agents. In addition to drug factors, the rheology of the red cells may change dependent upon the fluid environment in which they are suspended. The osmotic fragility of erythrocytes can be affected by pH, temperature, and the electrolyte and colloid composition of the suspending medium.[5,6,7]

In preliminary work performed at the Cleveland Clinic Foundation [8], an *in vitro* model of hemolysis was developed using a laminar flow chamber. This chamber applies onto the red cell a controlled degree of shear stress. With this chamber several different drugs have been tested to assess whether they might alter the cells ability to tolerate shear stress. From this work, it would appear that an anaesthetic based on propofol would improve red cell recovery along with use of chloroquine preoperatively. In addition, use of citrate anticoagulant would appear to improve red cell recovery when compared to heparinized saline. Before widespread application of these findings is undertaken, further work needs to be performed *in vitro* and confirmed in the clinical setting.

Blood Collection

***Suction*:** As blood is lost, suction is applied to clear the blood from the surgical field. How this suction pressure is applied, changes the shear forces applied to the red cell. Shear forces occur anytime a fluid moves in contact with a solid surface.[9] Shear-induced hemolysis can be produced with high suction pressures. So, the lowest tolerable suction pressure should be applied when sucking blood from the surgical field. In addition to shear-induced hemolysis, sub-haemolytic trauma can occur which will significantly shorten a red cell's life span following reinfusion.

To avoid haemolytic and sub-haemolytic stress, vacuum pressure should be regulated to 80-120 torr which is adequate for most surgical procedures.[10,11] The vacuum level can be temporarily raised to clear the field in the event of massive blood loss, then reduced to a lower level. It is important to remember that if multiple suction lines are attached to a collection reservoir, both lines need to be used simultaneously; otherwise, when one suction line is placed in blood and a separate line is sitting on top of the patient, then suction pressure will be halved.

Selection of suction tip style and the method of use can also affect the degree of shear stress and red cell recovery rates. Tips which have small calibre openings create high shear stress which can hemolyze cells during collection. Suction tips should be immersed in the shed blood during collection. Skimming, or sucking of blood at a blood/air interface will lead to increased turbulence and shear.

Swab/Sponge Rinsing: Fully soaked gauze pads, lap sponges or swabs may contain up to 100 mL of blood.[12] Of this blood, approximately 75% is retrievable by rinsing the swab in a basin of isotonic solution (normal saline, Ringer's Lactate, Hartmann's solution) and wrung out prior to their discard. The rinse solution is then periodically sucked into the cardiotomy reservoir when the rinse solution appears to be grossly bloody.

Many fear this practice because of cotton fibres possibly being entrained into the blood from the sponge, or they fear possible bacterial contamination being introduced into the system via the sponge. In unpublished data from the Cleveland Clinic, we found that no cotton fibres were retrievable from rinse solutions. Discussion with the manufacturer of these sponges revealed that no fibre shedding results from a tight weave of the cotton fibres and a double washing process. In addition, macroaggregate filtering at the collection reservoir should remove large particles such as cotton fibres.

As for bacterial contamination that might result from sponge rinsing, any bacteria that would be on the sponges would have come from the surgical wound. Thus, the patient has already been exposed to the bacteria. It is well described that cell salvage blood is routinely contaminated with bacteria.[13, 14] This contamination has not been correlated with clinical sequelae. If sponges are suspected to be grossly contaminated with bacteria, they should simply be discarded rather than rinsed.

***Anticoagulant*:** As blood is suctioned from the surgical field, an anticoagulant should be mixed with the blood. The purpose of the anticoagulant is to prevent clot formation in the collection reservoir or processing system. Clotting of blood in the collection system will result in the loss of otherwise recoverable blood as well as the need for reservoir and bowl replacement when large clots obstruct blood flow through the system. Either citrate or heparin can be used for anticoagulation during cell salvage. Some controversy exists as to which anticoagulant is best.[15,16]

Due to its low cost and ready availability, heparin is most commonly used. Added to a carrier such as normal saline at a dosage of 30,000 Units/L of heparin, the solution is titrated through the aspiration suction system at a rate of 15 ml per 100 ml of collected blood. When regulating the anticoagulant rate, it is better to err on the high side rather than risk under administration and loss of red cells to clotting. Over administration of heparin during shed blood salvage is of no consequence in a cell washing system. Adequate washout will remove all but a trace of heparin with less than 10 Units residual remaining in the final blood product.

Citrate has also been used as an anticoagulant. The administration rate for citrate bearing anticoagulants (ACD, CPD, etc.) is also 15 ml per 100 ml of collected blood. Again, over use of citrate anticoagulants is better than inadequate doses. On reinfusion, rapid liver metabolism makes citrate toxicity a difficult state to achieve. In compromised liver function, correction with small doses of calcium provides immediate and non-toxic reversal. At the Mayo Clinic in Rochester, Minnesota, 7500 units/L of heparin is mixed in a litre of the citrate solution. Use of this solution has been noted to eliminate the commonly observed protein deposits on the interior surface of the processing bowl.

If a leukocyte depletion filter is to be used during cell salvage processing, some thought might be given to the use of heparin rather than citrate. The degree of deformability of leukocytes is reduced in the presence of calcium.[17] If a leukocyte depletion filter is being used to remove bacteria, cancer cells, or amniotic fluid contaminants, this decreased deformability might also affect these contaminants. By decreasing the deformability of these cells, the ability to filter them out of the blood product may be enhanced. This is an area where further research is needed.

Collection Reservoir: The reservoir is the collection site for blood as it awaits processing. In general, three

times the size of the processing bowl is the minimum amount of blood which will be needed to fill a bowl. The reason for the three times multiplier is that the final product is concentrated into a range of 15-20 gm/dL haemoglobin levels. As blood is lost at haemoglobin levels much lower than this, there needs to be enough red cell mass to result in the final haemoglobin level of 15-20 gm/dL. In addition, some blood is destroyed during processing. Thus, approximately three times the bowl size is what is needed to process a complete bowl.

The collection reservoirs are generally available with filter sizes ranging from 40-120 microns. It is wise to avoid the smaller filters because smaller amounts of residual clot will prevent blood flow through the filter. At the Cleveland Clinic, the 120 micron size is used. When inadequate anticoagulation occurs and clot forms in the collection reservoir, red cells can be retrieved by mechanically agitating the reservoir while simultaneously infusing normal saline into the collection reservoir. This can be performed by using one of the suction lines, or infusing saline directly through ports on the top of the reservoir. These ports are available on some manufacturer's reservoirs but not all. Surprisingly, large quantities of red cells can be retrieved through this mechanical agitation.

Cell Salvage Machines

Cell salvage machines come in several designs. They all depend on two basic principles for their function; the difference in density of blood constituents, and a balance of centrifugal and hydraulic forces in the processing bowl.

As blood is pumped from the collection reservoir, it enters the bowl through a central straw (Figure 2), exiting from the bottom of the bowl while the centrifuge is spinning. The speed at which blood can be moved into and out of the bowl is partially dependant on the physical characteristics of this straw. For a given pressure generated by the roller pump, the resistance to flow will depend on the length of the straw and the radius of the straw. Resistance (R) to flow in a straight unbranched tube is defined by:

$$R = (8 \times \text{length} \times \text{viscosity})/(B \times (\text{radius})^4)$$

The radius of the straw in the Baylor bowl is greater than that of the typical Latham bowl. Because of the increased radius, there is decreased resistance to flow which is one of the features of the Baylor bowl which make it ideal for rapid processing. As the blood enters the processing bowl, the bowl is spinning rapidly to generate centrifugal force. Centrifugation is the process used to separate or concentrate materials suspended in a liquid medium.

