Transfusion Medicine Reviews 28 (2014) 235–242

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Journal Club

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Transfusion policy after severe postpartum haemorrhage: a randomized non-inferiority trial. Prick BW, Jansen AJG, Hop WCJ, et al. *BJOG* 2014;121:1005-14.

The transfusion of red cells to the postpartum patient should be avoided whenever possible due to the risks of alloimmunization that could cause hemolytic disease of the fetus and newborn and transfusion-transmitted infections, as these individuals will certainly live long enough to manifest a symptomatic infection. I also inform such healthy patients with a long life ahead of them of the risk of alloimmunization to human leukocyte antigens that could complicate organ transplantation in the future. In addition, healthy young women should be able to tolerate greater degrees of anemia as compared to older, hospitalized patients who have been randomized into previous transfusion randomized trials. This large, multicenter trial randomized 521 women at 37 centers with postpartum hemorrhage and hemoglobin levels of 4.8 to 7.9 g/dL to transfusion or no intervention. Forty eight! The investigators found no clear benefit of transfusing red cells to these severely anemic women. It would have been clearer to call the "no intervention arm" the "transfusion for symptoms only arm," as transfusion was allowed for serious symptoms in this group.

To be eligible for this trial, women had to have experienced a postpartum hemorrhage (>1000 mL blood loss or a 1.9 g/dL drop in hemoglobin), have a hemoglobin between 4.8 and 7.9 g/dL between 12 and 24 hours of delivery, and be hemodynamically stable (no dyspnea, syncope, tachycardia, or chest pain). The following outcomes were evaluated: quality of life between 3 days and 6 weeks, postpartum complications (infections and thromboembolic events), and hemoglobin level at 6 weeks. Randomization was successful in generating 2 balanced groups of women.

The median blood loss for both groups of women was 1500 mL, and the median hemoglobin value at randomization was 7.4 g/dL (interquartile range, 6.8-7.7) in both groups. Women randomized to transfusion received a median of 2 U of red cells and were discharged with a higher hemoglobin level (9.0 g/dL vs 7.4 g/dL; $P < .001$). I wonder if all these women needed 2 U or whether a single-unit policy during the study could have prevented some more transfusions, as a hemoglobin of 9.0 g/dL is likely unnecessary in such a young patient population. Overall, 13% of the women randomized to no intervention were transfused for anemic symptoms post randomization (and 3% of the women randomized to transfusion were not transfused, most commonly due to refusal to be transfused). There were 3 transfusion reactions (1 minor allergic reaction and 2 febrile nonhemolytic reactions), all in the women randomized to transfusion. Despite more red cell transfusions, hemoglobin levels were identical in both groups at 6 weeks (12.0 g/dL). Women randomized to no intervention were substantially more likely to receive oral and/or intravenous iron therapy (88% vs 40%), possibly the cause for identical hemoglobin levels at 6 weeks.

In terms of fatigue scores, women randomized to no intervention had slightly worse fatigue scores at days 3 and 7, with minimal differences at days 21 and 42. Noninferiority could not be demonstrated for their primary outcome (Multidimensional Fatigue Inventory Scale at 3 days) as the confidence interval crossed the noninferiority boundary. The scale is from 4 to 20, where 20 represents maximal fatigue. A score of 7 would represent a median score for a well individual. A difference of 2 points is thought to represent a meaningful difference. At 3 days, the score was 15.68 in the transfused women, compared to 16.45 in the nonintervention arm. By 42 days, the scores were 8.69 and 8.95 for the transfused and no intervention groups, respectively. Length of stay, breast feeding rates at 6 weeks, and complication rates were similar.

One of the other interesting findings is a large number of women declined to participate in the study (490 women in total), primarily due to a refusal to be randomized to a transfusion arm.

