Blood products on operational deployments

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AUSTRALIAN DEFENCE HEALTH POLICY recognises that the reliable supply of blood products is "essential for the provision of high quality emergency and definitive health care in peace and on operations".[1] The primary source of supply for blood products to the ADF is the Australian Red Cross Blood Service (ARCBS), even on overseas deployments. If this source cannot meet demand, current doctrine states that blood is to be collected from local ADF donors, or, alternatively, that "screened" blood from indigenous civilian or allied military sources is to be used.[1] It has recently become apparent that the ADF may need to provide Level 3 medical facilities on operational deployments for some time to come. It may be helpful to revise our current blood supply policies in the light of considerable US and European experience and expertise in addressing similar challenges.

Synopsis

- Providing blood products to deployed military medical facilities can be a significant logistic burden. With the current ADF system, the need for extra blood products to cope with unanticipated casualties inevitably leads to enormous waste of blood components with short shelf lives.
- Current procedures for the supply of frozen plasma are satisfactory, but there is significant wastage of packed red cells on ADF deployments, while platelets can only be supplied on demand from a civilian medical facility.
- Potentially better alternatives include the use of blood salvage, frozen blood products, and artificial red cells and platelets.

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Nature of the problem

A Level 3 trauma facility should ideally be able to provide fresh frozen plasma, packed red cells, and platelets. Fortunately, fresh frozen plasma is relatively stable at temperatures of –18°C, and has a shelf life of one year.[2] Current procedures are adequate for its supply. However, there are a number of problems with the current ADF blood supply policy with regard to other blood components. The greatest potential demand is for packed red cells, yet few of the packed red cell units held in deployed medical facilities are actually used. Most are discarded at the end of their 35-day shelf life.[1] This is a significant waste of a valuable civilian resource. Packed cells should be delivered at least every two weeks to avoid having a complete stock of very old units. The need for continual resupply and the difficulty of providing increased quantities at short notice are significant logistic burdens.

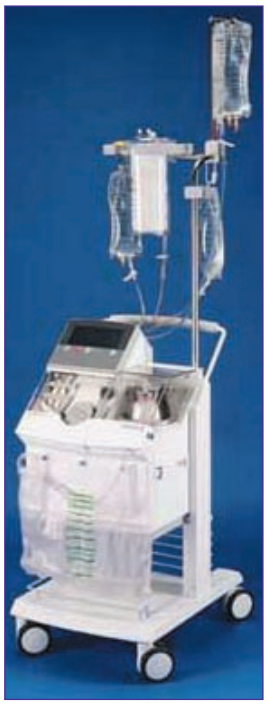
The shorter shelf life of platelets (five days, stored at 20–24 degrees while agitating) means they can only be supplied on demand from a civilian medical facility. This is barely acceptable even when the lines of communication are good, which will often not be the case. In practice, a casualty immediately requiring platelets must be transfused whole blood from a local donor. The difficulties and dangers of this are significant, as outlined below.

The use of deployed military personnel as directed blood donors for whole blood (when either red cells or platelets are required) is problematic. While all personnel are ideally screened for HIV, hepatitis B and hepatitis C before deployment, no test is 100% sensitive. Every available test has a "window period" during which the blood is infective, but the test will be negative. However, the sensitivity of blood donor screening tests for HIV and hepatitis C in Australian civilian practice has recently improved with the introduction of the Gen-Probe nucleic acid testing (NAT) branched DNA signal amplification assay performed on pooled batches of donor blood. The increased sensitivity of this test reduces the window period to 10–30 days for hepatitis C and 10 days for HIV,[3] a significant improvement on tests which rely on the detection of antibody, such as enzyme-linked immunosorbent assay (ELISA), which, using modern methods, have a window period of three weeks for HIV and around two months for hepatitis C. Furthermore, it is thought that blood from a donor with HIV is unlikely to be capable of transmitting infection in the first week or so following inoculation with the virus. Thus, if the test is performed *on the unit to be infused*, the *effective* window period (during which the test will not detect infective blood) is reduced to 1–2

days. This remarkably short window period does not apply if the test is performed to "qualify" an individual to donate at some future time. Nonetheless, large scale NAT testing of ADF members before deployment would reduce the possibility of an infection being missed because the donor was in the longer window period associated with ELISA.

