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Stranger danger—mortality after transfusions

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In the 1960s and 1970s hepatitis as a result of blood transfusion was relatively common, but at a recent talk on recent advances in the treatment of hepatitis I was surprised to learn just how high the mortality was after blood transfusion during this time period. In the USA an epidemiological study reported that 6% of nearly 30,000 patients with viral hepatitis had received one or more transfusions of blood or blood product within two weeks to six months before the onset of symptoms and the mortality in these patients was around 10%.1 In the yrs to come there were also new and emerging viruses and prions to add to the problem. On searching the more recent literature however, there aremany reports which still highlight higher mortality in patients who have had blood transfusions. Two immediate questions spring to mind: 1. Are there problems associated with the trans- fusion itself or 2. Does the original need for a transfusion result in increased mortality?

A list of the possible causes of increased mortality and mor- bidity associated with blood transfusion include ABO and non- ABO transfusion haemolytic reactions; transfusion related acute lung injury (TRALI); and infectious agents (both known and un- known) including viruses, bacteria, parasites and prions. The re- porting of all transfusion related deaths has been mandatory in the USA since 1976 and there are 'haemovigilance systems' in many countries. In the 2015 Serious Hazards of Transfusion (SHOT) report from the UK there were 26 deaths directly attrib- uted to blood transfusion, with haemolysis and transfusion associated circulatory overload and delayed transfusion being major factors.2 Acute transfusion reactions were associated with major morbidity in 86 patients. Transfusion transmitted infec- tion was a possible cause of death in one patient and TRALI ei- ther possible or probable in another four. The total major morbidity risk was 6.4 per 100,000 components issued and the risk for mortality was 1.01. The latest data available from the European Union haemovigilance system was from 2013 and re-ports 22 deaths.3 A recent report from the International Surveillance of Transfusion-Associated Reactions and Events database (STARE) has 409 deaths between 2006 and 2013 – an estimated rate of 0.3 per 100,000 components issued.4

Transfusion-related acute lung injury is clinically identical to acute respiratory distress syndrome (ARDS), but has a lower mortality – between 5 and 10%. In almost all patients white blood cell antibodies are identified in the plasma of the donor – par- ticularly from multiparous female donors, suggesting an im- mune mediated pathological process. Since 2006 collection of fresh frozen plasma and platelets from multiparous women has not been recommended in the UK and USA and other countries. TRALI however, is still being reported and many are now associ- ated with red cell transfusions rather than plasma. It is sug- gested that this could be as a result of the varying amount of residual donor plasma remaining in the red cell transfusion.5

In addition, it has been known for some time that a more re- strictive transfusion policy in the critically ill patient is associ- ated with a good if not better outcome. The Transfusion Requirements in Critical Care (TRICC) trial showed that a trans-
fusion trigger of <70g L-1 was no different to <100g L-1 and this has now been widely adopted into routine clinical practice.6 7 Many subsequent studies have confirmed this result (reviewed in Mirski and colleagues8). However, it is important to emphasise that many of these are non-inferiority trials and have therefore not shown an actual benefit. In addition, a recent meta-analysis has suggested that this approach in some patients may be detrimental because of a possible failure to cope with impaired oxy- gen supply.9

It has always been argued that the earlier trials of transfusion triggers in both the ICU and surgical populations used non-leucodepleted blood and that the results are not comparable with today's practice, as the use of leucodepleted blood products has now become universal. The suggestion is that some im- munological component within the non-leucodepleted blood was responsible for many of the longer term sequelae and mor- bidity, particularly increased infection risk. A meta-analysis in 2004 looked at the difference in outcomes between use of leuco- depleted and non-leucodepleted blood transfusions in a surgical population and failed to demonstrate a difference, apart from the suggestion of increased postoperative infections in the non-leucodepleted group.10

In addition, other studies have looked at outcome in a variety of patients after transfusion – for example those undergoing car- diopulmonary bypass surgery,11 percutaneous coronary inter- vention (PCI),12 major orthopaedic surgery13 or gastrointestinal haemorrhage.14 These are mainly observational studies and although the mortality in most was higher in the patients who re- ceive transfusions, the argument can always be made that it is the underlying reason for the transfusion or the more complex disease status that is driving the increased mortality. There are few good level 1 studies confirming increased mortality actually as a result of the transfusion.

