Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials

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Summary

Background Acute upper gastrointestinal bleeding is a leading indication for red blood cell (RBC) transfusion worldwide, although optimal thresholds for transfusion are debated.

Methods We searched MEDLINE, Embase, CENTRAL, CINAHL, and the Transfusion Evidence Library from inception to Oct 20, 2016, for randomised controlled trials comparing restrictive and liberal RBC transfusion strategies for acute upper gastrointestinal bleeding. Main outcomes were mortality, rebleeding, ischaemic events, and mean RBC transfusion. We computed pooled estimates for each outcome by random effects meta-analysis, and individual participant data for a cluster randomised trial were re-analysed to facilitate meta-analysis. We compared treatment effects between patient subgroups, including patients with liver cirrhosis, patients with non-variceal upper gastrointestinal bleeding, and patients with ischaemic heart disease at baseline.

Findings We included four published and one unpublished randomised controlled trial, totalling 1965 participants. The number of RBC units transfused was lower in the restrictive transfusion group than in the liberal transfusion group (mean difference –1·73 units, 95% CI –2·36 to –1·11, p<0·0001). Restrictive transfusion was associated with lower risk of all-cause mortality (relative risk [RR] 0·65, 95% CI 0·44–0·97, p=0·03) and rebleeding overall (0·58, 0·40–0·84, p=0·004). We detected no difference in risk of ischaemic events. There were no statistically significant differences in the subgroups.

Interpretation These results support more widespread implementation of restrictive transfusion policies for adults with acute upper gastrointestinal bleeding.

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Introduction

Acute upper gastrointestinal bleeding is a common medical emergency and important cause of morbidity and mortality worldwide.[1] Bleeding most often arises from non-variceal sources (non-variceal upper gastrointestinal bleeding), or from variceal sources in patients with portal hypertension and liver cirrhosis. Although the general approach to management is similar for each, prognosis differs and is affected by different underlying mechanisms of bleeding and burden of comorbidity. Regardless, transfusion of red blood cells (RBCs) is integral to management, and acute upper gastrointestinal bleeding is one of the leading indications for RBC transfusion.[2] Large observational studies show considerable variation in practice.[3,4]

Given the rapid development of anaemia, haemodynamic compromise, high burden of comorbidity, and anticoagulant use associated with acute upper gastrointestinal bleeding, transfusion requirements in these patients might differ from those in other critically ill populations. A Cochrane review of randomised controlled trials (RCTs) updated in 2010 comparing restrictive versus liberal RBC transfusion for acute upper gastrointestinal bleeding found no robust studies to inform this question.[5] Subsequently, two large RCTs[6,7] comparing transfusion thresholds for acute upper gastrointestinal bleeding have been published. Because acute upper gastrointestinal bleeding is a medical emergency needing urgent intervention, testing transfusion strategies in clinical trials is challenging. Additionally, the general movement toward restrictive transfusion in medical and surgical specialties would make it difficult to do further practice-changing RCTs in this population.

Pooling the results of all the available studies will help to assess the efficacy and safety of restrictive versus liberal transfusion strategies for acute upper gastrointestinal bleeding. We did a systematic review and meta-analysis of RCTs comparing restrictive and liberal RBC transfusion thresholds in adults with acute upper gastrointestinal bleeding to determine the effect on RBC transfusion, mortality, rebleeding, and ischaemic events. We also examined treatment effects for mortality and rebleeding in three prespecified subgroups: patients with liver cirrhosis, patients with non-variceal upper gastrointestinal bleeding, and patients with ischaemic heart disease at baseline.

Research in context

Evidence before this study

A Cochrane review in 2010 found only three small randomised clinical trials comparing restrictive and liberal red blood cell transfusion strategies for acute upper gastrointestinal bleeding. Subsequently, a large single-centre randomised controlled trial from a specialist bleeding unit suggested reduced mortality and rebleeding with restrictive transfusion, although the trial setting, stringent care processes, and exclusion of patients with cardiovascular disease limited the generalisability of the findings. A pragmatic, cluster randomised feasibility trial done in the UK showed no difference in clinical outcome between restrictive and liberal red blood cell transfusion. There is uncertainty about treatment effects overall, and in clinically important subgroups such as those with non-variceal bleeding and in patients with ischaemic heart disease.