However, there is no guarantee that HIV or hepatitis C will not be contracted outside Australia, as ADF medical officers will be well aware. NAT donor testing immediately before donation in a field hospital environment is impractical with the current complex, non-automated equipment. Hence, NAT probably offers little extra protection from infected ADF donors. In the field, we will continue to rely on "rapid" HIV tests immediately before donation. These tests rely on the identification of antibodies to HIV, using a much simpler protocol than ELISA and the Western blot test. While a battery of these rapid tests can have a sensitivity and specificity of >99%, there is a much longer window period before the patient produces a detectable amount of antibody.[4]

It is worth noting while discussing HIV testing that NAT is currently thought to be unsuitable as a clinical diagnostic test for patients beyond the ELISA window period, given its relatively low specificity of 95%–97%,[5] compared with >99% for ELISA screening.[4]



1: The Haemonetics Cell Saver – this device concentrates erythrocytes while removing much of the fat, cell debris and free haemoglobin present in salvaged blood.

Civilian experience has shown that blood-borne diseases are significantly more frequent in directed donors than in volunteers.[6] The scale of this problem may be worse in a military setting, given the disciplinary implications of admitting to intravenous drug use or unprotected sexual intercourse on operations. Potential donors may also occupationally acquire infections. Thirty-nine per cent of Australian anaesthetists suffer a needlestick injury in a 12-month period.[7] The risk of transmitting hepatitis B by needlestick from a patient who is hepatitis B e antigen positive is about 30%; the risk of transmitting hepatitis C from a patient who has circulating hepatitis C virus is about 3%; and the risk of transmitting HIV from a patient with HIV infection is about 0.3%.[8] Not all needlestick injuries are reported or even noticed: indeed only 17.5% of needlestick injuries were reported by British doctors.[9] In addition, many personnel will have received a variety of vaccines immediately before their deployment. The ARCBS recommends blood not be donated in the week following hepatitis B vaccination, and that plasma products only be used from donations collected in the four-week period following vaccination with a live vaccine (Margaret Burning, Leader, Donor Medical Services, ARCBS, personal communication).

Infections endemic in the area of deployment (eg, malaria, endemic in southeast Asia, and Chagas' disease, endemic in South America) may also be transmitted inadvertently from local directed donors.

There are other medical difficulties in relying on military personnel as a walking blood bank. In hot climates, dehydration may exacerbate the effects of a 500 mL blood donation and render the donor a casualty.

Finally, there are practical difficulties in administering a walking blood donor program. Volunteers are ideally identified in advance, risk profiles are assessed and blood is taken for screening serology, including identification of atypical antibodies. These results can take some weeks to filter back through the administrative chain. After five months deployment at our military hospital in Bosnia, only 30 of a potential pool of 500 soldiers had volunteered and were eventually classed as acceptable donors. In this time, many of the pool had been posted to inaccessible locations, or had returned home. Every six months the resident military units changed, and the whole process had to begin again. Thus, finding donors at short notice can be difficult. In a high threat environment, hasty transport of personnel for the purpose of blood donation may lead to more casualties.

The problems with using directed military donors are insignificant compared with the risks of using blood from the local civilian population. The HIV carriage rate in adults in some developing countries is greater than 20%.[10] Eighty per cent of the blood supply in many developing countries comes from paid donors or patients' family or friends,[11] despite the known increased risk of infection this incurs. The probability of HIV infection, using even the most rigorously screened blood, is unacceptably high, even if NAT testing is brought into the field hospital, which is currently not practical. US civilian blood banks will not accept donations from travellers returning from areas of high HIV prevalence.[12]

In addition, the health service in many third world countries is likely to be stretched beyond its limits in providing for the local population. Seeking assistance in treating Australian soldiers may conflict with achieving the goals of the mission. The moral issues raised in using a local population's meagre health resources (perhaps even requiring payment of local officials) to treat first-world soldiers make a policy which relies on "indigenous civilian resources" unlikely to be tenable.

Is there really a problem?

Fortunately, the clinical indications for blood product therapy have become more restricted in recent years. It is known that in young healthy patients losses of up to 30%–40% of blood volume can be treated adequately with crystalloid therapy.[13] Moreover, a restrictive approach to red cell transfusion (in which red cells were transfused only when the haemoglobin level fell below 7 g/dL) was shown to produce a superior out-

come in a recent large multicentre randomised controlled trial.[14]

When combined with rapid aeromedical retrieval to established civilian tertiary care hospitals, there may be little requirement for blood transfusion at deployed Level three facilities. However, routine aeromedical retrieval is unlikely to be possible. It would be lacking good sense to deploy a field hospital without a blood bank able to support its surgical capacity.