The total number of red cells transfused was 517 U in the transfusion arm and 88 U in the no intervention arm. Widespread implementation of a restrictive transfusion strategy could potentially save a lot of red cells worldwide and protect women from unnecessary transfusion complications. I congratulate these investigators on their persistence in completing this 7-year study. It greatly contributes to our knowledge of when to transfuse a postpartum patient, and the results can likely be generalized to other young patients with a reversible anemia from acute hemorrhage. Another article from the last quarter (that did not make the cut for this *Journal Club*) went one step further and stopped measuring hemoglobin levels postpartum in the absence of symptoms requiring transfusion support and dropped their transfusion rate from 5.5% to 1.8% (Steele HB, and Goetzl L. The practical utility of routine postpartum hemoglobin assessment. *Am J Obstet Gynecol* 2014; epub ahead of print). (JC)

Cryopreserved red blood cells are superior to standard liquid red blood cells. Hampton DA, Wiles C, Fabricant LJ et al. *J Trauma Acute Care Surg* 2014;77:20-7.

Techniques to cryopreserve red blood cells have been available for decades. Typically, red cells are frozen in glycerol. Given the cost and time to freeze and then deglycerolize the units, cryopreservation is typically reserved for rare antigen-negative products. In addition, upon thawing, cells are lost, and the time to expiration of the red cell unit may be significantly shortened. With this background, the title of

http://dx.doi.org/10.1016/j.tmrv.2014.08.001
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the manuscript by Hampton et al is quite provocative. The actual data, however, do not appear to support such a bold conclusion.

The authors previously studied tissue oxygenation in trauma patients randomized to receive leukoreduced red blood cells (LRBC) more than 14 days old, less than 14 days old, or cryopreserved red blood cells (CRBC). As the authors found no statistical differences between patients receiving old or young LRBC, these groups were combined for analysis.

Samples were obtained from the patients before and after each transfusion (a maximum of 2) with a final sample obtained 12 hours after the last transfusion. For the current study, these samples were tested for a variety of cytokines (interleukin [IL] 2, 4, 6, 8, 10; tumor necrosis factor; granulocyte-macrophage colony-stimulating factor; and interferon γ), C-reactive protein (CRP), nitric oxide metabolites, and 2,3-diphosphoglycerate acid (2,3-DPG). The red cell units were also tested for CRP.

Thirty-five patients received LRBCs, and 22 received CRBCs. Not surprisingly, as CRBCs are deglycerolized, they had a significantly lower CRP concentration. In regard to patient samples, individuals who received LRBCs, but not CRBCs, had significantly elevated values for tumor necrosis factor, IL-8, and D-dimer 12-hour posttransfusion when compared to baseline (all reported as "$P < .05$"). Patients receiving CRBCs also had significantly higher levels of 2,3-DPG at 12 hours ($P = .01$). Although samples obtained immediately posttransfusion are not mentioned for most other analytes, the authors note that this increase in 2,3 DPG first occurred only after a second unit of blood was transfused. The above findings are the basis for the authors' claim of the superiority of CRBCs.

There are, however, several issues with this conclusion. Many "significant" findings were based on comparing baseline values to 12-hour posttransfusion. Given the other medical issues facing trauma patients over a 12-hour period and the small number of subjects, any changes in laboratory values may have nothing to do with transfusion. Second, although the differences may be "significant," if one does enough statistical tests (eg, comparing levels of many different cytokines at multiple time points), just by chance, some results will have *P* values close to .05. Lastly, even if the results are truly different between groups, the actual clinical significance is far from certain. For example, it is by no means clear how an elevated IL-8 translates into worse outcomes. As such, at this time, blood bankers should not stock up on glycerol or begin transfusing thawed units to improve clinical care. (RH)

Can doctors reduce harmful medical overuse worldwide? Hurley R. *BMJ* 2014;348:g4289

I selected this article, which is an editorial in a general journal. In fact, I do not think the article even mentions the word transfusion! This article discusses how to agree on lists of interventions that should be used with more caution by health care professionals—in other words, not at all! It provides for the reader information about the "Choosing Wisely" campaign, which began in the United States in 2012 and which is now inspiring interest beyond North America. An example of interventions highlighted as potentially harmful and unnecessary is medical imaging after the start of low back pain; other commonly overused interventions would include antibiotics for upper respiratory tract infections. There is also quite a compelling map on the first page illustrating the variation in rates of elective tonsillectomy in children in England.