Added value of this study

Pooling the results of five randomised controlled trials, restrictive red blood cell transfusion was associated with a significantly lower risk of mortality and rebleeding overall. The treatment effect was consistent across subgroups, including patients with liver cirrhosis and those with non-variceal bleeding. Although there was no excess of ischaemic events with restrictive transfusion, these data should be interpreted with caution, because they were only reported in one trial.

Implications of all the available evidence

Restrictive red blood cell transfusion for acute upper gastrointestinal bleeding should be included in treatment guidelines worldwide. However, these results might not apply to patients with ischaemic heart disease, for which further evidence is needed, or in patients with exsanguinating bleeding, for whom decisions for transfusion should be individualised.

Methods

Data sources, searches, and study selection

We systematically searched MEDLINE (1946 to Oct 20, 2016), Embase (1974 to Oct 20, 2016), CENTRAL (the Cochrane Library 2016, issue 9), CINAHL (1982 to Oct 20, 2016), the Transfusion Evidence Library (1950 to Oct 20, 2016), and clinical trial databases (ClinicalTrials.gov and the WHO International Clinical Trials Registry; searched Oct 20, 2016). The full search strategy is available online (appendix).

We included RCTs that included participants aged 16 years and older with acute upper gastrointestinal bleeding and compared the following interventions: (1) RBC transfusion and standard care versus other intravenous fluid and standard care; (2) initial RBC transfusion to a maximum of two units versus initial RBC transfusion with no upper limit (and more than two units); (3) an RBC transfusion threshold of less than 80 g/L versus an RBC transfusion threshold of 80–110 g/L for women and 80–130 g/L for men. Eligible studies also had to report at least one of the following outcomes: mortality, rebleeding, number of RBC units transfused, or an ischaemic event (any of: acute myocardial infarction, stroke, or acute kidney injury). We included studies irrespective of language, sample size, or length of follow-up. Trials published in a language other than English were translated in full before data extraction. AO and MJRD independently assessed the eligibility of articles identified by the search for inclusion in the review and together decided whether they were eligible.

Data extraction and quality assessment

AO and MJRD independently extracted data using standardised data collection forms. They extracted data for general study characteristics (author, year of publication, sample size, length of follow-up) and participant characteristics (age, sex, mean Rockall score,[8] number of participants with variceal or non-variceal bleeding, and number of participants with liver cirrhosis or ischaemic heart disease). If available, we also extracted hazard ratios and associated 95% CIs and p values for clinical outcomes of interest. For studies that did not report hazard ratios, we extracted relative risks (RRs) and 95% CIs or calculated them based on the published data. We pooled hazard ratios and RRs. We extracted effect estimates (hazard ratios or RRs) for patients with a

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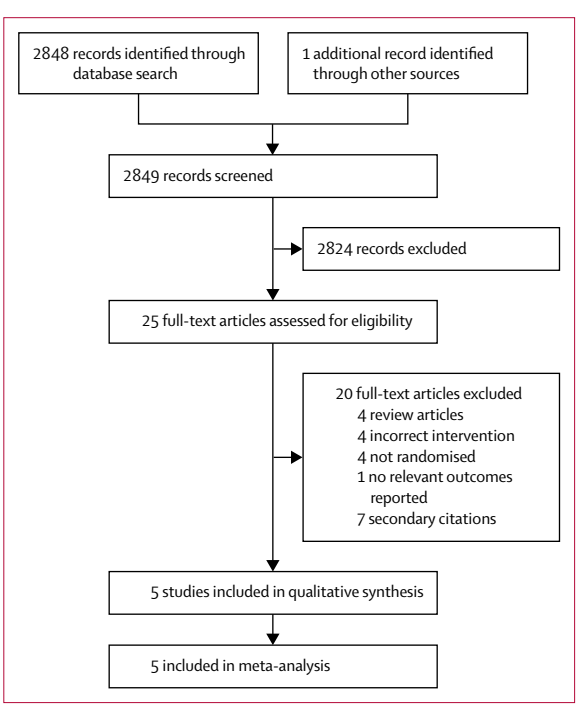

Figure 1: **Study selection**

non-variceal source of bleeding, liver cirrhosis, and with and without underlying ischaemic heart disease.

