DOES TRANSFUSION OF RED BLOOD CELLS MAKE A PATIENT FEEL BETTER?

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In patients with anemia, there is interest in understanding the impact of red blood cell (RBC) transfusion on outcomes such as fatigue. However, data from previous studies are mixed as to whether transfusion is linked to improvements in fatigue. One explanation for this is that prior studies have not examined whether changes in fatigue from transfusion may also affect patient activity levels. This is important because if transfusion reduces fatigue, patients may become more active, which could increase their fatigue. Thus, testing whether transfusion affects patients' fatigability, a measure of fatigue in the context of activity, may be more useful than testing the effect of transfusion on fatigue alone.[1]

While guidelines such as those from the Association for the Advancement of Blood & Biotherapies (AABB) are primarily based on the concept that RBC transfusion decisions for most hospitalized patients be based on hemoglobin (Hb) concentration,[2] these often do not account for the presence of symptoms of anemia, including fatigue. Also, study results differ in whether transfusion is associated with improvements in fatigue.[3] In addition to good laboratory values, patients experiencing iron deficiency anemia (IDA) seek a high quality of life that does not include fatigue. Presently, there is a dearth of studies evaluating the role of RBC transfusion and patient quality of life. Four studies published in recent years that attempt to shed some light on this topic will be reviewed in this document.

ASSESSING SELF-REPORTED FATIGUE

The first is a prospective observational study that included hospitalized general medicine patients with Hb levels of 10 g/dL. Self-reported fatigue was measured by using the Patient-Reported Outcome Measurement Information Systems–Fatigue (PROMIS-F) instrument,[4] and self-reported physical function was measured by using the PROMIS–Physical Function (PROMIS-PF) with mobility aid instrument. The PROMIS-PF measures self-reported physical activity performance based on whether a patient is able to ambulate 25 feet on a level surface.[1,4] Patient-reported fatigability was collected during hospitalization and by telephone seven days after discharge from the hospital. Among the 350 patients participating, transfusion was associated with lower fatigability levels seven days post hospital discharge (change in fatigue = β =–2.9; P = .03). Compared with patients receiving no transfusion, patients receiving either a 1-unit (U) (β = –2.6; P = .35) or

2- to 3- U (β = –7.3; P = .02) transfusion during hospitalization had lower fatigability levels seven days post hospital discharge. In patients receiving 2 to 3 U of RBCs, the reduction in fatigability levels at seven days post-discharge was not only statistically significant, but the reduction in fatigability (β = –7.3) was nearly three times that of a 1-U transfusion, and almost a one standard deviation (SD = 9) decrease from baseline (inpatient) fatigability levels. The authors concluded that transfusion during hospitalization reduces fatigability levels in patients with anemia after hospital discharge.[1]

The second study is a prospective observational study of hospitalized general medicine patients with Hb <9 g/dL. Fatigue was measured during an in-person interview and a 30-day post-discharge phone interview. Hb values and receipt of a transfusion were collected from hospital administrative data.[5]

Baseline fatigue was measured once during the patient's hospitalization with an in-person interview either on the first day of hospital admission for patients eligible or the day the patient became eligible for the study (Hb <9 g/dL at any point during hospitalization). Fatigue was again measured with a phone call 30 days post hospital discharge. The timing for the follow-up phone call was chosen because the effects of hospitalization from acute illness on fatigue may have diminished, yet the effect of the increase in blood count from transfusion is expected to remain significant.[5] Fatigue was measured using a 13-question fatigue subscale that is part of the Functional Assessment of Chronic Illness Therapy Anemia (FACIT-An) questionnaire.[6] The fatigue subscale measures patient fatigue throughout the past seven days, with scores ranging from 0 to 52, where lower scores reflect greater levels of fatigue.[6] A total of 9,676 patients were admitted to the general medicine service during the study period. A total of 6,189 (64%) patients consented for participation in the study and 4,442 (72%) patients completed the inpatient interview. A total of 1,429 (32%) of these patients had Hb <9 g/dL, and 1,135 (79%) of these patients completed the inpatient FACIT questionnaire. A total of 763 (67%) patients were reached for the 30-day follow-up interview; 513 (67%) of these completed the 30-day follow-up FACIT questionnaire.[5] The results demonstrated that the interaction between transfusions and the patient's nadir Hb was associated with reduced fatigue post-discharge for patients with higher baseline fatigue (20% most fatigued: β = 12, P = 0.02; 10% most fatigued: β = 17, P = 0.02). Patients aged <50 years with high baseline fatigue had significant reductions in fatigue from transfusion (20%: β = 23, P = 0.02; 10%: β = 29, P = 0.03). The authors concluded that in hospitalized patients with anemia, RBC transfusion during hospitalization is associated with reduced fatigue 30 days post-discharge for patients with high levels of baseline fatigue.[5]