The centrifugal force generated by a cell salvage processor is proportional to the rotation rate of the rotor (in rpm) and the distance between the rotor centre and the walls of the bowl. Heavier, larger particles will sediment against the walls of the bowl with the smaller, lighter particles sedimenting closer to the core of the bowl. As the blood enters the bowl, the denser constituents of the blood are forced towards the outer wall of the bowl, where it separates into vertical concentric columns on the basis of relative density. Red cells are held along the outer wall, while the plasma and irrigating solutions are forced towards the centre.

As blood is pumped into the bowl, hydrostatic force of the pumping will be exerted on the contents of the bowl. If blood is pumped at too fast a rate, or with too great a force, this hydrostatic force will overcome the centrifugal force on the red cells, thus pushing the cells out of the top of the bowl and into the waste bag. If rapid processing is required in order to keep up with massive blood loss, the filling of the bowl with blood and the subsequent washing can be speeded by increasing the pump rate. Because the hydrostatic force can overcome the centrifugal force when rapid pump speeds are chosen, the bowl pack needs to be observed carefully in order to guarantee that red cells are not being lost.

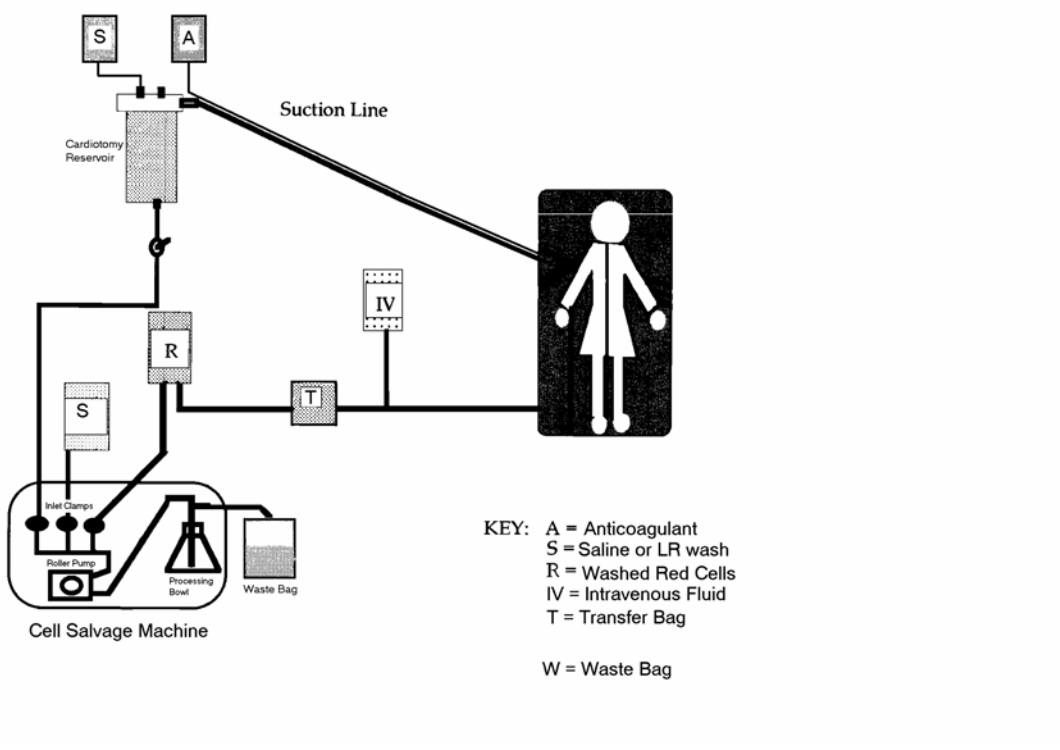
Pumping of shed blood continues until packed red cells have nearly filled the available space in the processing bowl. Filling the bowl with red cells, forces unwanted irrigation fluids and contaminated plasma into an exit port on the top of the bowl and thence to a waste bag which also holds sterile air forced from the bowl. Concentrating red cells while expressing irrigants and plasma removes 70% to 90% of the soluble contaminants in salvaged blood. However, the most damaging and hazardous contaminants are retained and concentrated in the bowl with the red cells. If re-infused, these contaminants would pose considerable danger to the patient by triggering disseminated intravascular coagulopathy. These contaminants can only be removed with certainty by cell washing.

Wash solution is introduced into the red cell pack by pumping through the central straw of the processing bowl. This wash solution is generally normal saline but one investigator suggests that a more balanced isotonic solution such as Lactated Ringer's solution may offer slight advantages when compared to normal saline.[18, 19] This advantage relates to minimizing the chloride load which would be administered to the patient.

The wash solution percolates through the red cell pack with the wash solution carrying away lighter debris and irregular agglomerates into the wash bag. Washing is considered complete when the effluent line appears clear to the eye and a wash volume of at least three times the bowl volume has been used.

To empty the washed blood, the roller pump is reversed, and clean, packed red cells are aspirated from the bowl through the straw and into a holding

Figure 1: This figure illustrates the steps which are taken to harvest and process shed surgical blood.



bag. Simultaneously, sterile air is drawn from the waste bag back into the bowl. Once the bowl is emptied of blood, another cycle may begin. It is important that the blood in the holding bag be moved into a transfer bag prior to re-administration. Air will accumulate in the holding bag over time. If blood is administered directly from the holding bag, the patient is placed at risk of air embolism. Through the use of a transfer bag, blood is moved out of the holding bag, followed by air being "burped" out of the transfer bag back into the holding bag. Under no circumstances should a pressure cuff be used on the holding bag when blood is being directly reinfused into the patient.

Selection of Operating Parameters

Selection of processing parameters by the operator determines collection efficiency and yield of red cells, as well as functionality of those cells and their cleanliness.

Bowl Size: The first operator decision is choice of bowl sizes. Generally, bowl size should be determined by the speed of blood loss and the anticipated blood loss. For cases where rapid blood loss is expected, a large bowl should be chosen. When slow oozing is anticipated, processing and return of blood may be optimized by using a smaller bowl.

Fill, Wash and Empty Rates: Modern autotransfusion machines offer pump flow rates which range from 100 ml/min to 1500 ml/min depending on the manufacturer. Maximal flows may be dictated during trauma or rapid blood loss surgery while slower flow rates may be more appropriate during orthopaedic or spine repair. Fill, wash and empty flow rates will determine product hematocrit, contaminant washout efficiency, and residual contaminant levels.

Fill Speed directly affects the resultant hematocrit achieved in the collection bowl. At any given inlet hematocrit, slower fill speeds will give higher packed cell densities in the bowl. The longer time period during which the bowl has to fill, the greater order the red cells will achieve and the denser they will pack. Faster fill rates produce increased disorder, with resultant lower hematocrits.

The desirable range for bowl hematocrit is greater than 40%. Hematocrits below this range can result in substandard washout and high residual particulate levels. Values over 60% are generally preferred because they raise the patient's hematocrit by a greater degree.