Jairath and colleagues[6] reported the results of their cluster randomised trial as mean differences. We re-analysed the individual patient data from the trial to calculate hazard ratios to facilitate meta-analysis and to be consistent with the trial by Villanueva and colleagues.[7] We did this by multilevel modelling of time-to-event data with treatment as a fixed effect and study site as a random effect. Villanueva and colleagues[7] reported results for adults with non-variceal upper gastointestinal bleeding but Jairath did not.[6] To enable meta-analysis, we used the individual patient data from the study by Jairath and colleagues[6] to calculate hazard ratios for adults with non-variceal upper gastointestinal bleeding. We otherwise adhered to the prespecified statistical analysis plan.[9] We assessed the risk of bias using the Cochrane Risk of Bias tool.[10]

Data synthesis and analysis

We pooled estimates of treatment effects for each outcome by random effects meta-analysis using the generic inverse variance method.[11] We used this method because we anticipated that studies would include patients from different populations, different time periods, and different health-care systems, thereby resulting in the estimation of different yet related intervention effects. We report continuous outcomes as mean difference and dichotomous outcomes as RRs with their 95% CIs. We assessed heterogeneity using the I^2 statistic. We also assessed the p value for the I^2 statistic to determine the strength of evidence for heterogeneity. We anticipated that few eligible studies would be identified, with varying levels of detail regarding baseline characteristics of participants. Therefore, we explored heterogeneity using sensitivity analyses in relation to study design (parallel *vs* cluster). In accordance with Cochrane guidance, we did not analyse publication bias because our search identified fewer than ten studies.[11] We compared treatment effects across subgroups using a test for interaction.

We calculated the absolute risk reduction (ARR) for significant outcomes using the formula ARR=(1–RR)×(assumed control risk).[12] The assumed control risk was calculated using the pooled event rate (in events per patient-month of follow-up) in the control groups of the trials that reported length of follow-up. Results were expressed as percentages. We calculated the number needed to treat as 1/ARR.

We did all analyses using RevMan (version 5.3.5), Stata (version 14), and *R* (version 3.2.0). We considered a p value of less than 0·05 statistically significant.

Role of the funding source

There was no funding source for this study and the corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Our search returned 2849 abstracts and we excluded 2824 on the basis of the title and abstract. The reasons for exclusion were: incorrect patient population, incorrect intervention or comparator, and incorrect trial design. We reviewed 25 full-text articles and excluded 20 because the studies were non-randomised or review articles, the intervention of interest was not used, or no relevant outcomes were reported (figure 1). Accordingly, we included five studies[6,7,13–15] in the meta-analysis, including 1965 adults (919 assigned to a restrictive transfusion strategy and 1064 assigned to a liberal transfusion strategy; table 1). Four studies were completed.[6,7,13,15] The study by Lee and colleagues[14] is ongoing with interim results reported in a conference abstract. The report by Villarejo and colleagues[15] was published in Spanish and translated into English before data extraction.

The trials by Villanueva and colleagues[7] and Jairath and colleagues[6] contributed 1825 (93%) of 1965 of the total study participants (table 1). In four trials, participants were assigned to two differing RBC transfusion strategies (three using haemoglobin thresholds[6,7,14] and one using

	Country	Design	Intervention haemoglobin threshold	Follow-up	Outcomes reported
Blair et al, 1986[13]	UK	Single centre, parallel group	Restrictive: 80 g/L; liberal: no threshold (all received two units of red blood cells)	Not stated	Laboratory measures of coagulation (primary), mortality, rebleeding, red blood cell transfusions
Lee et al, 2014[14]	South Korea	Single centre, parallel group	Restrictive: 80 g/L; liberal: 100 g/L	Not stated	Rebleeding*
Jairath et al, 2015[6]	UK	Multicentre, cluster randomised	Restrictive: 80 g/L; liberal: 100 g/L	28 days	Feasibility (primary), mortality, rebleeding, acute myocardial infarction, stroke, transfusion reactions, acute kidney injury, bacterial infection, red blood cell transfusions, duration of hospital admission
Villanueva et al, 2013[7]	Spain	Single centre, parallel group	Restrictive: 70 g/L; liberal: 90 g/L	45 days	Mortality (primary), rebleeding, acute myocardial infarction, stroke, transfusion reactions, acute kidney injury, bacterial infection, red blood cell transfusions, duration of hospital admission
Villarejo et al, 1999[15]	Argentina	Single centre, parallel group	Restrictive: haematocrit 21%; liberal: haematocrit 28%	Not stated	Mortality, rebleeding, acute myocardial infarction, stroke, duration of hospital admission*