ASSESSING COMORBIDITIES AND TRANSFUSION FREQUENCY

The third study was conducted in Turkey. Its main goal was to investigate the impact of comorbidities and transfusion frequencies on the quality of life of patients with myelodysplastic syndromes (MDS).[7] Each patient was asked to complete the SF-36 quality of life questionnaire upon study entry. SF-36 is a set of generic, coherent and easily administered quality-of-life measures with a scoring range of 0 as the lowest and 100 as the highest. These measures rely upon patient self-reporting and have been widely used.[8] One hundred and four patients with MDS were enrolled in the study. Quality-of-life assessment was done at study entry using the SF-36 questionnaire, which resulted in physical and mental component scores of 39.8±9.7 and 42.6±11.4, respectively. Of the 104

patients with MDS included in the study, the median number of RBC and platelet transfusions were 2 (range: 0 – 128) and 0 (range: 0 – 58), respectively. The number of RBC transfusions was found to have significant positive correlation with both physical and mental component scores of SF-36 test ($p = 0.042$, $p = 0.018$). However, this was not seen with platelet transfusions. The authors concluded that before treatment decisions for MDS patients, a quality of life score should be determined.[7]

The fourth study, Transfusion Requirements in Cardiac Surgery III (TRICS III), a multi-center randomized controlled trial, examined restrictive versus liberal RBC transfusion for patients undergoing cardiac surgery. However, it is uncertain if transfusion strategy affects long-term health-related quality of life (HRQOL).[9] In this planned sub-study of Australian patients in TRICS III, the authors sought to determine the non-inferiority of restrictive versus liberal transfusion strategy on long-term HRQOL and to describe clinical outcomes 24 months postoperatively. The restrictive strategy involved transfusing RBCs when hemoglobin was <7.5 g/dL; the transfusion triggers in the liberal group were: <9.5 g/L intraoperatively, <9.5 g/L in intensive care, or <8.5 g/dL on the ward. HRQOL assessments were performed using the 36-item short form survey version 2 (SF-36). Primary outcome was non-inferiority of summary measures of SF-36 at 12 months. Secondary outcomes included noninferiority of HRQOL at 18 and 24 months.

Six hundred seventeen patients received allocated randomization; HRQOL data were available for 208 of 311 in the restrictive and 217 of 306 in the liberal group. After multiple imputation, non-inferiority of restrictive transfusion at 12 months was not demonstrated for HRQOL, and the estimates were directionally in favor of liberal transfusion. Non-inferiority also could not be concluded at 18 and 24 months. After conversion of individual SF-36 data into SF-6D (6-dimensional health state short form)[10] data (expressed as a value between 0 and 1), the differences in QALYs (restrictive group minus liberal group) throughout 24 months between transfusion groups was -0.038 (95% CI -0.103 to 0.028) and did not reach statistical significance ($p = 0.268$). The authors concluded that in this multi-center RCT, non-inferiority could not be established with a restrictive compared to a liberal transfusion strategy for patients undergoing cardiac surgery at moderate risk of complications with regard to HRQOL at 12 months. Further analysis suggested that noninferiority could not be established at either 18 or 24 months. The study raised the question of possible long-term reduction in HRQOL with restrictive strategies.[9]