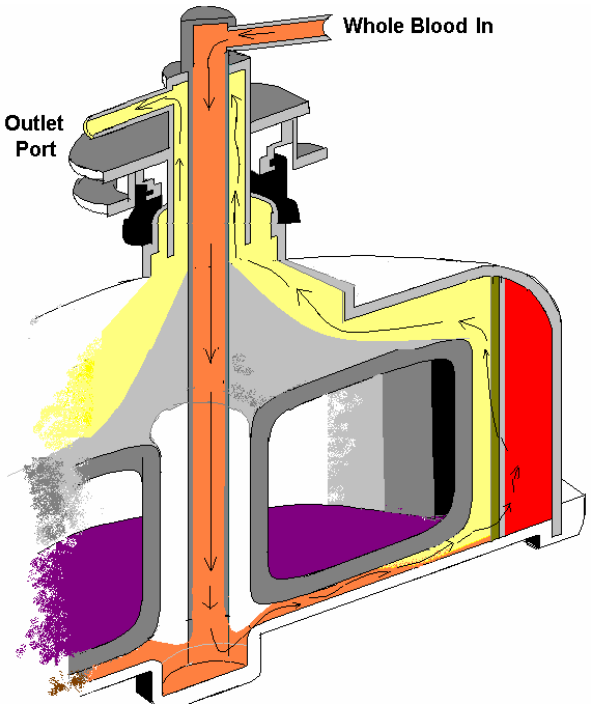
Wash Speed/Wash Volume: With the Latham design and its angled sides, wash speeds greater than the fill speed will disrupt the pack and lift it from its desired position within the bowl pushing viable red cells out of the bowl. The cells which are lost are the least dense, youngest and most desirable cells. Higher flow rates also encourage shunting and incomplete washout. Slower flow rates promote a more even distribution of the wash solution through the red cell pack, provide greater time for particulate removal, and result in a

cleaner product for the same total wash volume. In a Latham bowl, the slower the wash - the better the quality. In contrast, makers of the Baylor bowl, with its vertical sides, advocate using wash flow rates higher than the fill rate to achieve optimal wash efficiency and effectiveness. They report no difficulty with loss of red cells under these conditions.

Larger wash volumes improve removal of contaminants for all manufacturers' equipment and bowl designs. For relatively clean blood such as that from a cardiopulmonary bypass circuit or a gush of whole blood from a severed vessel, minimum wash volumes are probably adequate. Minimum wash volume would be three times the bowl volume or 675 ml of wash for a 225 ml bowl. Most operators include a safety margin by routinely washing with 1000 ml for an adult bowl and 500 ml for a small bowl. Blood from a wound drain or blood which has been allowed to pool in the wound for a long time requires higher wash volumes. Under any washing regimen, the operator should inspect the effluent line to determine if the volume employed has been adequate. The effluent wash solution should be clear at the end of the wash cycle, without any colour or cloudiness.

Empty Flow Rate: The rate the bowl empties following processing should be set at the same rate or lower than the fill cycle. Emptying at too high a rate risks damaging the red cells. With high fill rates, the blood in the bowl will be of a lower hematocrit, and so equally high empty rates can be safely employed. With low fill rates and the resultant high hematocrit product, low flow rates should be used. In cases where very high hematocrits have been achieved, the empty rate may have to be lowered to substantially less than the fill rate to effect complete recovery from the bowl. Too rapid an empty rate can also cause premature triggering of air detectors, signalling an empty bowl when substantial blood volume remains. While repeated processing does no harm to red cells, the patient is denied clean blood ready for reinfusion. Accuracy in quantifying the volume of processed red cells is also valuable in estimating surgical blood loss. A formula for calculating blood loss can be found in the appendix.

Figure 2: This figure is a cross-section of the Baylor bowl demonstrating how fluid flows through the bowl. It also illustrates the role of the central straw. Centrifugal force pushes the dense red cells to the perimeter of the bowl while the less dense plasma fluid and proteins is pushed out the top of the bowl by hydrostatic force.



Partially Filled Bowls: The red cell content of salvaged blood is seldom known, so it is quite common to process what seems like an adequate amount of collected blood only to find that not enough cells are present to fill the bowl. This is termed a "partial bowl". When washed, partial bowls will have biochemical contaminants removed to a greater extent than a full bowl but the concentration of cellular contaminants will be greater than a bowl which has been washed when completely filled.[20,21] This higher concentration of cellular contaminants may place the recipient at risk of possible coagulation dysfunction.

Many practitioners recommend discarding partial bowls rather than risk coagulopathy. Several options exist for handling a partial bowl rather than discarding it. The first option is to ignore the risk and readminister this partial bowl. Generally, the amount of red cell mass present in a partial bowl does not warrant taking this risk. A second option is to move washed packed cells from the holding bag back into the processing bowl using the "concentrate" function key. Reprocessing of washed cells does them no harm, and ensures adequate washing of the residual blood while increasing overall recovery rate. A third option is to return the blood to the collection reservoir, and then refill the bowl at a higher fill speed. Using the higher fill speed decreases the packing of the red cells so that fewer cells are needed to fill the bowl. Generally, this option only works when a full bowl is nearly achieved at regular fill rates. A fourth option would be to filter the partial bowl with a leukocyte depletion filter. This filter will remove most cellular and particulate contaminants thus making it acceptable for re-administration.

Maximising Washout Quality

In addition to optimizing red cells returned to the patient, attention to optimizing the quality of the product readministered is required. In order to optimize the blood quality being returned to patients, the American Association of Blood Banks (AABB) has issued peri-operative standards[22] to guide in the manufacture of a cell salvage product. In addition, a guidance document[23] is available which instructs the reader in how to comply with these standards. Implementation of these standards is mandatory if cell salvage is to be performed safely. Primary to these guidelines is the requirement for dedicated personnel to operate the equipment. Without this dedication, inadequate washing and concentration of the cell salvaged blood can lead to complications such as disseminated intravascular coagulation, or acute renal failure.

In many institutions this guideline is not followed. Under this circumstance, cell salvage is frequently instituted by the operating room circulating nurse who has other operating room responsibilities, and frequently, little training in safe cell salvage application. As the surgical procedure proceeds, large quantities of blood will collect in the cell salvage collection reservoir at the same times as when the circulating nurse's responsibilities are greatest. As a result, nurses will process the blood at their convenience. Periodically pressing the start button on the cell salvage machine as she passes by conducting other tasks in the operating room. Thus, no observation takes place of the adequacy of processing.

This processing "by convenience" is highlighted by an article on cell salvage from the Cleveland Clinic, in an era prior to dedicated cell salvage personnel. O'Hara and colleagues[24] reported on a lack of red cell avoidance with cell salvage in patients undergoing abdominal aortic aneurysm repair. They reported an average cell salvage unit hematocrit of 31%. Hematocrits of cell salvage blood should range between 40-75% depending on the method of processing. Lower hematocrits in the salvaged unit will haemodilute patients negating any positive benefit. Additionally, this lower hematocrit suggests that a partial bowl pack has been washed thus leaving residual cellular contaminants in the blood which could potentially be harmful to a patient. In this circumstance, the circulating nurse was not observing the equipment and frequent partial bowls were being washed. This early wash was being triggered by excessive hemolysis in the salvaged blood.

In addition to mandating dedicated personnel for this equipment, the AABB standards require a measure of the quality and concentration of the product produced. Quality indicators are of a controversial nature. Some practitioners advocate periodic albumin washout while others advocate potassium washout.[21] Free haemoglobin has also been advocated. At the Cleveland Clinic Foundation, evaluation of the colour of the effluent wash solution is used as a measure of the washout quality. This practice stems from a close correlation between the elimination of free haemoglobin and the colour of the effluent solution. Many practitioners also periodically measure bacterial contamination. As has been previously discussed, bacterial contamination of salvaged blood is routine and little correlation is found with clinical sequelae.
In addition to a measure of wash quality, a measure of concentration is also recommended. Hematocrit or haemoglobin concentration is simply measured and can be performed on all units of blood. Adequate concentration is important to assure washout of cellular contaminants. Several of the manufacturers of cell salvage equipment are now incorporating devices within their system to measure hematocrit.