*No primary outcome specified for Lee et al[14] or Villarejo et al.[15]

Table 1: **Characteristics of included studies**

	Participants (n)	Mean age (SD; years)	Male (n, %)	Female (n, %)	Cirrhosis (n, %)	Variceal bleed (n, %)	Non-variceal bleed (n, %)	Ischaemic heart disease (n, %)
Blair et al[13]			34 (68%)	16 (32%)				
Restrictive	26	60 (18)	..	..	0	0	26 (100%)	0
Liberal	24	64 (18)	..	..	0	0	24 (100%)	0
Lee et al[14]*								
Restrictive	32	..	..	..	..	..	..	..
Liberal	31	..	..	..	..	..	..	..
Jairath et al[6]†								
Restrictive	403	58 (20)	244 (61%)	159 (39%)	45 (11%)	25 (6%)	261 (65%)	61 (15%)
Liberal	533	60 (20)	322 (60%)	211 (40%)	91 (17)	56 (11%)	331 (62%)	76 (14%)
Villanueva et al[7]								
Restrictive	444	64 (16)	314 (71%)	130 (29%)	139 (31%)	101 (23%)	343 (77%)	0
Liberal	445	66 (15)	291 (65%)	154 (35%)	138 (31%)	109 (24%)	336 (76%)	0
Villarejo et al[15]								
Restrictive	14	..	..	..	0	..	..	0
Liberal	13	..	..	..	0	..	..	0

*Ongoing; results were obtained from an abstract. †Endoscopy was not done for 117 adults in the restrictive group and 146 adults in the liberal group, therefore the source of bleeding could not be identified; imbalanced recruitment by treatment group is probably due to the small number of clusters.

Table 2: **Baseline characteristics of participants in included studies**

haematocrit thresholds[15]) and in one trial participants were assigned to transfusion versus no transfusion.[13] One trial was done before the routine use of endoscopic therapy and high-dose proton pump inhibition, although this trial included only 50 participants.[13] The two largest studies[6,7] enrolled unselected patients and thus enrolled participants with non-variceal upper gastrointestinal bleeding as well as patients with liver cirrhosis and variceal bleeding (table 2). Only one trial included patients with acute upper gastrointestinal bleeding regardless of age or comorbidity, and this was the only trial to include patients with ischaemic heart disease at baseline.[6] Length of follow-up was reported for two studies, one at 28 days and one at 45 days (table 1).

Two studies had a low risk of bias for all categories[6,7] and the remaining three studies[13–15] had an unclear risk of bias for most categories, except the study by Villarejo and colleagues,[15] which had a high risk of bias due to attrition (appendix).

Four studies reported the mean number of transfusions received by adults in each study group (figure 2). The pooled mean difference was –1·73 units (95% CI –2·36 to –1·11, p<0·0001) in favour of the restrictive transfusion strategy. Heterogeneity was moderate (I^2 63%, p=0·043). In a sensitivity analysis, we excluded the study by Jairath and colleagues[6] because it was a cluster randomised trial. With this exclusion, the estimate of effect increased slightly (mean difference –2·03 units, 95% CI –2·44 to –1·61, p<0·0001) and heterogeneity was reduced (I^2 29%, p=0·24).

