Blood transfusion practices: a little consistency please

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In this issue of Blood Transfusion, Verlicchi and Colleagues[1] report their observational study in which they combined data from different sources to demonstrate variability in transfusion rates among patients undergoing orthopaedic surgery in seven public and private hospitals in the area of Ravenna (Italy). The overall percentage of patients requiring transfusion varied from 28% to 74% among the hospitals, and the likelihood of receiving a transfusion was greater in females, increased with age, and was also greater in patients undergoing hip surgery than in those undergoing knee surgery. More blood transfusions were used for interventions following fractures than for non-traumatic conditions, although it should be noted that patients in the former group were older and more frequently female. The transfusion rate was higher in the public hospitals than in the private institutions, although this difference was not statistically significant when procedures essentially performed only in public facilities were excluded from the analysis.

Why should physicians practicing in the same region or even in the same institution and performing the same procedures on patients produce such different rates of transfusion? To begin with, whether or not a patient receives a blood transfusion often has as much to do with the physician's tolerance level of anaemia and transfusion practices, or "transfusion behaviours" as termed by Verlicchi and Colleagues[1], as it does with the patient's actual physiological need for correction of the anaemia. This leads to inconsistent transfusion practices and, often, inappropriate transfusions. Yet transfusion indications are not so clear cut, even in high-risk critical care patients[2] and patients with acute coronary syndromes[3], given that transfusion triggers cannot be precisely defined, and the question of whether a non-bleeding patient will benefit from blood transfusion, particularly a patient whose haemoglobin concentration is in the middle range of published guidelines (i.e., between 7 and 10 g/dL)[4], has remained challenging. While there is mounting evidence in published studies to suggest that conservative transfusion practices are at least as effective as liberal ones, if not superior[2-6], the conclusions of the studies are still open for debate given the limitations of the studies: many were observational or retrospective, leucocyte-depleted blood with reduced immunomodulatory effects[7] was not consistently used for the transfused patients, and the studies could not entirely account for all confounding factors that may have contributed to worse clinical outcomes observed in transfused patients (that is to say, more severely ill patients tend to receive more transfusions)[8]. Furthermore, it is known that anaemia, if left untreated, can have adverse affects on patients, particularly those with significant cardiovascular disease or in neurocritical care patients[9-11], prompting physicians to transfuse even if the benefits of transfusion are not entirely certain. Then again, under-transfusion has received its share of attention in published articles as well[12,13]. Perhaps more information could be gleaned from a study of transfusion versus no transfusion; however, withholding transfusion would be considered unethical. Studies to date have, therefore, realistically only been able to consider more versus less transfusion, and there have been overlapping haemoglobin cut-off points distinguishing between conservative and liberal transfusion practices among the published studies[6]. More recent studies have focused on the immunomodulatory effects of transfusion which may be affected by the duration of blood storage in addition to leucocyte depletion. While some authors have concluded that there is an association between transfusion of older blood (i.e., blood more than 14 days old) and worse clinical outcomes[14], others have not found this association to be valid[15]. It will be interesting to see the outcome of two new randomised controlled trials, one evaluating restrictive versus liberal transfusion triggers in critically ill patients

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(Restrictive and liberal transfusion strategies in intensive care; RELIEVE)[16] and another evaluating the effects of transfusing fresher versus older red cell units (Red cell duration study; RECESS)[17].

The known infectious and non-infectious risks of transfusion also underlie the resolve to determine optimal transfusion practices. Such risks of course can never be entirely eliminated despite improvements in donor screening and testing methods, as evidenced by recent documented cases of human immunodeficiency virus (HIV) transmission via blood transfusion in the United States[18]. Yet other well-known transmissible disease risks apart from HIV and hepatitis, such as malaria[19], babesiosis[20], leishmania[21], and *Trypanasoma cruzi* (Chagas disease)[22] amongst others, are not universally tested for while the risks of transmissibility for some other agents, such as prion disease (variant Creutzfeldt-Jakob disease)[23] and the newly-discovered xenotropic murine leukaemia virus-related virus (XMRV, thought to be linked to chronic fatigue syndrome and prostate cancer)[24], have yet to be definitively established. Meanwhile, efforts to reduce the risk of transfusion-related acute lung injury (TRALI) are hampered by the limited knowledge of the mechanisms that lead to this non-infectious complication which results in non-cardiogenic pulmonary oedema during or shortly after transfusion. Antibodies to human leucocyte antigens (HLA), or in some cases to granulocyte antigens, are thought to be causative in most cases and have led some donor centres to employ the crude measure of excluding plasma collections from female donors who are generally considered to be at higher risk of harboring HLA class I or class II antibodies as a result of pregnancy-related exposures[25]. Yet again, the risk cannot be entirely removed by such measures since mechanisms unrelated to HLA antibodies, such as activation of primed neutrophils, have also been hypothesised in a smaller number of cases[26]. Finally, elimination of human error that leads to mistransfusion of incompatible blood remains another challenge[27].

The fact that costs escalate with higher rates of transfusion should not be overlooked, so it is of course desirable to minimise unnecessary transfusions from this standpoint, too.

The results reported by Verlicchi and Colleagues[1] are not surprising given that variation in transfusion practice has been previously described and is a well-known problem[28,29]. Furthermore, their study did not consider several key issues examined by other reports of transfusion in orthopaedic patients such as clinical outcomes and use of blood conservation techniques. In their study, Carson *et al*.[30] showed that peri-operative transfusion did not affect 30- and 90-day post-operative mortality in elderly hip fracture patients, though certainly, this retrospective analysis is subject to the limitations noted above. The authors of a more recent randomised study[31], the first to limit transfusions in adult orthopaedic patients to leucocyte-depleted blood, concluded that implementation of a restrictive transfusion policy did not affect duration of hospital stay across three hospitals. Interestingly though, even with implementation of the restrictive policy, transfusions increased in one of the institutions despite a low rate of deviations from the protocol in the study. Meanwhile, Feagan *et al*.[32] linked higher rates of allogeneic transfusion in elective orthopaedic surgery to underutilisation of blood conservation strategies, particularly autologous predonation and to a lesser extent, cell salvage and normovolaemic haemodilution, in 19 Canadian hospitals. Likewise, in a European study, Muñoz *et al*.[33] advocated better strategies for the use of transfusion alternatives and blood conservation techniques for orthopaedic surgery to reduce the need for allogeneic blood transfusion. Nevertheless, the analysis performed by Verlicchi and Colleagues[1] is admirable considering that comparison of transfusion data, particularly across multiple hospitals, is not such an easily accomplished task since clinical documentation of transfusions is often lacking. Yet the authors persisted in teasing out necessary clinical information from the blood bank information system, the hospital discharge database, and, for some patients, the laboratory information system to provide combined information that could be used to analyse and compare transfusion practices more efficiently.

In the end, the report by Verlicchi and Colleagues[1] serves to remind us once again of the difficult road that lies ahead toward improving transfusion practices. Though more studies are necessary in order to determine the true benefits versus the risks of blood transfusion, in both the short-term and the long-term, possibly the major obstacle to making transfusion practices more consistent and in line with

published guidelines and evidence-based-medicine is the overall lack of knowledge regarding transfusion shared by clinicians across specialties as evidenced by published data[34-36]. This evidence would seem to indicate that medical education in transfusion medicine continues to lag behind. Thus, no matter what the conclusions of future studies on transfusion efficacy turn out to be, there will be little impact on blood utilisation overall if we continue to fail to educate the end users. Ultimately, I believe, it is only by reversing this trend in medical education that we, as transfusion medicine specialists, will begin to see improvements - and consistency - in blood transfusion practices.

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