There is a well-known immunosuppressive effect associated with blood transfusion which has manifest as enhanced graft survival after renal transplantation, reduced recurrence rate of Crohn's disease, increased recurrence of resected malignancies and increased incidence of postoperative bacterial infection. The immunological mechanisms of these effects are variously ascribed to the transfusion of intact allogeneic white cells, sol- uble white cell derived mediators and soluble HLA components which may trigger the production of anti-inflammatory cyto- kines including interleukin-4 (IL-4) and IL-10.15

It is usual for transfused leucocytes to be recognised by the recipient's immune system and removed within days of the transfusion. Despite this, using genetic testing it is possible to detect donor leucocytes much later; this is known as micro- chimerism (i.e. co-existence of relatively small numbers of dis- parate cell populations within the host). However, there may also be engraftment and proliferation in the recipient.16 Such microchimerism can be transient but can last for many yrs.

Even leucodepleted blood can still contain donor leucocytes and a recent study from Australia has shown persistent donor white cell populations in trauma patients after transfusion of ei- ther non-leucodepleted or leucodepleted blood.17 Nine of 55 pa- tients (16%) transfused with non-leucodepleted red blood cells,and three of 31

patients (9.6%) transfused with leucodepleted blood had evidence of microchimerism. This was particularly ap- parent in those patients who had had splenic injury (P ¼ 0.007). It is notable that the microchimerism seen in this study was pre- sent up to 12 yrs after the initial transfusion. There was no evi- dence of any relationship of microchimerism with the number of red cell units transfused.

A recent study in Canada used a longitudinal cohort ap- proach to look for a possible association of blood donor age and sex with outcome after transfusion.18 A total of 30,503 recipients received 187,960 red cell transfusions from 80,755 donors be- tween October 2006 and December 2013. Recipients of blood from the younger donors had an increased risk of death (1.08; 95% CI, 1.06-1.10; P < 0.001 for donor age 17-19.9 yr and 1.06; 95% CI, 1.04-1.09; P < 0.001 for donor age 20-29.9 yr). In addition, mor- tality was higher in the patients receiving blood transfusions from female rather than male donors (1.08; 95% CI, 1.06-1.09; P < 0.001).

Is autologous transfusion the answer? To date the available randomized controlled trials of autologous compared with allo- geneic transfusion, have not demonstrate a benefit in terms of transfusion related immunomodulation. There has been an interesting ex vivo study, where blood was salvaged from pa- tients during hip replacement surgery and then exposed to lipo- polysaccharide and venous blood from the same patient in the laboratory, with results compared with just the patients' own blood plus lipopolysaccharide. There was no effect on tumour necrosis factor alpha (TNFa) release, but there was increased IL-10 release in the mixture containing the salvaged blood.19 This same effect occurred only in the cellular fraction of the salvaged blood and was regardless of leucodepletion and gamma irradi- ation, suggesting that the red cells themselves are potentially re- sponsible for the immune effect.

The immunomodulatory effects of transfusion are still to be worked out, along with the possible measures that can be taken to prevent these complications. The relative roles of red cells and leucocytes, both of which seem able to induce an immune response, are still to be fully elucidated. The possible effects of cell collection techniques and storage time on immune function in the recipients are still not fully known. Should immunother- apy be used at the same time as the transfusion process? Are more complex compatibility testing procedures needed to pre- dict those recipients more likely to demonstrate immune toler- ability and chimerism? Transfusion can save lives but is it possible to manage without it in some situations? Patients should at least be appraised of the risks of transfusing or not transfusing bearing in mind the immune consequences that are becoming more appreciated.

Declaration of interest

None declared.

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