TRANSFUSION TRIGGERS IN CRITICAL CARE AND PERIOPERATIVE PATIENTS: A META-ANALYSIS OF RANDOMIZED TRIALS

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Introduction:

- The landmark Transfusion Requirements in Critical Care Trial has piqued interest in 'restrictive' versus 'liberal' transfusion thresholds for allogenic packed red blood cells (pRBCs) [1]
- While pRBCs restore oxygen carrying capacity, they also come with risks, are costly, and have limited supply [2]
- There has been concern that the balance of risk and benefit for a restrictive versus liberal transfusion strategy may be different for critical care and perioperative patients due to differences in pathophysiology and acuity or time-course of oxygen demands

Objective:

- To perform an updated meta-analysis of restrictive vs liberal transfusion strategies in critical care and perioperative patients, with particular focus on whether clinically-relevant outcomes differ between these two groups of patients

Methods:

Literature Search

- Comprehensive searches of Medline, Embase, and Cochrane Library were performed up to 15 October 2015 to identify randomized controlled trials (RCTs)

Study Selection

Population:
- Adult surgical or critically-ill patients

Intervention:
- 'Restrictive' versus 'Liberal' transfusion trigger defined by either hematocrit or hemoglobin concentration (e.g. 7g/dL versus 10g/dL)

Outcome:
- Primary: All-cause mortality at 30 days (or closest time)
- Secondary: Transfusions, myocardial infarction, stroke/TIA, heart failure, infection, and hospital length of stay

Data extraction and analysis

- Data were independently extracted in duplicate
- Random-effects meta-analysis was performed to derive odds ratios (OR) and weighted mean differences (WMD), including 95% confidence intervals (CI)
- Pre-defined subgroup analyses included critical care vs surgical setting; cardiac vs non-cardiac surgery; and study quality defined by the Cochrane Risk of Bias
- Tests for subgroup interaction were performed to test whether effect sizes differed significantly across subgroups
- Number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH) were calculated for significant ORs
- Trial sequential analysis was performed to assess whether sufficient sample size has been achieved across studies to support a definitive conclusion
- Funnel plots and Egger's regression were employed to assess for statistical evidence of publication bias

Figure 1: 30 Day Mortality for Restrictive vs Liberal Transfusion (Critical Care and Periop)