Implementation of these standards has significantly reduced plasma and platelet transfusion in surgical procedures where non-dedicated nurses were performing the case and were doing so without measures of the quality of the product that they were producing.

Conclusion

Many factors influence the efficacy of cell salvage processing. The ability of this technology to avoid allogeneic transfusion is directly dependent on the skill of the operator and the processes which are established to insure that a high quality blood product is produced. If the guidelines outlined in this article are followed, most red blood cell transfusions become unnecessary.

APPENDIX I

Operative Blood Loss Derived From Cell Salvage

$$\text{Blood Loss} = \frac{(Hs/Hp) \times Vb \times Nb}{SE}$$

Where:

Hs = Average Hct of washed salvaged red cells;
Hp = Average patient Hct during salvage;
Vb = Volume of the processing bowl;
Nb = Number of bowls processed;
SE = Estimated salvage efficiency.

Salvage efficiencies can vary depending on vacuum levels, sucker tip size, diligence of salvaging efforts, contact time of blood in the wound, and other factors. With good procedural methodology, 60% of lost red cells can be recovered (SE). As the quality of the salvage effort declines, so does efficiency of recovery, and assignment of lower values may be appropriate.

Example 1: During abdominal aortic aneurysm repair, four bowls of 225 ml each were salvaged and returned. Low suction levels were used, lap pads (swabs) were washed, and the surgeons applied anticoagulation to the wound site to prevent clotting. Salvage efficiency was felt to be optimal at about 60%. Measured hematocrit in the washed cells was 61%. 63%, 66%, and 63% with an average of 63%. Patient hematocrits measured during the respective collection periods were 37%, 33%, 32%, and 30%, averaging 33%. Using these numbers, blood loss is calculated as follows:

Blood loss =
(63%)×(225ml/bowl)×(4 bowls)/(33%)×(60%) = 2863 ml

Example 2: During a revision hip, blood was fractionated and sequestered, with red cells readministered as needed. Five 125 ml bowls were processed. Small suction tips were used with elevated vacuum, and considerable blood was lost to drapes and gauze pads. Salvage efficiency was estimated at 40%. Hematocrit in the bowls was 66%, 70%, 68%, 65%, and 71%, averaging 68%. Concurrent patient values were 32%, 30%, 34%, 30%, and 28% averaging 30.8%.

Blood loss =
(68%)×(125 ml/bowl)×(5 bowls)/(30.8%)×(40%) = 3450 ml

APPENDIX II

Emerging Applications

Optimizing autotransfusion requires implementation of cell salvage in all surgical procedures where high blood loss is anticipated. Historically, contraindications to the use of cell salvage has limited its utility in areas where blood transfusion is common. Several areas traditionally contraindicated for washed cell salvage are receiving increasingly favourable re-examination. These contradictions are tumour surgery, caesarean section, and in trauma where bowel contents may have contaminated the collected blood. A discussion of each of these areas follows.

A. Amniotic fluid contamination

The primary concern with applying cell salvage in obstetrics is the entrainment of amniotic fluid into salvaged blood. Theoretically, this entrained amniotic fluid may cause an amniotic fluid embolism upon re-administration. The mechanism for amniotic fluid embolism is not clear; therefore, any studies demonstrating that salvaged blood is clean for one parameter may not extrapolate to the unknown mechanism of amniotic fluid embolism. Bernstein and colleagues[25] demonstrated that amniotic derived tissue factor, a component of amniotic fluid thought to be associated with disseminated intravascular coagulopathy, is completely eliminated with washing. Again, tissue factor may be one of many elements that lead to the amniotic fluid embolism[26, 27]; thus, washing of this tissue factor would not assure that amniotic fluid embolism would not occur. Some investigators[28, 29] feel that particulate contaminants may be responsible for amniotic fluid embolisation. Durand[30] showed that, despite washing, cell salvaged blood still contained significant foetal squamous cells, foetal haemoglobin and bacterial contamination. We have found that leukocyte depletion filters are highly effective at removing these particulate contaminants.[31] The filters work through the use of a small-pore microfiber web and a negative surface charge.[32]

Despite these concerns about adequate washing and amniotic fluid embolism, investigators have proceeded to administer cell salvaged blood in obstetrics. Three reports encompassing approximately three hundred patients[33, 34, 35] have now been published where cell salvaged blood was readministered to a bleeding parturient. This re-administration was without filtering. No evidence of amniotic fluid embolism were reported in these patients suggesting that it is indeed safe. No impact on the coagulation system from readministering cell salvage blood has also been noted.[36]

Despite these reports, several precautions should be taken when salvaging blood in obstetrics. First, minimizing the aspiration of amniotic fluid through a double suction setup is advisable. One suction should

be connected to the cell salvage reservoir and used for suctioning of blood. The other should be connected to the regular wall suction and used only for aspiration of amniotic fluid. In this way, the volume of amniotic fluid contamination is minimized. Secondly, the utilization of leukocyte reduction filters at the completion of processing can reduce the foetal squamous cell contamination to a level comparable to maternal blood contamination. Lastly, foetal red cell contamination is present. An Rh incompatibility between mother and infant may suggest that the Rhogam dose following delivery may need to be modified. This issue is yet to be studied.

B. Trauma

The application of cell salvage technology in trauma has traditionally been considered inadvisable because of the risk of stool contamination. Bacterial contamination of cell salvage blood routinely approaches 30% of the units processed with bacteria primarily from skin flora.[37] This contamination has been assumed to be inconsequential but the contaminants of frank stool have been thought to be different than merely skin flora. The insignificance of bacterial contamination relates to several issues. First, during the course of most operations, a bacteremia is present which accounts for the routine administration of prophylactic antibiotics. Bacteria exposure through cell salvage should be equally susceptible to these antibiotics. Secondly, allogeneic blood obtained from the blood bank is not bacteria-free.[38,39] Thus, the alternative to cell salvage carries its own risk of bacterial administration. Lastly, postoperative infection rate is lower in patients receiving autologous blood as compared to homologous blood because of immunomodulation which occurs following homologous blood exposure.[40] For all of these reasons, it seems reasonable to use cell salvage under trauma conditions.

