HOW DO I SELECT EVIDENCE-BASED TRANSFUSION THRESHOLDS FOR IMPLEMENTING PATIENT BLOOD MANAGEMENT WITH RED BLOOD CELLS?

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Building a patient blood management (PBM) program involves establishing standards or benchmarks from which to measure performance. Blood transfusion, a tangible treatment modality, is often the primary emphasis and one that holds enhancement opportunities. When considering red blood cell (RBC) transfusion, it is important to determine for each patient when it is necessary and beneficial and when it could potentially be inappropriate or harmful.

EVIDENCE

The seminal work of Hébert et al. presented the concept of restrictive transfusion practice as non-inferior to the liberal utilization of RBCs.[1] Its results, along with those of numerous other similar studies, remain relevant today. A recent systematic review examined 30-day mortality and clinical outcomes among adults and children (excluding neonates) in medical and surgical settings.[2] The review comprised 48 trials with data from 21,433 participants. The most frequently used restrictive and liberal thresholds were hemoglobin (hgb) levels from 7.0 to 8.0 g/dL and 9.0 to 10.0 g/dL, respectively. The data showed that a restrictive transfusion threshold reduced the risk of receiving at least one RBC unit by 41% (risk ratio [RR] 0.59, 95% confidence interval [CI] 0.53 to 0.66) with a large degree of heterogeneity between trials ($I^2 = 96\%$). Restrictive thresholds did not impact 30-day mortality or morbidity (e.g., infection, pneumonia, thromboembolism, stroke, myocardial infarction [MI] or cardiac events) when compared with a more liberal strategy. The safety of a restrictive approach remains unclear in specific clinical situations, including chronic cardiovascular disease, brain injury, thrombocytopenia, chronic bone marrow failure, cancer or hematological malignancies. These findings provide a level of confidence when setting thresholds at the restrictive range, but acknowledge that there are clinical states where a higher threshold is acceptable until more evidence suggests otherwise.

Patients in better overall health are more likely to tolerate a restrictive strategy for RBC transfusion than those who are ill or experiencing multiple co-morbidities. A re-analysis of the original Hébert et al. study revealed potential risk associated with restrictive thresholds in patients with ischemic heart disease and those with high acute physiology and/ chronic health evaluation (APACHE) scores.[3] It should also be noted that for patients undergoing cardiac surgery, the mortality rate was higher in the restrictive transfusion group (4.2 vs. 2.6% $p<0.05$).[4]

Ducrocq et al. explored if restrictive transfusion is clinically non-inferior to liberal practices for major adverse cardiovascular events (MACE).[5] MACE includes all-cause mortality, recurrent MI, stroke or ischemia resulting in emergency revascularization at 30 days. The thresholds used for the restrictive and liberal cohorts were hgb levels of ≤8.0 g/dL and ≤10.0 g/dL, respectively. Non-inferiority was defined as a 1-sided 97.5% CI for a relative risk of the primary outcome to be less than 1.25. The results demonstrated that the restrictive transfusion strategy was non-inferior to the liberal strategy, which showed a risk ratio of 0.79 [1-sided 97% CI, 0.00-1.18]. However, the CI for acute MI and anemia was above the non-inferiority level, thus suggesting that caution should be used in applying restrictive strategies in these circumstances.

Vincent cautions against the use of strict application of guidelines derived from randomized controlled trials (RCT) that used hgb as the only threshold for transfusion.[6] Instead, several clinical indicators need to be taken into consideration when weighing the merits of transfusion as a treatment modality. The use of big data and artificial intelligence could potentially identify which factors are applicable to guide transfusion decisions.

CLINICAL INDICATIONS

Several studies have continued to underscore that hgb or hematocrit should not be the sole clinical signal for transfusion. Nevertheless, hospital transfusion criteria often include laboratory values as thresholds and apply ambiguous language, such as "symptomatic anemia" or "failure of conservative measures." The American Red Cross recommends RBC transfusion for patients with symptoms occurring from tissue hypoxia or lack of oxygen-carrying capacity caused by insufficient red cell mass, patients in need of an exchange transfusion, and acute blood loss not responsive to crystalloid volume replacement. RBC transfusions are contraindicated to treat anemia that can be managed with other therapies such as pharmaceuticals. RBCs should not be transfused as a means to increase blood volume, augment wound healing or make a patient feel better.[7]

AABB guidelines for RBCs are based on RCTs investigating hgb thresholds and length of storage.[8] The guidelines do not endorse RBC transfusion until the hgb level is at least 7.0 g/dL for stable hospitalized patients, including those in intensive care. For patients undergoing cardiac or orthopedic surgery, or those with pre-existing cardiovascular disease, a threshold of 8.0 g/dL is recommended. Threshold exclusions include hematology/oncology patients at risk for bleeding, those with acute coronary syndrome and those dependent upon transfusion therapy. Storage age of RBC units for adults and neonates should not be limited to fresh blood only but utilized within standard issue dating (i.e., 3-4 weeks). A general practice statement is included in the guidelines suggesting that other clinical parameters and alternatives should be included in the transfusion decision-making process.

