

Editorial

Frozen blood: time for outcomes

Critical haemorrhage was the main early driver in attempting to solve the problems preventing blood transfusion from entering medical therapeutics. Transfusions performed before knowledge of the ABO blood groups resulted in a bimodal outcome, with spectacular success for many patients and death for others. Discovery of the ABO blood groups by Karl Landsteiner over 100 years ago overcame this problem and whole blood transfusion established its role in the modern medical armamentarium¹.

However, the original transfusion process presented significant logistical difficulties with anticoagulation and preservation. Early transfusions required the donor to be in the immediate vicinity or directly connected (vein-to-vein) to the recipient. The development of anticoagulation and preservation of blood broke down this barrier, allowing the separation of the donor from the recipient in time and space. However, this progress presented new problems that remain unresolved to this day. The donor/supply side of the transfusion chain enabled small hospital-based blood banks to evolve into large blood supply centres, with the transfusion knowledge base and 'control' being product focused^{2,3}. The timely supply of allogeneic blood to patients with critical haemorrhage has increasingly presented logistic challenges, as the patient is commonly in a setting far removed from central blood supply agencies. Canadian physician Norman Bethune overcame this problem during the Spanish Civil War by establishing the first mobile blood bank, enabling the delivery of donor blood to a war zone⁴.

During the 20th century there was continuing improvement in blood preservation methods, usually driven by demands for high inventory levels and the increasing use of blood as a result of advances in surgery, haematology and oncology. Supply of labile blood products (red cells, platelets and fresh-frozen plasma) for these clinical settings can usually be planned and controlled in a timely fashion similar to any 'cold chain', which is typically seen in the fresh food industry. The main driver of the blood supply chain is now intravenous immunoglobulin and plasma fractionated products that do not present the preservation, storage and other potential hazards of the labile blood components.

Although a relatively small group in the blood usage picture, acutely haemorrhaging patients (especially

in the trauma and peri-partum settings), are most likely to be saved by the immediate availability of blood transfusions. Many of these patients are likely to have an associated coagulopathy requiring more complex diagnostic and therapeutic management⁵. There is no questioning the efficacy of appropriate and timely blood transfusion management for this group of patients. There will never be randomised controlled trials or a level I evidence base for this aspect of clinical management. As one of my colleagues (an evidence-based medicine zealot) ironically acknowledged, efficacy of transfusion in acutely bleeding patients is self-evident. On the other hand, we need more data and evidence to assist in fine-tuning aspects of clinical care and the quality and quantity of blood components. With impressive advances in early resuscitation methods, rapid retrieval, diagnostic methods and damage control surgery, the management of haemotherapy and application of point of care analysis of haemostasis has fallen behind. In previous years, most patients who received over 20 units of blood transfusion died from their injuries or inability to stem the haemorrhage. If haemorrhaging patients can receive more effective initial resuscitation with the labile blood components, clinical outcomes are likely to improve.

In this issue of the Journal, Holley et al⁶ summarise the challenges in the management of acutely haemorrhaging patients in isolated and military settings. As with so many advances in science and medicine, military conflicts have been the stimulus for innovation and blood transfusion is no exception. During World War II, there were several different approaches to transfusions in conflict zones, with different approaches by the United States and the British military. Experience during World War II confirmed that the availability of acid citrate dextrose preserved blood for transfusion as close to the conflict zone as possible was essential⁷.

Holley et al⁶ summarise the technical and practical clinical aspects and experiences with the use of frozen blood components in military settings. The preservation of tissues, cells and fluids has been part of evolution for 10,000 years, dating from the end of the paleolithic era of hunter gathers. From an evolutionary perspective, preservation generally related to food, except for post-death rituals; function and viability not being of concern. Methods used

have included drying, salting, fermenting, pickling and canning, to mention a few. It was not until modern times, with the invention of refrigeration and cryopreservation, that controlled freezing and thawing became a reality; the intent being to return the cryopreserved material to a functional state. Modern medicine is now inextricably dependent on cryopreservation for a wide range of medical therapies. Initially, this was primarily preserving plasma in the blood sector, but better cryopreservation methods have extended into important fields such as *in vitro* fertilisation and haemopoietic stem cell transplantation.