This being said, Boudreaux undertook a study to evaluate the washing of blood grossly contaminated with Escherichia coli.[41] He found that reductions in bacterial count were obtained but they were dependent upon the size of the inoculum. The greater the inoculum, the greater the final concentration. The use of leukocyte depletion filters may also play a role here. These filters have been found to reduce bacterial contamination in allogeneic blood.[42, 43] In recently published data[44], significant reductions in bacterial counts can be obtained with leukocyte depletion filters. When a combination of washing and filtering is undertaken, 95-99% of the bacterial load can be removed. This level of removal may still leave significant bacteria in a blood product if the starting point is very high as it would be in blood that has frank stool contamination. Thus, if frank stool contamination is present, the blood should be discarded. If the possibility exists of mild to moderate bacterial contamination, cell salvage washing and filtration accompanied by broad-spectrum antibiotics would produce a safe product.[45]

C. Cancer surgery

The last area of controversy is cell salvage in cancer surgery. As mentioned earlier, immunomodulation occurs with allogeneic transfusion. The issue of whether this immunomodulation affects tumour growth is unresolved; however, there is substantial evidence to suggest that outcome is worse for patients undergoing cancer surgery when they received allogeneic blood.[46,47,48] Thus, avoidance of allogeneic blood is important. Likewise, administration of tumour laden blood from cell salvage would also seem to be contradictory to a good patient outcome; however, during tumour surgery, hematogenous dissemination of cancer cells is common.[49,50,51] For cell salvage during tumour surgery, the use of leukocyte depletion filters is advocated. These filters have been used for filtration of malignancy in cell salvage for urologic surgery [52, 53], pulmonary surgery[54], and in a variety of cell lines which were used to contaminate discarded blood.[55, 56] These studies all concluded that leukocyte depletion filters were highly effective at removing tumour cell contamination. One investigator feels that irradiation of salvaged blood contaminated with tumour is the method of guaranteeing no viable tumour cells.[57 58] Though this method seems reasonable, irradiation of a cell salvage product is impractical in most hospitals. Two recent outcome studies [59, 60] of patients undergoing radical prostatectomy have compared cell salvage blood to autologous blood or no blood transfusion. These studies found no difference in cancer recurrence suggesting that cell salvage is equivalent to autologous transfusion and may even be better than allogeneic transfusion for patient survival.

Biography for Jonathan H. Waters, M.D.

Jonathan H. Waters received an undergraduate degree in physics from the University of Missouri followed by a doctorate in medicine from George Washington University. Post-graduate training in Anesthesiology occurred at New York University Medical Center. Following training, Dr Waters spent four years serving as an anesthesiologist in the United States Navy at the Naval Medical Center, San Diego. His Navy experience was followed by three years at the University of California, Irvine. In 1997 he moved from UCI to the Cleveland Clinic Foundation. When this paper was accepted for publication he was Head, Section of Anesthesia for Obstetrics & Gynecology in the Department of General Anesthesiology. He was also Medical Director, Autotransfusion Services in the Department of Clinical Pathology. He chaired the Cleveland Clinic Foundation's Transfusion Review Committee and served as a consultant to the American Red Cross, Northern Ohio branch. He has authored 34 peer-reviewed publications and is currently editing a book on Autotransfusion techniques. Currently, he is Chief, Anesthesia Services, Magee Womens's Hospital, University of Pittsburgh Medical Center, Department opf Anesthesiology, 300 Halket Street, Suite 3510 Pittsburgh, PA 15213. **Correspondence to:** watejh@upmc.edu

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Inter-relationship of Iron and Blood Loss

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Abstract

Iron is absolutely essential for oxygen carriage in the human body. This function monopolises most of the body iron although other physiological areas where this element is used in much lesser amounts are also crucial. Blood loss creates a very rapid loss of iron. If blood loss is minimal, compensation occurs due to utilization of body iron stores but if these are insignificant or the blood loss is chronic or major, oral intake, which is minimal, quite often is inadequate for compensation to occur significantly rapidly. Absolute limits on normal absorption, dietary factors and timing of oral dosage may further diminish intestinal availability of iron, regardless of dosage. Parenteral iron may be required in many situations but often is administered inappropriately.

Introduction

The evolutionary step from anaerobic to aerobic metabolism was of huge significance to the living organism. Given the same substrate, the addition of one molecule of oxygen meant an eighteen-fold increase in energy production. In man, oxygen management falls into three areas:

- Intake into the body.
- Transport to tissues.
- Tissue utilization and energy production.

The second of these proposals, oxygen transport, will be considered.

Oxygen Transport

Oxygen dissolves directly in plasma but at ambient body pressure and temperature. If one were to assume blood was only water, each litre would hold approximately 2.9ml of oxygen. A resting requirement of approximately 250ml/min could only be achieved with a cardiac output of 120 l/min rising to 6000 l/min during exercise.[1]

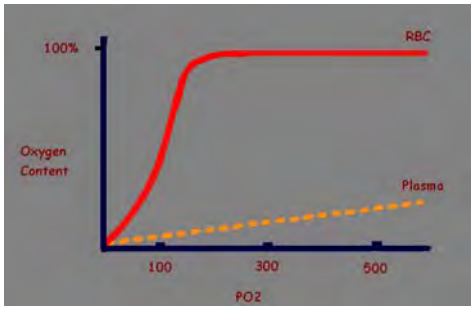

Figure 1: The ambient pressure of 100% oxygen needs to rise to over 2.5 atmospheres to dissolve sufficient oxygen to sustain human life. This is easily achieved with normal haemoglobin levels.

Species have developed alternate means of carrying oxygen, thus greatly reducing the cardiac output required to achieve their requirements. All these means entail reversible oxygen binding to a specialized respiratory pigment. In the human this pigment is haemoglobin and is found in red blood cells. One gram of haemoglobin is capable of combining with 1.39 mls of oxygen. Therefore, with normal haemoglobin levels a human can carry 190-210 ml oxygen per litre of blood.[2] This relationship can be viewed in Figure 1.

Haemoglobin

Haemoglobin is an allosteric protein (see Figure 2).[3] Allosterism is the property where regulator and effector sites are spatially distinct.[4] O_2 binding to haemoglobin is regulated by H^+, CO_2 and organic phosphates. Binding occurs to a prosthetic (non-protein) moiety of the molecule. This nonpolypeptide unit is a heme group, a protoporphyrin consisting of

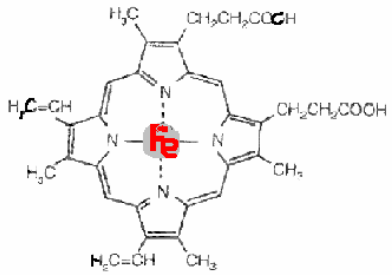

Figure 2: Protoporphyrin ring with central iron atom.

four pyrrole rings linked by methane bridges to form a tetrapyrrole ring.

The central four nitrogen atoms of the protoporphyrin ring can form two additional bonds with an iron atom.

Haemoglobin consists of four polypeptide chains bound together by non-covalent attractions and each containing a heme group (see Figure 3). In the human adult these polypeptide chains are usually 2α and 2β although major changes occur in the foetus and minor, usually unimportant, adult variants are not uncommon. However, these latter changes can be of significant functional importance.

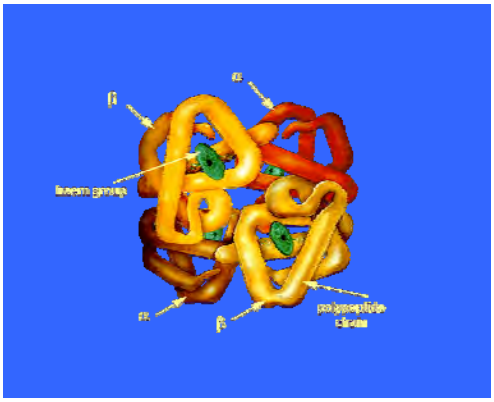

Figure 3: Haemoglobin: 2α and 2β polypeptide chains each with heme group.