There is a general consensus that one threshold does not fit all patients and that further precision prescribing is applicable for more complex patients. Several societies, including the American

Society of Anesthesiologists[9], the Society of Thoracic Surgeons[10], the American College of Physicians[11] and others, have also developed RBC guidelines.

In recent years, challenges with the blood supply have the questions about best practices for the thresholds to determine when to transfuse. In particular, researchers have questioned if a hgb of 6 g/dL is a safe threshold for a subset of hemodynamically stable non-bleeding patients.

Goal-directed therapy for RBC administration aims to meet the body's demand for oxygen, especially for vital organs such as the brain, which is sensitive to hypoxia. Physiologically, there exists an oxygen reserve as delivery exceeds consumption fourfold. If the intravascular volume is maintained and cardiac status is unimpaired during a bleeding event, oxygen delivery will theoretically be sufficient until the hematocrit falls below 10%. This occurs through a compensatory mechanism consisting of increases in cardiac output, a right shift of the oxygen-hgb dissociation curve and surges in the extraction of oxygen.[12] In one study, healthy resting adults were bled to a hgb of 5 g/dL without impairment of critical oxygen delivery.[13] However, the oxygen-carrying capacity of blood does not reflect the delivery to tissues. The intervening variable is the ability to resist hypoxia through compensatory mechanisms, which differ by individual.

Clinical measures that reveal compensatory mechanisms are heart rate, blood pressure, urine output and respiratory rate. Hgb and hematocrit do not measure oxygen delivery or metabolic demand. However, central venous oxygen saturation (Svo_2) captures the balance between oxygen delivery and consumption. This was studied in cardiac surgery through a RCT with a RBC threshold of hgb <9 g/dL and Svo_2 less than 65%. As a result, fewer patients were transfused with the Svo_2 parameter (68% vs. 100%). Although the study was underpowered for safety, the results show promise for future trials that explore physiologic measures to guide RBC transfusion decision-making.[14]

PBM PROGRAM GUIDELINE APPLICATION

Choosing RBC thresholds for adoption can be accomplished through the acceptance of an existing guideline. Available guidelines use a restrictive hgb threshold of ≤7 g/dL, with exceptions when a higher threshold may be appropriate. Electronic health records (EHR) allow for improved decision support and the addition of clinical indications to the ordering process. As a result, organizations have embedded clinical criteria into the blood ordering process. Defaulting the RBC unit quantity to a single unit encourages the transfusion of one unit at a time and then reassessing the patient based upon a post-transfusion laboratory value and clinical condition before ordering additional units.

Going through the process of choosing RBC thresholds, then implementing them, only makes sense if there will be ongoing measuring of adherence. Areas for quality and safety improvements can be discovered through adherence evaluation. This can be accomplished by gathering data for RBC transfusions by pre-transfusion hgb values and determining the percentage meeting hgb threshold criteria (hgb ≤ 7 g/dL), possible exceptions (hgb 7.1 – 8.0 g/dL) and those potentially outside of guidelines (hgb > 8.0 g/dL). Transfusions given outside established thresholds can be reviewed to determine if the RBC transfusion was warranted due to active bleeding, hemodynamic instability, or another reason that would not be reflected in the data report and may require chart review.

Moerman et al. used post-transfusion hgb to gauge practices to mitigate the limitation that pre-transfusion thresholds do not account for the clinical setting, making it difficult to determine if a transfusion was appropriate. Although the post-transfusion threshold was set at >10.5 g/dL communication of the data resulted in a 21% decrease in blood utilization.[15] In addition, restrictive transfusion adherence was studied in a medical intensive care unit finding that 30% of RBC transfusions occurred at hgb ≥ 7 g/dL with 12.3% of patients without clinical indicators for the transfusion.[16] These results suggest that, despite the dissemination and publication of clinical guidelines as well as efforts of PBM programs, non-beneficial RBC transfusions continue to occur.

CONCLUSION

Hgb values are insufficient to use solely as the basis of RBC transfusion decision-making but can be used in tandem with physiological factors and comorbidities. A current limitation is the unavailability of a noninvasive means of accurately and reliably measuring oxygen delivery and oxygen consumption and the ability to determine when demand exceeds supply. The evidence supports a restrictive transfusion strategy as being safe with allowances for instances when a higher threshold may be more efficacious. Beyond establishing RBC transfusion guidelines, a method to measure adherence should be included with implementation.

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