Four studies had all-cause mortality as an outcome, but no deaths occurred in the trial by Villarejo and colleagues[15] and so it was not included in the meta-analysis. The pooled risk of all-cause mortality was significantly lower

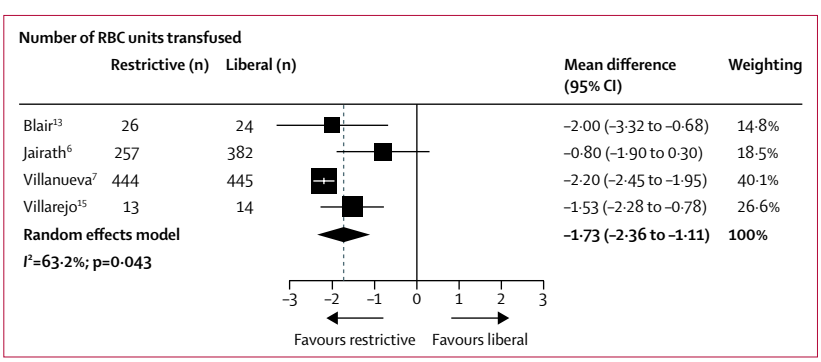

Figure 2: **Pooled mean difference for number of transfusions**
RBC=red blood cells.

in patients managed with a restrictive transfusion strategy than in those managed with a liberal transfusion strategy (RR 0·65, 95% CI 0·44–0·97, p=0·03; figure 3A). There was little evidence of heterogeneity (I^2=0%, p=0·37). There was no significant difference in the RR for patients with cirrhosis compared with those who had non-variceal upper gastrointestinal bleeing ($p_{interaction}$=0·27; appendix). The effect of restrictive versus liberal transfusion varied in adults with baseline ischaemic heart disease (RR 4·38, 95% CI 0·86–22·31) and without baseline ischaemic heart disease (RR 0·58, 95% CI 0·27–1·26), but neither estimate was statistically significant ($p_{interaction}$=0·03). The overall ARR was 2·22% (95% CI 0·32–3·55) for all-cause mortality and the number-needed-to-treat to prevent one death using a restrictive transfusion strategy was 45 (95% CI 28–315).

All five studies reported rebleeding as an outcome, but no events occurred in the trial by Villarejo and colleagues.[15] The pooled relative risk of rebleeding was

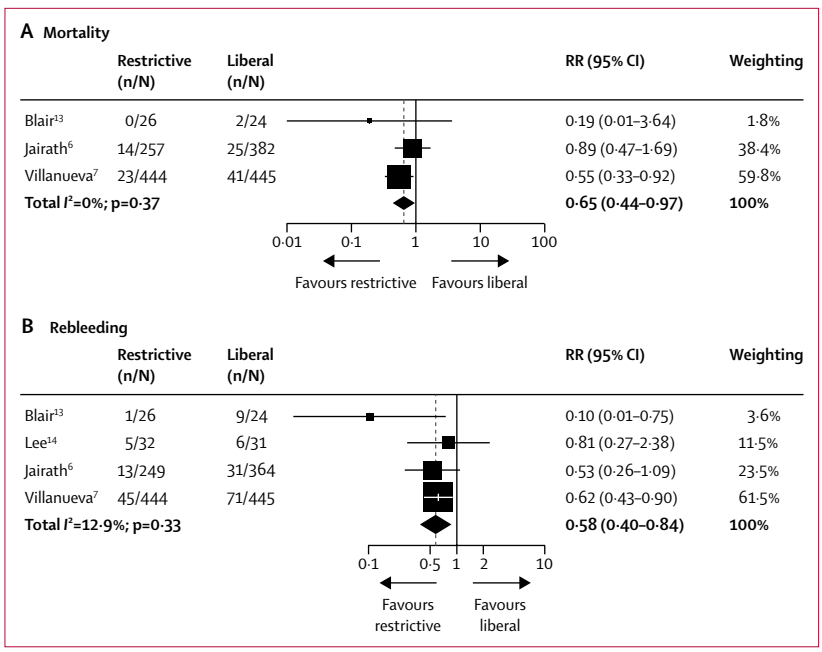

Figure 3: **Pooled RR of all-cause mortality (A) and rebleeding (B)**
No deaths occurred in either group in one trial (Villarejo and colleagues[15]) so it was not included in the meta-analysis. RR=relative risk.