Levels of medical support, with blood holdings

	Characteristics	Blood replacement available
Level 1	Unit level. Immediate life saving care. Includes self-aid, combat medics, and regimental aid post staffed by general duties medical officer.	Crystalloid/Haemaccel only.
Level 2	Lowest level medical unit (eg. Field Medical Company). Basic resuscitation and stabilisation. Basic laboratory and x-ray facilities. May include life saving surgical/anaesthetic capability.	Crystalloid/Haemaccel only. Group O blood if isolated from level 3 support. (Note US doctrine routinely has Group O blood at this level.)
Level 3	Field Hospital. Resuscitation, initial wound surgery. Post-operative treatment including critical care.	Red cells (groups A, B, O), fresh frozen plasma.
Level 4	General Hospital. Definitive care, recovery, and return to unit or to level 5 facility.	Red cells (groups A, B, O), fresh frozen plasma, possibly platelets.
Level 5	Convalescent and rehabilitation hospital.	As required.

Alternatives to current practice

Perioperative blood salvage

Intraoperative and postoperative blood salvage equipment which returns washed red cells is used routinely in civilian cardiac and orthopaedic practice. Up to 50% of blood lost may be recovered. The post-transfusion survival of intraoperatively recovered red cells is comparable to that of allogeneic cells (ie, greater than 90% at 24 hours).[15] The main concern in blood salvage during trauma surgery is the potential for infection. No existing system of blood filtering or washing can completely eliminate bacteria. Hence, blood recovered from a contaminated field is not routinely salvaged. There is, however, some evidence showing that, if potentially contaminated blood is immediately reinfused, the procedure may be of benefit.[16,17]

The main risk of perioperative blood salvage is dilutional coagulopathy, as the salvaged blood is deficient in coagulation factors and platelets. The equipment required for blood salvage is relatively expensive and complicated to assemble (a commonly used example is the Haemonetics Cell Saver, pictured in Figure 1). It is usually operated by cardiac perfusionists or senior specialist anaesthetic nurses, who are unlikely to be able to maintain the necessary skills in a purely ADF setting. Thus, while considered safe and worthwhile in large civilian centres, cell salvage may not be appropriate for a deployed field hospital.

A less complicated alternative is to return unwashed blood to the patient immediately. Unfortunately, this increases the risk of contamination, and the amount able to be reinfused is limited by the risks of dilutional coagulopathy and renal failure (due to the presence of free haemoglobin). There is also an increased risk of fat embolism, depending on the nature of the field from which blood was salvaged.

Frozen red cells

When ice forms in plasma, the dissolved solutes become more concentrated, killing red cells by hypertonic stress. Glycerol was shown to protect red cells against freezing injury in 1950, but it must be washed away before transfusion.[18] By "bonding" to the water molecule, glycerol prevents much of the solvent water from entering the non-solvent ice phase, reducing cellular damage.[18] Several different protocols with slightly different efficacies have been reported,[19] but all methods rely on the same basic principle.

Frozen red cells have a number of clinical advantages over conventional liquid red cells. The most obvious is long term storage. The safety and therapeutic effectiveness of red cells stored at –80ºC for as long as 21 years has been demonstrated. After thawing and washing, the red cells had a mean freeze–thaw–wash recovery value of 90%, a mean 24-hour post-transfusion survival rate of 85%, normal or slightly impaired oxygen transport function, and minimal haemolysis.[19]

Being able to store frozen cells for long periods would reduce the large waste of packed cells currently necessary in deployed military hospitals. There is the additional advantage that blood can be stored until the donor is tested for blood-borne diseases a number of months after the donation itself; this overcomes entirely the problem of the "window period" in testing for diseases such as HIV.

White blood cells are virtually eliminated during the extensive washing required to deglycerolise the thawed red cells. This prevents febrile non-haemolytic transfusion reactions in patients sensitised to white blood cells by previous blood transfusion or pregnancy. Additionally, almost all of the donor plasma is removed, preventing the urticaria often seen when IgA-deficient patients are given conventional packed cells.[18]

Frozen blood is used routinely in civilian hospitals in the United States (J Ritzenhaler, Blood Technologist, Massachusetts General Hospital, personal communication). Freezing red cells allows the accumulation of compatible blood for patients who have developed multiple rare blood group antibodies. They may also be used when cytomegalovirus-negative red cell preparations or leucocyte-depleted red cells are indicated but not available.

Fear of HIV has also encouraged an autologous frozen blood industry. The economics of such programs were rigorously

evaluated more than 20 years ago. The cost of entirely converting to a frozen blood supply on a large scale was estimated to be 76% greater than the cost of the liquid packed cell system.[20] Unfortunately, there have been no more recent studies of cost.

