Blood transfusion in acute upper gastrointestinal bleeding: is giving more blood always better?

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Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency which results in significant morbidity and mortality worldwide. The incidence of UGIB ranges from 50 to 150 per 100,000 adults per year (1,2). UGIB leads to a decrease in circulatory blood volume, which in turn results in hypotension and reduced tissue perfusion. This can lead to unfavourable end organ damage such as myocardial infarction or kidney injury. Although there have been considerable advances in endoscopic intervention for the management of bleeding, 30-day mortality rates still range between 5–14% (3).

Red blood cell (RBC) transfusion is a key element in the management of patients with UGIB as it is one of the steps potentially required for resuscitation of the patient. Transfusions for treatment of UGIB accounted for 21% of RBC usage in Western Australia (3). As RBCs are a limited resource and reliant on donation from the general public, it is important to ensure that this resource is used appropriately. Furthermore, there has been increasing evidence that excessive RBC transfusion can be associated with higher re-bleeding rates and mortality (3,4). There has been concern that RBC transfusion may also result in increased mortality rates even up to 2 years post-transfusion. Taha et al showed hazard ratios of 1.88 and 1.71 for death after transfusion in UGIB at 30 days and 2 years, respectively (4). Avoidance of RBC transfusions may be beneficial economically as well as with regards to patient outcomes.

While RBC transfusion is clearly indicated in cases of massive UGIB, there are no definitive protocols to guide the triggers for and the amount of transfusion required in non-exsanguinating UGIB. The 2016 National Institute for Health and Clinical Experience (NICE) UGIB guidelines recommend that decisions on blood transfusion should be made based "on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion" (5). Both the Gastroenterological Society of Australia and the American Society for Gastrointestinal Endoscopy do not offer any guidance on triggers for RBC transfusion in UGIB. Hence, it is not surprising that a survey conducted on 815 clinicians in the United Kingdom showed that there was considerable variation in triggers for transfusion that was dependent on sub-speciality (surgeons versus clinicians) and years of clinical experience (2). Clinical trials are challenging to carry out as blinding is difficult and in acute UGIB, a transfusion can be life-saving and cannot be denied.

The recently published article by Odutayo *et al.* in the Lancet was a systematic review and meta-analysis of randomized controlled trials which evaluated restrictive versus liberal blood transfusions in UGIB. The authors aimed to determine the effect of RBC transfusion on patient mortality, rebleeding rates and number of ischaemic events (6). The authors searched a range of databases for randomized controlled trials involving patients aged 16 years and older with acute UGIB comparing RBC transfusions with intravenous fluid or RBC transfusions with different thresholds. The database search identified 2,848 records. However, the majority of the records did not

fulfil eligibility criteria and only 5 studies were included in the meta-analysis. Exclusion criteria included non-randomized trials, incorrect intervention, comparator or patient population (6).

In total, the five studies comprised a total patient population of 1,965 adults, of which 919 were in the restrictive transfusion strategy group and the remaining 1,046 patients were in the liberal transfusion group (6). Four of the five studies were single centre trials. The haemoglobin threshold for intervention differed between studies. Most of the studies utilised a cut-off of 80 g/L for the restrictive transfusion group and 100 g/L for the liberal transfusion group, with one study using a haematocrit threshold (7,8). As the statistical analysis varied between trials, the authors had to re-analyse data from certain individual patient groups in order to facilitate meta-analysis.

Odutayo *et al.* found that all-cause mortality obtained from the pooled data was significantly lower in the restrictive transfusion group (RR 0.65; 95% CI, 0.44–0.97, P=0.03) (6). The absolute risk reduction was 2.22% with a number needed to treat of 45 to prevent one death with the restrictive transfusion strategy (6). The relative risk of re-bleeding was also lower in the restrictive transfusion group. (RR 0.58; 95% CI, 0.40–0.84, P=0.004) (6) The lower re-bleeding risk also applied to patients with non-variceal bleeding. The subgroup analysis did not reveal any difference between the groups with regards to acute myocardial infarction, stroke or acute kidney injury. The authors did not detect a difference in mortality between patients with non-variceal bleeding and patients with cirrhosis (6).

A systematic review is only as good as the studies included in it. This meta-analysis included studies conducted between 1986 and 2015, spanning almost 30 years. As only 5 trials were included, the subgroup analyses were underpowered for detection of small differences. Three of the five trials were small studies with less than 100 patients across both arms. As such, the majority of the data were obtained from the two larger trials by Jairath and Villanueva. The above factors affect the generalisability of the findings from this meta-analysis.

All five trials had different criteria for transfusion and reported their outcomes in different ways. In order to allow meta-analysis, the authors had to pool the data despite the different transfusion cut-offs. Although inevitable, this reduced the validity of the results.

A limitation of the meta-analysis was that it did not have sufficient data regarding the outcomes of transfusion in patients with ischaemic heart disease. Only one study reported on acute coronary syndrome as an outcome. The trial by Villanueva, which made up a significant number of patients in the meta-analysis, excluded patients with a recent ischaemic event at trial entry (8). Even though subgroup analysis showed no increased risk of ischaemic heart disease in restrictive transfusion, there is insufficient evidence to back this up currently.

A Cochrane review in 2010 which used data from 3 trials found that RBC transfusion was associated with increased mortality with a relative risk of 5.4 (1). This result was in line with the conclusions from Odutayo's systematic review. The lower re-bleeding rates in patients who have had restrictive transfusion demonstrated in the meta-analysis are broadly consistent with other observational studies carried out (3,9). A Western Australian study further quantified this by determining that in patients with a haemoglobin of more than 90 g/L, transfusion of more than 4 units of RBC was associated with at least an 11-fold risk of re-bleeding (3).

It is unclear why liberal blood transfusion is associated with increased mortality rates. It is postulated that patients who receive more blood are at higher risk of hospital-acquired infections as a result of immunomodulatory effects. Another possible reason is that the volume load that comes with liberal blood transfusion causes circulatory compromise, particularly in patients with heart or renal failure. In cirrhotic patients with variceal bleeding, blood transfusion can increase portal pressures resulting in higher rates of re-bleeding. In non-variceal bleeding, the causes of increased re-bleeding rates are not well understood.

When applying the results of this meta-analysis to the general population, clinicians should bear in mind that majority of the patient population came from the Jairath and Villanueva trials. Both these trials were conducted in tertiary hospitals with 24 h access to endoscopy (7,8). Furthermore, patients in the Villanueva trial underwent endoscopy within 6 hours of presentation and had appropriate therapeutic intervention to manage their UGIB (8). In smaller or more peripheral hospitals which do not have immediate access to endoscopy services, patients may require more blood transfusion as a bridge while awaiting transfer to another centre for definitive treatment of their UGIB. In these circumstances, clinical judgement should dictate management of each individual patient depending on their presentation and co-morbidities.

Despite the widespread usage of RBC transfusion in UGIB, evidence regarding appropriate triggers for transfusion is still lacking. The safety of restrictive

transfusion for management of UGIB in patients with ischaemic heart disease still cannot be adequately answered. With the current evidence base available, restrictive transfusion of RBCs in UGIB is recommended. However, the risks versus benefits of transfusion should be weighed up in individual patients and clinical judgement should be used. A large, well-run clinical trial which aims to determine the appropriate trigger for RBC transfusion post UGIB is required for these questions to be answered.

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Footnote

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