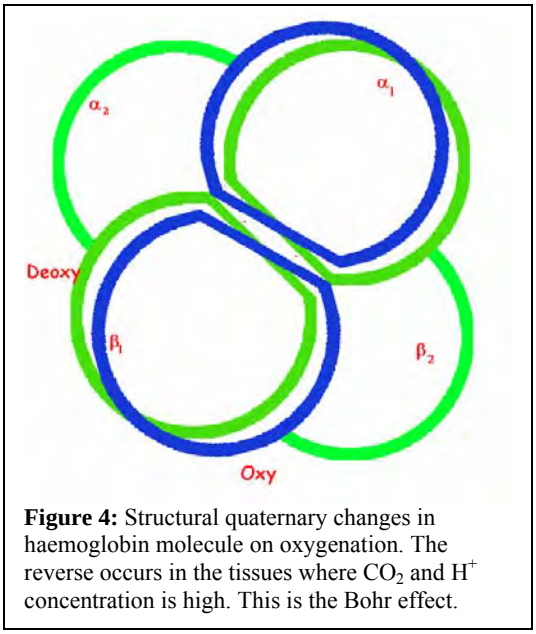

Figure 4: Structural quaternary changes in haemoglobin molecule on oxygenation. The reverse occurs in the tissues where CO_2 and H^+ concentration is high. This is the Bohr effect.

This quarternary structure is the key to haemoglobin being the efficient oxygen carrier that it is. Under the influence of H^+, CO_2 and 2,3,DPG the $\alpha_1\beta_2$ region acts as a switch: a rotational change of about 15^0 and a translation of 0.8Å takes place (see Figure 4).

This $\alpha_1\beta_2$ interface is of vital importance for it is closely connected to the heme group and structural changes in either may have marked effects on the other. Nearly all mutations in this area affect oxygen binding.

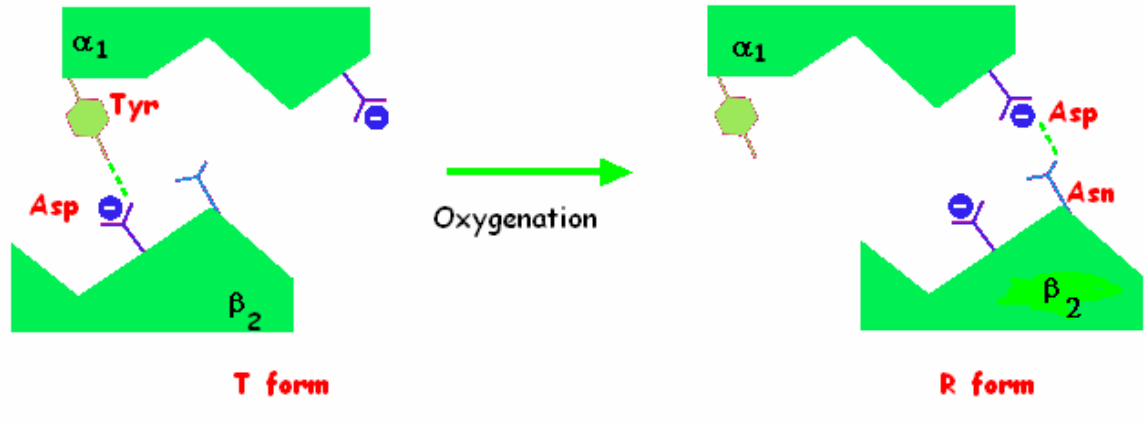

Figure 5: The $\alpha_1\beta_2$ interface switches from the T to the R form on oxygenation. The dovetailed construction of this interface allows the subunits to readily adopt either of the two forms.

H^+, CO_2 and 2,3 DPG affect the hydrogen bonding in the terminal amino acids of the polypeptide chains of haemoglobin. The terminal carboxylates participate in electrostatic interactions that tie the tetramer. The quarternary structure of deoxyhaemoglobin is termed the T (taut) form; that of oxyhaemoglobin, the R (relaxed) form (see Figure 5).

These structural changes take place some distance from the heme group but a very significant effect takes place there. In deoxyhaemoglobin, the iron atom is about 0.4Å out of the porphyrin plane toward the proximal histidine, so that the heme group is convex in the same direction. Upon contact with oxygen, the iron atom moves into the porphyrin plane forming a strong bond with O_2, and the heme becomes more planar (see Figure 6). This establishes iron as central to oxygen carriage.

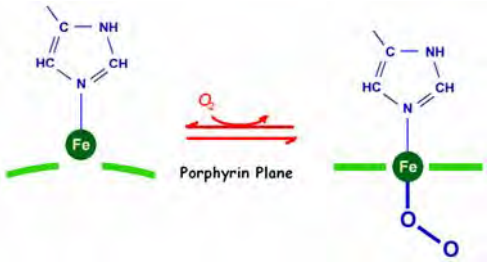

Figure 6: Iron movement to form a strong bond with oxygen.

Although iron is extremely common as the "final stage" in oxygen transport in the animal kingdom, it is not universal, for with many invertebrates, copper assumes this role.[5]

Iron has a role in a number of important functions in the body:

- Transport and storage oxygen (haemoglobin and myoglobin)
- Enzymes for energy production
- Immune and CNS Function

Although the first of these headings is being mainly considered, all functions seem to become involved when significant iron deficiency occurs.

Iron Absorption

On an average, the adult human body contains 2.5 – 5g of iron. This is distributed mainly between haemoglobin (60-70%) and the iron storage molecules ferritin and haemosiderin (20-30%) [6] with the remainder found in myoglobin except for a very minimal but crucial amount found in the enzymes of energy transport. A good daily western diet contains about 15-20mg of iron of which about 10% is absorbed. An almost equal amount is lost through faeces and sweat. Absorption can be increased to a maximum of 4mg/day in iron deficiency states[7]. If one considers that *1ml of blood contains 0.5mg iron*[8], it can be seen that very little chronic blood loss is required to deplete stores and lead to subsequent anaemia. A similar but accelerated situation exists with acute blood loss of any significant quantity.

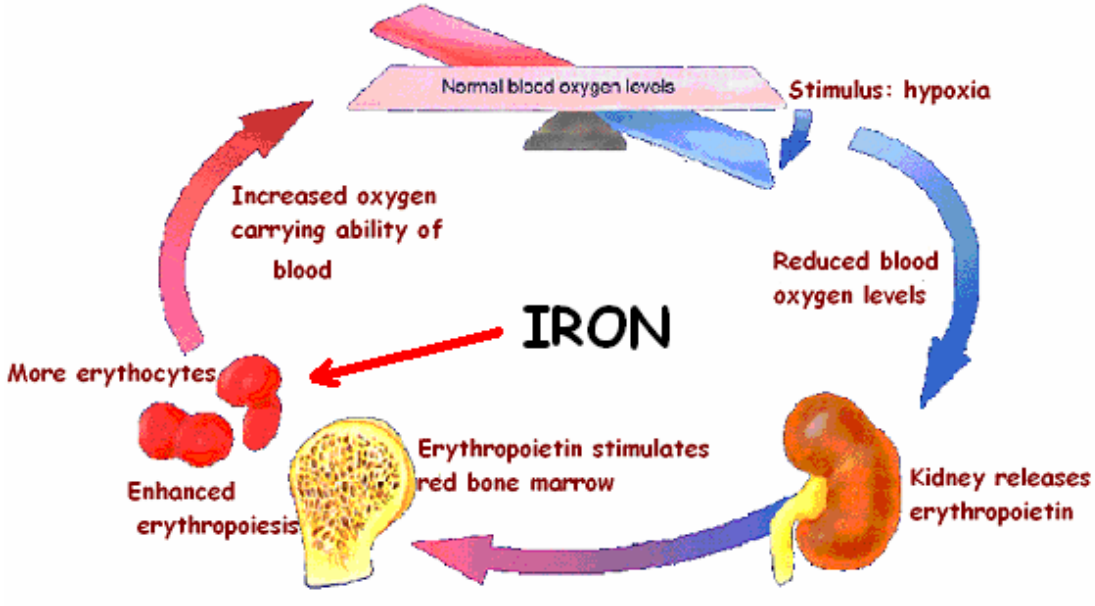

Figure 7: Production of erythropoietin and role of iron in erythropoiesis.