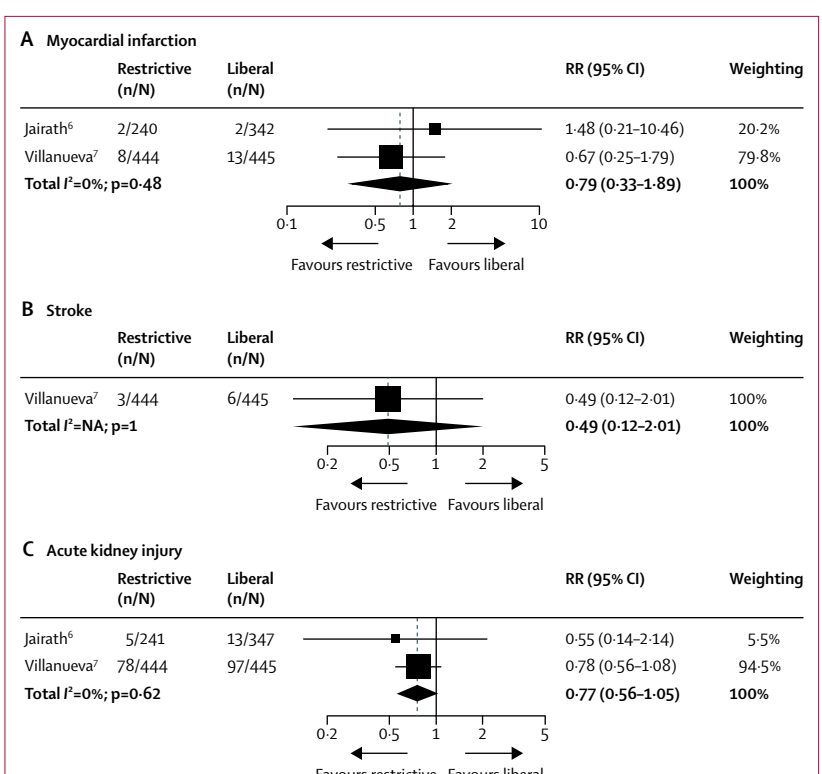

Figure 4: **Pooled RR of ischaemic events**
(A) Myocardial infarction, (B) ischaemic stroke, and (C) acute kidney injury. No myocardial infarctions occurred in either arm in one trial (Villarejo and colleagues[15]) and so it was not included in the meta-analysis. RR=relative risk. NA=not applicable.

significantly lower in adults managed with a restrictive transfusion strategy than in adults managed with a liberal transfusion strategy (RR 0·58, 95% CI 0·40–0·84, p=0·004; figure 3B). There was little heterogeneity (I^2=13%, p=0·33) and results did not change when the interim results from Lee and colleagues were excluded.[14] Treatment effects were similar in adults with cirrhosis (RR 0·53, 95% CI 0·30–0·95) and those with non-variceal upper gastrointestinal bleeding (0·55, 0·35–0·88; $p_{interaction}$=0·92; appendix) and in adults with ischaemic heart disease (0·50, 0·23–1·12) and in those without (0·69, 0·13–3·77; $p_{interaction}$=0·74). The overall ARR was 4·21% (95% CI 1·44–6·03) for rebleeding and the number-needed-to-treat to prevent one rebleeding event using a restrictive transfusion strategy was 24 (95% CI 17–70).

Three trials reported data for acute myocardial infarction,[6,7,15] two reported data for stroke,[7,15] and two reported data for acute kidney injury.[6,7] We detected no difference between restrictive and liberal transfusion strategies for acute myocardial infarction, ischaemic stroke, or acute kidney injury (figure 4).

Discussion

To our knowledge, this study is the most up-to-date systematic review and meta-analysis of randomised trials comparing restrictive and liberal transfusion strategies among adults with acute upper gastrointestinal bleeding, including re-analysis of individual participant data from a cluster-randomised trial.[6] We identified five RCTs enrolling 1965 participants with acute upper gastrointestinal bleeding and were able to compare treatment effects in clinically important subgroups, including patients with liver cirrhosis, non-variceal upper gastrointestinal bleeding, and ischaemic heart disease. A restrictive transfusion threshold was associated with a reduction in the number of RBCs transfused. Acute upper gastrointestinal bleeding is the leading indication for RBC transfusion in England,[2,4] therefore implementation of restrictive practices is likely to have considerable resource and financial implications for blood transfusion services. Even a moderate absolute reduction in RBCs for acute upper gastrointestinal bleeding of 13%, a treatment effect reported from one of the trials in this systematic review, could lead to savings in the UK of more than £3 million annually for the blood alone.[6,16]