CONCLUSIONS

The four studies reviewed affirm the need to not just transfuse based on laboratory values but also on how a transfusion may affect the patient's quality of life. The potential variation in the effect of transfusion on fatigue by patients' baseline fatigue level is important because the severity of a patient's fatigue represents the physiologic burden of their anemia, so that patients with higher fatigue levels may be more likely to benefit and experience reduced fatigue from a transfusion. Since anemia has multiple pathophysiologic mechanisms, patients with the same Hb concentration but different clinical characteristics (i.e. comorbidities, age) may experience different levels of fatigue from their anemia.[11] Therefore, understanding whether the effect of transfusion on fatigue varies by patients' baseline fatigue, may help clarify whether transfusion during hospitalization

improves patients' fatigue. Moreover, it may help clinicians understand whether measures of patients' fatigue should be incorporated, along with Hb concentration, into transfusion decisions for hospitalized patients with anaemia.[5] The relationship between transfusion strategy and long-term HRQOL is expected to reflect the balance between the short and long-term risks associated with RBC transfusion[12,13] against the benefits of avoiding transient lower hemoglobin values during the intervention period.[9]

Future studies should track hemoglobin levels more closely after discharge; and explore metrics such as the rate of rise of Hb after blood loss or the time spent below anemia thresholds rather than an absolute Hb value at a single point in time; while concurrently measuring physical and mental ability beyond the short term.[9] More work needs to be done. All four studies called for additional research on this important, but a sometimes underappreciated question remains: does transfusion make a patient feel better?

1. Prochaska MT, Zhang H, Babajide R, Meltzer DO. The effect of red blood cell transfusion on fatigability after hospital discharge. *Blood Adv*. 2020;4(22):5690-5697. doi:10.1182/bloodadvances.2020003364
2. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA*. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
3. Prochaska MT, Newcomb R, Jiang D, Meltzer DO. The effect of red-blood-cell transfusion on fatigue in hospitalized patients with anaemia. *Vox Sang*. 2018;113(7):669-677. doi:10.1111/vox.12704
4. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 Suppl 1):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55
5. Prochaska MT, Newcomb R, Jiang D, Meltzer DO. The effect of red-blood-cell transfusion on fatigue in hospitalized patients with anaemia. *Vox Sang*. 2018;113(7):669-677. doi:10.1111/vox.12704
6. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*. 1997;13(2):63-74. doi:10.1016/s0885-3924(96)00274-6
7. Sarici A, Ar MC, Yokus O, et al. The impact of transfusion burden and comorbidities on the prognosis of patients with myelodysplastic syndromes. *Transfusion and Apheresis Science*. 2020;59(5). doi:10.1016/j.transci.2020.102845
8. RAND Corporation. 36-Item Short Form Survey (SF-36). Published 1992. Accessed February 11, 2023. *https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html*
9. Hu RT, Royse AG, Royse C, et al. Health-related quality of life after restrictive versus liberal RBC transfusion for cardiac surgery: Sub-study from a randomized clinical trial. *Transfusion*. 2022;62(10):1973-1983. doi:10.1111/trf.17084
10. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271-292. doi:10.1016/S0167-6296(01)00130-8
11. Prochaska MT, Newcomb R, Block G, Park B, Meltzer DO. Association Between Anemia and Fatigue in Hospitalized Patients: Does the Measure of Anemia Matter? *J Hosp Med*. 2017;12(11):898-904. doi:10.12788/jhm.2832
12. Bhaskar B, Dulhunty J, Mullany D v., Fraser JF. Impact of Blood Product Transfusion on Short and Long-Term Survival After Cardiac Surgery: More Evidence. *Ann Thorac Surg*. 2012;94(2):460-467. doi:10.1016/j.athoracsur.2012.04.005
13. Shishehbor MH, Madhwal S, Rajagopal V, et al. Impact of Blood Transfusion on Short- and Long-Term Mortality in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2009;2(1):46-53. doi:10.1016/j.jcin.2008.09.011