The Choosing Wisely campaign was the subject of a meeting in Amsterdam following which this article was written, and the author followed up on a number of different relevant issues. It was agreed that there is a need for emphasis on encouraging better higher quality care: success requires professionalism in decision making by health care workers aimed at quality improvement, not cost cutting. Medical ownership of the campaign, with doctors deciding what should be included in the list of unnecessary interventions, was also important. This might, for example, get around concerns about lists being developed by government departments. Finally the Choosing Wisely campaign engages with public media to communicate to patients more effectively and to emphasize that costlier medicines and interventions may not always be necessary or needed.

Several other points of interest struck me in this editorial. I was surprised that a recent survey of 600 doctors had indicated that over a half of them would order a hypothetical test that they knew to be unnecessary if a patient insisted. Clearly, health care staff may order unnecessary interventions for many reasons, but recognizing the different reasons might help to understand why such diverse practice continues.

It is, of course, too early to say whether a campaign such as Choosing Wisely will reduce harm and indeed help increase efficiencies (and reduce health care costs), but I sense it is clearly part of a growing awareness that doing "nothing" or "less" is often the right option and needs promoting. Exposing patients to risks albeit sometimes small for unnecessary interventions helps no one.

As I said at the beginning, this article does not mention blood transfusion, but I think all of us will read across to transfusion medicine. Maybe, we all should be developing our own list of key or commonly overused transfusion indications or guidelines when not to transfuse. The American Association of Blood Banks has published a Choosing Wisely list, and Hibbs et al promptly published a letter in response to this editorial reminding the reader to also "transfuse wisely" (Hibbs SP and Murphy MF. Transfuse wisely. *BMJ* 2014 Jul 22; 349:g4701). Finally, I was also interested in a list of 5 questions provided by the Choosing Wisely campaign for patients to ask doctors about interventions:

1) Do I really need this test or procedure
2) What are the risks?
3) Are there simpler, safer options?
4) What happens if I don't do anything?
5) How much does it cost?

(SJS)

Feeding preterm infants during red blood cell transfusion is associated with a decline in postprandial mesenteric oxygenation. Marin T, Josephson CD, Kosmetatos N, et al. *J Pediatr* 2014; epub ahead of print.

Severe necrotizing enterocolitis (NEC) is a dreaded complication in very-low-birth-weight infants, associated with a high mortality rate and long-term morbidity in surviving infants. The etiology is thought to be multifactorial, but numerous publications have pointed the finger at transfusion as a triggering factor. Several creative acronyms have been developed: TRAGI (transfusion-associated acute gut injury), TR-NEC (transfusion-associated NEC), and TRAMI (transfusion-associated acute mesenteric injury). This publication suggests that the last term, *TRAMI*, may fit the underlying pathophysiology best. The hypothesis is that a proportion of NEC cases (perhaps up to one-quarter) have 3 things that line up to cause this entity: an immature gut, feeding during and/or after the transfusion, and then some iatrogenic injury from stored red cell transfusions. These authors sought to determine if mesenteric oxygenation was different when they compared infants who were fed during transfusion to infants whose physicians held their feeds. Remarkably, there was a difference. Note: There has been no documented increase in NEC in trials comparing liberal transfusion strategies vs restrictive strategies, hence leaving everyone uncertain as to whether this transfusion complication is a true entity.

This single-center study from the United States evaluated 19 infants less than 33 weeks of gestation in their intensive care unit who had an order for red cell transfusion and were hemodynamically