For all-cause acute upper gastrointestinal bleeding, the pooled results show that restrictive RBC transfusion was associated with a reduction in mortality, supporting the results of the trial by Villanueva and colleagues.[7] The mechanism by which liberal RBC transfusion leads to increased mortality is unclear, although several hypotheses exist. First, transfusion is associated with immunomodulatory effects, which can increase the risk of hospital-acquired infections.[4,17,18] Second, liberal transfusion is associated with circulatory overload,

which could cause harm both in older patients with ischaemic heart disease and in patients with cirrhosis through worsening of portal hypertension. Third, the increased rebleeding could increase mortality, given the excess mortality in patients who have rebleeding compared with those who do not.[1] We detected no statistically significant difference in mortality between adults with cirrhosis and adults with non-variceal bleeding.

Restrictive transfusion was associated with a lower risk of rebleeding for all-cause acute upper gastrointestinal bleeding, and the effect was consistent for patients with cirrhosis and those with non-variceal bleeding. This finding has important implications for clinical practice because strategies to prevent rebleeding are a key part of the management of acute upper gastrointestinal bleeding.[1] For patients with liver cirrhosis, a liberal approach to transfusion can increase portal pressures, which is likely to directly mediate rebleeding.[19] The causes of non-variceal bleeding are incompletely understood but are thought to be related to impaired clot formation and stability because transfusion can counteract the splanchnic vasoconstrictive response to hypovolaemia and impair coagulation.[18]

Whether patients with ischaemic heart disease can be safely managed with a restrictive transfusion strategy is unclear. This issue is particularly relevant to patients with non-variceal bleeding, in whom comorbidity is common; almost 40% of these patients also have ischaemic heart disease.[3,20,21] In a meta-analysis[22] of transfusion strategies in more than 40 RCTs across various medical and surgical areas, a restrictive transfusion strategy (in most cases a threshold of 80 g/L) was associated with a 78% increased risk of a new acute coronary syndrome compared with a liberal transfusion strategy, which was statistically significant (absolute risk 2·7% liberal transfusion *vs* 4·6% restrictive transfusion), but no increased risk of mortality. Although we recorded no increased risk of acute coronary syndrome, these data should be interpreted with caution, since only one study reported this outcome[6] and the other large trial by Villanueva and colleagues excluded patients with a recent history of an ischaemic event at trial entry.[7] Thus, improving the evidence base for a safe transfusion threshold in patients with ischaemic heart disease is a research priority. Until further studies are done, we think that the default recommendations of a restrictive transfusion strategy should not apply to these patients.[23]

Our study has some limitations. First, differing transfusion thresholds were used in the trials, which could reduce the validity of pooling data since exposure to anaemia would be longer with lower values, although three of five trials set a restrictive threshold of 80 g/L of haemaglobin. Second, most of the data came from two RCTs, which could affect the generalisability of our findings. One of these trials was a feasibility trial and thus caution must be used to not overintepret these results; nonetheless, both trials used modern approaches to the management of acute upper gastrointestinal bleeding. The trial by Villanueva and colleagues[7] was an efficacy trial, done under strict protocols of care in a specialist institution with access to endoscopy within 6 h for all patients; therefore, these results should be interpreted in the context of each institution's access to endoscopic therapy, since this in itself could affect thresholds for transfusion and other clinical outcomes.[4,18] Third, we included few trials in our analyses so the subgroups are underpowered for the detection of small differences. Fourth, random effects meta-analysis using the DerSimonian–Laird method has limitations when the number of trials is small. However alternative frequentist strategies might be too conservative.[24] Fifth, we included data from studies done over a period of 30 years, which could lead to heterogeneity. Sixth, small numbers of patients were included in some of the subgroup analyses, which could affect the generalisability of the findings. Finally, we were unable to obtain further methodological or outcome data from the abstract presentation by Lee and colleagues,[14] or from the trial by Villarejo and colleagues.[15]

In conclusion, the results of this meta-analysis suggest that for patients with acute upper gastrointestinal bleeding, use of a restrictive transfusion strategy is associated with a reduction in mortality and rebleeding. These results may not apply to patients with ischaemic heart disease or severe haemorrhage, for whom decisions for transfusion should be based on clinical judgement and individualised risk.