Oral iron is irritant to the stomach. In view of this, enteric coated medications have been used. However, as iron is mainly absorbed in the duodenum, the efficacy of these enteric-coated preparations is questioned as intestinal iron delivery will occur well after absorption sites have been passed. Certain compounds, (phosphate, bicarbonate, bile acids) retard absorption so oral iron preparations should be given at least one hour before or 1½ hours after meals.[9] Similarly, other compounds such as Vitamin C, glucose, fructose and some amino acids increase absorption. These can be used to therapeutic advantage.

History

It is interesting to look at the history of treatment with iron[10] for it provides a good insight into the status of management of the most common form of anaemia and perhaps, if one wishes to speculate further, into a possible pathway taken to manage blood loss. Like all advances in medicine, it follows a typical sinusoidal development curve.

Sydenham (1681) is credited for the first rational use of an iron-containing substance to the then prevalent "green sickness" or chlorosis of adolescent women. This was in direct contrast to bleeding and purging, the then current accepted method of management. He wrote: "……. (after) giving a chalybeate (an iron-containing substance) 30 days running. This is sure to do good. To the worn out or languid blood it gives a spur or fillip…… Clear proof of this is found in the effect of steel in chlorosis. The pulse gains strength, the face (no longer pale and deathlike) a fresh ruddy color." This is a classical description of successful treatment of a patient suffering from severe iron deficiency anaemia.

In 1713, Lemery and Geoffrey provided more direct evidence of the relationship by showing iron was present in blood. In 1832 the French physician Blaud recognized the failure in the treatment of chlorosis had been due to the use of too-small doses of iron. He developed the "veritable pills of Blaud" which were used in the treatment of anaemia until the last decade of the nineteenth century. Then however, the teachings of Bunge and others cast doubt on this straightforward approach to the treatment of chlorosis. Smaller doses of iron were used, treatment became inefficient and doubt was cast on the efficacy of this form of therapy. This philosophy continued until the third and fourth decades of the twentieth century until Faber and others resurrected the lessons taught by earlier physicians.

The middle half of the twentieth century saw considerable advances in knowledge of the physiology of iron. In 1937 the studies of McCance and Widdowson suggested limited daily absorption and excretion of the element. The role of transferrin in iron transport was elucidated (Laurell 1947) whilst the quantitation of iron stores in plasma ferritin and marrow were studied by Bothwell and others in 1979.

In the very latter part of the century there seems to have been some decrescence in the study of the part played by iron in erythropoiesis. Considerable emphasis is being placed on the role of erythropoietin[11] but it must be remembered that iron and erythropoietin have an almost mutual relationship. Perhaps it would also be prudent to remember the findings of McCance and Widdowson. There has been little work to define iron requirements when erythropoiesis is stimulated by exogenous erythropoietin.

Iron administration

Iron has traditionally been administered orally. However, as has been pointed out, this route of administration is fraught with many problems that may greatly affect the quantity of iron the body may actually absorb. All these problems aside, there is an absolute physiological limit to this quantity.

Situations may occur where the desired dosage to be absorbed will be greater than these physiological limits. Here, one may need to resort to parenteral administration; the choices being intramuscular or intravenous. The author does not use the former for the following reasons:

- Intramuscular iron is quite painful.
- There is substantial long term tissue staining.
- Intramuscular iron has been associated with neoplastic change[12].

This means the intravenous route of administration needs to be sought should significant quantities of iron be required.

Intravenous Iron

This may be given in two methods of administration:

- Intermittent
- Total

Before judging the polemics of either method, let us look at the amount of iron that is commonly required. One usually does not embark on parenteral iron therapy until there is evidence of significant impairment to wellbeing, that is, ferritin and serum iron are precipitously low and haemoglobin levels have commenced to decrease. Should this situation be present, the total recommended dose of iron (in mg) required to correct the situation is calculated by the formula:

0.23 x bodyweight in kg x (150 – pt Hb in g/l) + 500 (to reconstitute iron stores).[10]

In the author's experience, this underestimates the amount of iron required. This is where a grey area in the administration of iron exists. In the United States total intravenous dosage is not approved with the new iron preparation being used: ferric gluconate

(Ferrolicit®, Schein Pharmaceutical Corp, Florham Park, NJ).[13] A similar situation exists in Europe where the commonly used iron preparation is iron sucrose (Venofer ®, Vifor International) This technique of total infusion has not been proven with these newer products.[14] In Australia, the preparations available are iron polymaltose (Ferrum-H®, Baxter Healthcare, Old Toongabie, NSW) and Venofer.

Intravenous Iron, Theoretical Risks

There are a number of theoretical risks with intravenous administration of iron; anaphylaxis, iron overload and immunosuppression. The author would like to comment on these problems:

Anaphylaxis. This condition originated with the use of iron dextran which had a 0.6% incidence of severe anaphylactoid reactions.[13] It seems to have created an aura of paranoia with the use of intravenous iron. One needs to put the situation into context; the incidence of such reactions is not uncommon with antibiotics and anaesthetics yet we have no hesitation in using these medications. The new generation of iron preparations have proven themselves remarkably safe.[15, 16] Iron dextran and these new compounds are comparatively reviewed by Fishbane.[17]

Iron overload. Communication with an expert on haemochromatosis and iron overload diseases, indicates that this is not a problem with the amount of iron used.[18] On consideration, one can come to this conclusion. All situations where intravenous iron should be used are either proven iron deficiency states or times where there has been considerable haemorrhage and thus iron loss. Indeed, if one examines the previously quoted formula for the amount of parenteral iron required to compensate for deficiency, one sees a replenishment (500mg) factor. In the author's experience, the maximum amount of iron ever given in one dose has been 2.5g. and this has always been in situations of proven severe iron deficiency.

Immunosuppression. Iron has a seemingly ambivalent position when consideration is made of its function in immunosuppression. It is established it has a role in immune function.[16] Considerable work has been done in the animal model to show that heavily iron overladen animals are susceptible to infection[20] and mechanisms for this have been proposed.[21, 22] Very little work has been done in humans[23] and thus, what has been done, refers mainly to chronically iron overloaded animals. The author contends it is not relevant to iron deficient patients.

Practical Problems

The author has over 14 years experience in the use of intravenous iron, and in that time he has never experienced significant problems. However, he has received anecdotal reports from colleagues who have also used intravenous iron and have almost emulated his administration regimen. The reports have invariably been a metallic taste and hypotension. These appear to be due to too rapid an infusion rate of iron. A proposed mechanism has been over-saturation of transferrin[24] although this has been questioned.[25] Other adverse effects such as nausea and facial reddening have been reported in other studies[13] but the author has never seen these or had reports of them from colleagues.