Frozen red cells have been used effectively in deployed military hospitals. A US military hospital during the Vietnam War reported that frozen red cells were a satisfactory alternative to walking donors.[21] The problems of transport and storage at –80°C were readily overcome. That hospital carried only group O negative frozen units. Eighteen per cent of the units transfused at the hospital had been frozen; however, this does not reflect totally the importance of the system. The main impact was to reduce the number of liquid units that had to be kept on hand for contingencies, substantially reducing wastage. The requirement to give Rh-negative patients Rh-positive blood because fresh O negative blood was in short supply was also substantially reduced.

2: *The Haemonetics 115 cell washing system, as employed by the Royal Netherlands Army in Bosnia.*

Our experience at a NATO field hospital in Bosnia in 2000 was similar. In support of 8000 deployed soldiers, the hospital had only 20 units each of O positive and O negative liquid red cells. One hundred units of frozen cells, of the full mixture of different blood groups, were also carried. Type-specific blood could thus be given to most patients. Our small blood bank could prepare two units per hour, after an initial delay of half an hour, using the Haemonetics model 115 cell washing system and associated equipment (Figures 2-4). These robust units are simple to operate and relatively inexpensive at US$8700 (about $16 000). It was rare that we had so little notice that we needed to use liquid, non-type-specific units. No extra personnel were required: the facility was run by a pathology non-commissioned officer in addition to his usual duties, overseen by the pharmacy officer. The frozen blood units had been prepared by the civilian Netherlands Blood Bank and provided at a cost of about 1800 guilders (A$1400) each. All donors had been recalled six months after their donation to be retested for HIV, hepatitis B and hepatitis C before the units were released to us for use. There was thus no problem with the "window" period.

If a unit was thawed and not used, protocol at the time dictated that the unit be discarded within 24 hours. However, with the use of a new closed processing system, which excludes microbial contamination, a thawed unit will have the standard shelf life of 30 days (T Sandberg, Pharmacist, Royal Netherlands Army, personal communication). The cells were transported using dry ice in temperature-recording insulated containers. Storage at the hospital was in a –80°C freezer (Figure 5).

3: *Hetich Rotanta TR centrifuge.*

This system was no more difficult for the logistic chain than the regular transport of fresh cells, and, as it only had to be done once, the burden was in fact substantially less.

The Australian Red Cross Blood Transfusion Service does not routinely prepare frozen red blood cells. However, the technology for freezing and maintaining packed cells is relatively simple. The equipment and expertise could conceivably reside within the ADF, in collaboration with the ARCBS. Once prepared, frozen cells have a shelf life of many years. In the current Australian military context, few of the units of blood are likely to be transfused: hence the requirement for ongoing supply is likely to be minimal. It should be possible to maintain a frozen "store" which could accompany any major deployment at short notice, with the simultaneous activation of procedures to prepare more frozen cells to replace any that are used. Alternatively, as the cells are so stable and in such widespread use in the US and Europe, it might be possible to obtain units from overseas.

Frozen platelets

In Bosnia we maintained a panel of walking blood donors entirely as a source of platelets. Red cell requirements were met by the fresh and frozen packed cell system described above. However, in the near future, the Royal Netherlands Army will introduce a frozen platelet system, removing the need for walking donors.

The technology to freeze platelets is more complex and more recently developed than that for red cells. A number of methods have been investigated, but cryoprotection with dimethyl sulfoxide appears to be the most effective.[22] Platelets frozen in this manner exhibit a range of biochemical and morphological abnormalities,[22] but it has been shown that cryopreserved platelets are more effective than fresh platelets.[23,24] Cryopreserved platelets will soon enter civilian clinical practice, and appear to offer substantial advantages over a walking donor panel for platelet transfusion in a military setting. The shelf life of frozen platelets has not been fully investigated in the literature, but experiments have shown little decline in function after storage of up to two years.[24]

Preserved liquid stored platelets

Storing liquid platelets at temperatures lower than 25°C to prolong their shelf life induces similar activation to that triggered by agonists such as thrombin. There are a number of experimental strategies which attempt to reduce this

activation, including sequestration of calcium and paraformaldehyde treatment followed by lyophilisation. Though promising, these techniques appear to offer few advantages over the prospect of frozen platelets, as reviewed by Alving et al.[25]

4: Forma Scientific thawing bath.

Red cell substitutes

Red cell substitutes fall into three general classes: perfluorochemicals, liposome-encapsulated haemoglobin, and other modified haemoglobin-based oxygen carriers.