Contributors

CD devised the search strategy. AO, MJRD, MT, and GSC acquired, analysed, and interpreted the data. SJB and SH did the statistical analyses. AJS, BCK, RFAL, MFM, and VJ provided original data from their studies. AO, MJRD, and VJ wrote the first draft. AO, MJRD, MT, AJS, CD, GSC, SH, SJB, BCK, RFAL, ANB, MFM, and VJ revised the report.

Declaration of interests

AJS, BCK, RFAL, MFM, and VJ were original authors of trials included in this systematic review. AO, MJRD, MT, CD, GSC, SH, SJB, and ANB declare no competing interests.

References

1 Jairath V, Barkun AN. Improving outcomes from acute upper gastrointestinal bleeding. *Gut* 2012; **61:** 1246–49.

2 Wells AW, Llewelyn CA, Casbard A, et al. The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfus Med* 2009; **19:** 315–28.

3 Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; **60:** 1327–35.

4 Jairath V. Acute upper gastrointestinal bleeding—time for some new triggers? *Transfus Med* 2013; **23:** 139–41.

5 Jairath V, Hearnshaw S, Brunskill SJ, et al. Red cell transfusion for the management of upper gastrointestinal haemorrhage. *Cochrane Database Syst Rev* 2010: CD006613.

6 Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet* 2015; **386:** 137–44.

7 Villanueva C, Colomo A, Bosch A, et al.Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368:** 11–21.

8 Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38:** 316–21.

9 Kahan BC, Jairath V, Murphy MF, Doré CJ. Update on the transfusion in gastrointestinal bleeding (TRIGGER) trial: statistical analysis plan for a cluster-randomised feasibility trial. *Trials* 2013; **14:** 206.

10 Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March, 2011), Cochrane Collaboration, 2011.

11 Sterne JAC, Egger M, Moher D, eds. Addressing reporting biases. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March, 2011), Cochrane Collaboration, 2011.

12 Deeks JJ, Higgins JPT, Altman DG, eds. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March, 2011), Cochrane Collaboration, 2011.

13 Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. *Br J Surg* 1986; **73:** 783–85.

14 Lee JM, Chun HJ, Lee JS. Target level hemoglobin correction in patients with acute non-variceal upper gastrointestinal bleeding. *Gastroenterology* 2014; **146:** abstract S-321.

15 Villarejo F, Rizzolo M, Lopez E, Domeniconi G, Arto G, Apezteguia C. Anemia aguda en la hemorragia digestiva alta. Márgenes de seguridad para su manejo sin transfusiones de glóbulos rojos. *Acta Gastroenterol Latinoam* 1999; **29:** 261–70 (in Spanish).

16 Campbell HE, Stokes EA, Bargo D, et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. *BMJ Open* 2015; **5:** e007230.

17 Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA* 2014; **311:** 1317–26.

18 Villanueva C. Gastrointestinal bleeding: blood transfusion for acute upper gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol* 2015; **12:** 432–34.

19 McCormick PA, Jenkins SA, McIntyre N, Burroughs AK. Why portal hypertensive varices bleed and bleed: a hypothesis. *Gut* 1995; **36:** 100–03.

20 Barkun A, Sabbah S, Enns R, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *Am J Gastroenterol* 2004; **99:** 1238–46.

21 Crooks CJ, West J, Card TR. Upper gastrointestinal haemorrhage and deprivation: a nationwide cohort study of health inequality in hospital admissions. *Gut* 2012; **61:** 514–20.

22 Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *BMJ* 2016; **352:** i1351.

23 Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF, Guideline Development Group. Blood transfusion: summary of NICE guidance. *BMJ* 2015; **351:** h5832.

24 Friede T, Röver C, Wandel S, Neuenschwander B. Meta-analysis of few small studies in orphan diseases. *Res Synth Methods* 2017; **8:** 79–91.