Administration Regimen

The traditional method of parenteral iron administration is to give a test dose seeking the possibility of an anaphylactoid reaction. With iron polymaltose (Ferrum-H®) the recommended test dose is 25mg[26], whilst neither Ferrlecit® nor Venofer® seem to have this requirement. However, both of the latter regimens recommend dosage restrictions over a given time frame. In neither regimen is there restriction to the rate at which each individual dose is given and no mention is made of a total dosage regimen. There is a recommended total dose with Ferrum-H, which depends on the patient's haemoglobin, and there is an inferred rate of administration of 200mg iron/hr. The author always is slightly more conservative in his rate of administration.

Over the years the author has developed his own regimen. He assumes that problems are going to occur. Accordingly, 1 ampoule (100mg iron) of iron polymaltose is mixed with 500ml normal saline. Using a constant infusion pump, the infusion is commenced at 1ml/hour. This administers an infinitesimally small dose of iron. The infusion rate is doubled every 15 minutes if no untoward effects are noted. This continues up to 128ml/hour when the fluid load delivered may cause patient inconvenience. The next litre of fluid is mixed with a maximum of 12 ampoules of iron polymaltose and delivered at the maximum rate reached previously or at a rate where the iron dosage never exceeds 100mg/hour. Sometimes with large doses of iron (2.5g), the infusion may take up to 36 hours. The author is physically present with the patient until 2mg of iron is delivered after which the nursing staff are instructed to return to the previous rate of infusion should signs of iron overload become apparent, or cease the infusion and contact the author should a situation of concern occur. As was previously stated, in 14 years of using this method of administration, the author has never seen significant problems.

Resultant improvement in haemoglobin

Significant rises in haemoglobin levels have been recorded with the use of physiological doses of iron. These rises vary with the mode of administration:

- Oral 0.6g/L/day
- Total intravenous 6-14g/L/day
- Addition of erythropoietin 30-50g/L/day

Economic considerations

Although the costs considered are Australian, they are very indicative of those globally. In Australia the cost of 250mg of iron polymaltose is A$0.76. This is approximately the equivalent of the iron content of one unit of blood. The minimal cost of the latter is approximately A$250 (collection, cross-match, additives and packaging) It does not include more covert complications such as clerical error, immunomodulation, TRALI, infection or prion transfer or the employment costs of those people administering the blood. Once these are factored in, the difference in cost between an ampoule of iron and a unit of blood becomes extremely disparate.

Illustrative Case

A 36-year-old Jehovah's Witness female admitted to the author's institution with a history that 9 days previously she had been operated on at another hospital for myomectomy of uterine fibroids. During operation, heavy haemorrhage was encountered, necessitating hysterectomy. Preoperatively, her haemoglobin was 84g/L whilst postoperatively it had fallen to 47g/L. No treatment was given for her postoperative anaemia.

She was discharged on day 6 feeling quite well but had then started complaining of increasing tiredness, lethargy and buzzing in her head which was "driving her mad". She went to a local hospital where her haemoglobin was found to be 42g/L. She was given iron tablets and was sent home with the suggestion that she seek a haematology consultation.

On admission to our institution, she was a very pale but otherwise well looking lady. She had walked from the lift to her room at the end of a long corridor and had carried out a prolonged conversation without any shortness of breath. She had no chest or abdominal pain. Her only complaint was an unbearable buzzing in her head and some feeling of faintness when sitting up suddenly.

On examination her blood pressure was 120/80 lying and sitting and pulse rate of 120/min. There were no cardiac murmurs and abdominal examination revealed a well healing midline scar with no evidence of infection. Hess test was negative.

HemoCue® testing showed a haemoglobin of 43g/L. A little blood was drawn for more formal testing. This clotted normally. There was nothing in her past history to suggest problems and she ate a normal diet. A provisional diagnosis of well compensated anaemia from blood loss was made.

Treatment with erythropoietin was considered but it was felt she probably had a more than adequate endogenous erythropoietin response, had consumed all her body iron stores and was suffering from severe iron deficiency. In view of the seemingly adequate compensation it was decided to try treatment initially with iron and supplements, withhold erythropoietin. Accordingly, she was given 2000mg iron polymaltose as a slow infusion over 30 hours together with 1000µg vitamin B_{12} and 15mg folic acid.

	Hb	MCV	Retics
Day 1	43g/L	71 fl	0.03
Day 2	47g/L	72 fl	0.035
Day 7	82g/L	80 fl	0.108
Day 22	112g/L	85 fl	

Figure 8: Relevant haematology results.

Within hours of commencing the intravenous iron, she felt much stronger and the buzzing in her head had markedly decreased. It was absent by the next morning. She was discharged on day 3 totally asymptomatic. Pathology testing of blood was kept to a minimum in an effort to conserve blood. Figure 8 contains a précis of relevant haematology results.

Discussion

This report represents a typical case of severe iron deficiency, be it from haemorrhage or for other reasons. On correction, we saw the rise in reticulocyte count starting within 24 hours. This has been noted by other workers.[28] However, there is insufficient concurrent rise in haemoglobin to explain the resolution of symptoms such as tiredness, lethargy and ear buzzing within hours of commencement of treatment. The author has noted this many times when administering intravenous iron to severely iron-depleted patients. His theory for this is replenishment of iron in areas other than haemoglobin, such as the enzymes of energy transfer.

There is little argument about the use of iron in the situation of iron deficiency anaemia without inflammatory states (chronic inflammatory disease, neoplasia or surgery). Intravenous administration has been found to be more effective than the oral route[27]. However, many clinicians continue to treat haemoglobin values rather than considering patient signs or symptoms if any are present and embark on the traditional, easy, but non-evidence based method of treatment; blood transfusion. This may not be in the best interest of the patient. *Unless there are clinical signs suggesting there is a need to increase tissue oxygen delivery, there is no indication for blood.*[29] Indeed, all surgical situations can and have been managed without resorting to the use of allogeneic blood transfusion.[30]

Uncertainty arises when an inflammatory state is present. The author has found that in chronic inflammatory states it is common to suffer from an anaemia where all parameters of iron status (serum ferritin, iron, transferrin) are abnormal (usually elevated). These situations may be apparently hypo-

responsive or resistant to erythropoietin. Yet if smallish doses (250mg) of intravenous iron are administered concurrently, one soon sees a rise in reticulocyte count and haemoglobin levels. Similar results have been reported in uremic patients.[31]

Post-surgery, the body response is similar to an acute inflammatory reaction. Work done in this area is non-conclusive.[32, 33, 34, 35] It is the author's practice to commence all patients with an operative blood loss greater than 500ml on oral iron supplementation on day 2 postoperatively or when bowel function returns. Should their haemoglobin level be below 70g/L, this iron is given intravenously and if it is below 55g/L, erythropoietin supplementation is added.

Conclusions

The following conclusions can be reached:

- Iron is a simple but underutilised element in management of blood loss anaemia.

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- Its use involves low technology and low cost, making it useful in all societies.

- With the use of oral iron, physiological constraints need be remembered for optimal utilization.

- Traditionally, suspicion has inhibited the use of parenteral iron. However, when used, the intravenous route is kinder and more acceptable to the patient.

- Although new and safer parenteral iron preparations have become available, they have not yet received sufficient use in all manners of administration. More evidence is required to fully establish these substances.

- More research into postoperative iron handling is required. This needs be done in the context of demonstrating optimal absorption. Similarly, there needs be more evidence regarding the fate of postoperative parenteral iron.

- Greater quantification of body erythropoietin requirements together with the optimal amounts of iron to satisfy these requirements is needed in a variety of pathological situations.

Finally, it can be seen that a good knowledge of body iron dynamics can greatly reduce or obviate the need for blood transfusion.

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