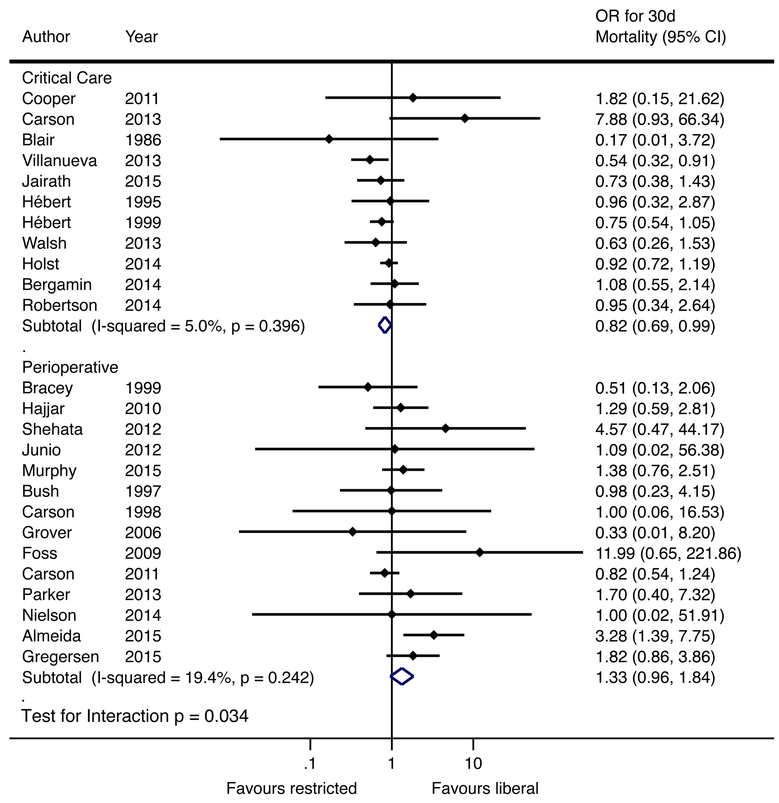

Table 1: Clinical Outcomes Summary for Prespecified Subgroups

Outcome	Subgroup	OR [95%CI]	NNTB or [NNTH]	Test for Interaction
Table 1A: Critical Care and Perioperative Care Subgroups				
Mortality	Critical Care	0.82 [0.69-0.99]	33	0.034*
	Perioperative	1.33 [0.96-1.84]	-	
Transfused Patients	Critical Care	0.04 [0.01-0.14]	2	0.113
	Perioperative	0.24 [0.09-0.66]	4	
Myocardial Infarction	Critical Care	0.71 [0.23-2.23]	-	0.174
	Perioperative	1.58 [0.99-2.49]	-	
Stroke/TIA	Critical Care	0.63 [0.40-0.99]	79	0.215
	Perioperative	1.00 [0.61-1.64]	-	
Renal Failure	Critical Care	1.00 [0.59-1.70]	-	0.783
	Perioperative	1.09 [0.87-1.36]	-	
Pneumonia	Critical Care	1.10 [0.57-2.14]	-	0.146
	Perioperative	0.45 [0.21-0.97]	101	
Transfusion Reaction	Critical Care	0.48 [0.25-0.92]	63	0.833
	Perioperative	0.99 [0.10-9.60]	-	
Table 1B: Non-Cardiac Surgery and Cardiac Surgery Subgroups				
Mortality	Cardiac	1.28 [0.82-1.98]	-	0.706
	Non-Cardiac	1.47 [0.86-2.52]	-	
Myocardial Infarction	Cardiac	1.15 [0.33-4.03]	-	0.628
	Non-Cardiac	1.66 [1.01-2.70]	[84]	
Other clinical outcomes did not differ for cardiac and non-cardiac subgroups				

*** denotes p < 0.05**

Results:

Eligible Studies

- Of 6055 citations screened, 25 RCTs were included (10,617 patients)
- Eleven trials were in the critically-ill and 14 were in perioperative patients
- Six of 25 studies were deemed to be at high risk of bias
- Statistical evidence of publication bias was not found

Mortality at 30 days

- In critical care patients, 30-day mortality was reduced for restrictive versus liberal transfusion (OR 0.82; 95% CI 0.69-0.99; NNT=33; Figure 1; p=0.035)
- However, in surgical patients, the restrictive strategy led to the opposite direction of effect for 30-day mortality (OR 1.33; 95% CI 0.96-1.84; Figure 1)
- The test for interaction across the critical care and surgical subgroups was significant (p=0.034), suggesting that the effect of restrictive transfusion is truly different in the critical care setting versus the perioperative setting (Table 1A)
- Trial sequential analysis demonstrated immaturity of the evidence base
- Within perioperative studies, subgroup analysis by cardiac versus non-cardiac surgery did not reveal significant difference for 30-day mortality (Table 1B)

Allogenic pRBC Utilization

- Fewer patients were transfused in the restrictive group compared with the liberal group (47% vs 75%; OR 0.127; 95%CI 0.061 – 0.263) (Table 1A)
- Fewer units of pRBCs were transfused for the restricted vs liberal group (-1.5 units; 95% CI -1.14 to -1.8; p<0.001).

Secondary Clinical Outcomes

Most secondary clinical outcomes did not reach statistical significance for the restrictive vs liberal approach with the exception of:
- In perioperative patients, pneumonia was reduced in the restrictive group (Table 1A)
- In critically-ill patients, stroke/TIA and transfusion reactions were reduced in the restrictive group (Table 1A). Hospital length of stay was also reduced (WMD -1.03 days; 95% CI -1.64, -0.42; p<0.001)
- In non-cardiac surgery patients, myocardial infarction was increased with a restrictive vs liberal approach (Table 1B)

Conclusion and Discussion:

- In critical care patients, a restrictive transfusion strategy may reduce the risk of mortality at 30 days, whereas in the perioperative setting there is an opposite direction of effect, indicating potential for increased risk of mortality
- The test for interaction across the critical care versus perioperative subgroups was significant, suggesting an underlying difference in the direction of mortality effect between the two groups
- Secondary clinical outcomes also supported potential benefits for a restrictive strategy in critical care patients (reduced stroke, transfusion reactions, length of stay), but not in perioperative patients
- Given the significant test for interaction and immature evidence base as demonstrated by trial sequential analysis, more randomized studies are necessary before a restrictive strategy—as advocated by ASA guidelines [3]—can be unequivocally recommended in perioperative patients

References: [1] Hebert P et al. (1999): NEJM; 340: 409-17; [2] Klein H et al. (2007): Lancet; 370: 415-26; [3] ASA Taskforce on Perioperative Blood Management. (2015): Anesthesiology; 122:241-75 **Acknowledgements:** We thank Jessica Moodie and Amy Newitt for performing the systematic searches.