Perfluorochemicals are synthetic molecules in which large quantities of a variety of gases can dissolve. However, high concentrations of inspired oxygen are required to adequately load the molecules in the lungs. They also have a relatively short half-life in the circulation. The complement activation and cytokine release caused by older formulations have been largely overcome. Problems persist with an influenza-like syndrome due to macrophage activation, and unexplained sequestration of 15%–20% of circulating platelets.[11]

There is more research interest at present in various forms of modified haemoglobin as a red cell substitute. Free haemoglobin rapidly breaks down in the circulation to dimers, which accumulate in the kidneys, causing nephrotoxicity. The first attempts to overcome this problem involved modification of the haemoglobin molecule to prevent its breakdown, along with modification of the 2,3 DPG binding site to alter the oxygen affinity. A number of forms of these compounds are currently in phase III clinical trials (as reviewed by Chang[26]). However, there remain several obstacles to effective clinical use. Some forms of modified haemoglobin avidly bind nitric oxide, resulting in excessive vasoconstriction. There are none of the normal red cell antioxidant enzymes present, potentially worsening the effect of ischaemia–reperfusion injury.[27] The circulation half-life of the best modified haemoglobins is 24 hours, compared with 40 days for donor blood.

Nonetheless, there is the hope that such substitutes may have a role in the acute resuscitation of patients in haemorrhagic shock. Recent randomised controlled trials have differed in their conclusions as to the efficacy of modified haemoglobin in acute blood loss. Sloan et al. compared diaspirin cross-linked haemoglobin with saline for initial resuscitation, demonstrating an increased mortality in the modified haemoglobin group.[28] In contrast, Gould et al. found that polymerised haemoglobin was as effective as allogeneic red cells in the treatment of acute blood loss.[29]

New generations of modified haemoglobin include recombinant haemoglobin, which binds nitric oxide with less affinity, and haemoglobin conjugated to catalase or superoxide dismutase. Attempts are also being made to encapsulate haemoglobin and antioxidant enzymes in "artificial cells". At present these attempts are limited by short circulation time and technical difficulties with consistent production.[26] Progress will undoubtedly be made in this area, but clinical trials are still some time away.

5: Advantage –80°C freezer.

Platelet substitutes

Phase 2 clinical trials of an "infusible platelet membrane" (IPM) product have been encouraging. Infusible platelet membrane is prepared from fresh or outdated human platelets. It retains the glycoprotein Ib receptor and platelet factor 3, and so has procoagulant activity. Factor V, serotonin group IIb/IIa complex and HLA class I and II antigens are absent from IPM. Seven of 10 thrombocytopenic patients with active bleeding given IPM showed a decrease or cessation in their haemorrhage.[23] The median preinjection bleeding time of 15 minutes was reduced to six minutes within four hours of IPM administration.[30] As with red cell substitutes, however, the clinical use of artificial platelets will not be seen for some time.

Conclusion

There are a number of significant problems with the current policy for supply of blood products to deployed military units. While appreciating the relatively high initial cost, use of frozen red blood cells has the potential to safely reduce both the wastage of ARCBS packed red cells and the risks of acquiring blood from other sources in an emergency. Because of the time required for thawing and washing, frozen blood would supplement, rather than replace, the use of liquid packed cells. The use of frozen platelets would remove entirely the risks and difficulties of administering a walking donor panel. The development of red cell and platelet substitutes should continue to be watched with interest.

Most recent Australian operational military medical experience has been in short term deployments, or in operations in combination with a larger force capable of supplying more logistically difficult items, such as blood. In these circumstances, blood supplies in the field may not have been a significant problem. However, this should not hamper efforts to improve our deployable medical effectiveness.

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Behind the scenes

Australian Defence Human Research Ethics Committee (ADHREC)

In 1964, at a meeting in Helsinki, Finland, the 18th World Medical Association General Assembly adopted a set of ethical principles to be followed whenever humans participate in a research project. The *Declaration of Helsinki* was the first comprehensive declaration of such principles. The most recent amendments to the Declaration were adopted by the 52nd World Medical Association General Assembly in October 2000.

In 1982, the National Health and Medical Research Council of Australia (NHMRC) published a statement with guidelines on human involvement in experimentation. In 1988, the Chief of the Defence Force and the Secretary for Defence established the Australian Defence Medical Ethics Committee (ADMEC) as a non-statutory body. ADMEC first met in November 1989.

In June 2001, the Honourable Peter Reith, Minister for Defence, approved the name change to the Australian Defence Human Research Ethics Committee (ADHREC). The name change is consistent with the national nomenclature and reinforces the scope of the committee's charter with regard to human factors research in the Australian Defence Force. This charter encompasses any research in the ADF involving humans directly or indirectly.

The Surgeon General Australian Defence Force chairs the committee, which presently includes seven other members, each appointed for five-year terms. The committee currently meets five times a year.

Institutional ethics committees are an important component of all research (both animal and human) in Australia. ADHREC performs ethical review of human research within the ADF on behalf of all service personnel.

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