The modern history of cryopreservation of cells has its origins in 1949 when Polge et al discovered the cryoprotective properties of glycerol on fowl sperm⁸. It did not take long to demonstrate that red blood cells could be cryopreserved, thawed, washed and freed of cryoprotectants, with post-transfusion studies confirming an 85–90% survival rate⁹. This led to optimism that frozen red blood cells would solve problems relating to inventory shortages, responding to crises, provision of red cells to remote areas and conflict zones, and stockpiling rare blood groups. However, the high cost, logistics of preparation and short shelf-life of thawed red blood cells dampened this enthusiasm. The only areas of interest that did not wane were the storage of rare blood groups and the challenges for blood supply to the military. The United States Navy pursued the cryopreservation option, while the United States Army invested in the development of haemoglobin substitutes. It is fair to say that, to date, cryopreservation has prevailed as the technology is now established and cryopreserved red blood cells and haemostatic blood components are a reality. Additionally, the methodology and logistics have been tried and tested successfully in war zones. This was experienced by the United States Navy during the Vietnam War and more recently in Afghanistan, as summarised in the review by Holley et al⁶.

One may ask why the uptake of frozen blood preservation has been so slow. From my observation in clinical practice, if a diagnostic or therapeutic procedure is readily available and easy, it will be used frequently, without due consideration for the appropriateness, cost effectiveness or potential consequences. In contrast, if a diagnostic or therapeutic procedure is complex, logistically or technically difficult and of limited availability, its practice will be ignored at worst or not viewed as an optimal standard of care at best, regardless of clinical importance. In my opinion, the latter is the case with critically haemorrhaging patients, despite the fact that blood transfusions may be life saving for these

individuals. The evidence base for the understanding of the pathophysiology of haemostasis, the logistics of point of care testing and debates over the most appropriate blood component therapy and how it should be delivered are all challenging. Ironically, it is becoming apparent that the former situation is commonly witnessed with inappropriate blood transfusions in elective settings, particularly in haemodynamically stable anaemic patients who are transfused without due consideration for the risks and appropriate standards of care.

Holley et al⁶ make a convincing case that frozen blood storage and delivery in geographically challenged locations should be a high priority. Admittedly, logistic and economic barriers continue to hold back progress. Health administrators and politicians need to seriously address this issue, as scientific and technological processes have already been established. We are talking about the lives of young people with eminently treatable conditions, if the haemotherapy is optimally managed; it may be costly to achieve, but can no longer be delayed. Cost-effectiveness should not be the prime criterion. These are disadvantaged patients who are, in the case of the military, putting their lives on the line. Increasingly centralised blood services, although making economic sense on the supply side, may not be the best for geographically isolated, acutely bleeding patients or for overseas military and humanitarian endeavours. To put forward another perspective for consideration concerning economics, cost-effectiveness has never been the criteria for testing for infectious agents in the blood supply.

In my view, the time has come to realistically address the problem of better clinical outcomes for exsanguinating patients most in need of urgent and life saving blood transfusions. The practice of ‘returning’ donors nearer the patients, as practised with walking blood donor banks, is increasingly losing support due to practical and safety concerns. The move from a product focus to a patient focus demands we do the same for critically bleeding patients¹⁰. Diagnostic technology and therapies need to be as close to the patient as possible. Haematology and transfusion medicine have been dragging the chain in this respect and the drivers for change will be difficult to hold back. Geographically isolated Australians and serving military personal have an efficient food ‘cold chain’ like other Australians and should reasonably expect efforts to be made to achieve the same for blood supplies. To quote Ashley Brilliant, “In order to be ready when needed, you must also be ready when not needed”.

J. ISBISTER

*Sydney Medical School, Royal North Shore Hospital,
Sydney, New South Wales, Australia*

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