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REVIEW ARTICLE

Transfusion thresholds: the need for a patient-centered approach in hematologic disorders that require chronic transfusion therapy

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Abstract

Transfusion is an essential life-sustaining treatment for many patients. However, unnecessary transfusion has been reported to be related to worse patient outcomes. Further, owing to the recent pandemic, blood supply has been more challenging to maintain. Many studies have been conducted to elucidate the optimal transfusion threshold for many clinical conditions, and most suggested that a restrictive transfusion strategy has advantages over a liberal transfusion strategy. Hematologic disorders, which require chronic transfusion in many cases, have not been the main subjects of such studies, and only little evidence is available regarding the optimal transfusion threshold in these patients. According to several recent studies, a liberal transfusion strategy is preferable for patients with hematologic disorders due to their quality of life. A patient-centered approach is needed for proper management of hematologic disorders.

Key Words Transfusion threshold, Hematologic disorders, Quality of life

INTRODUCTION

After the discovery of the first human blood groups (ABO) by Dr. Landsteiner in 1900, blood transfusion became a key life-saving intervention for many patients [1, 2]. The excessive use of blood transfusions has recently been demonstrated to negatively affect patient outcomes; hence, high expectations are being placed on patient blood management (PBM) programs, which can induce proper blood transfusion [3-5]. In particular, owing to the decrease in blood donation and blood supply worldwide after the emergence of coronavirus disease 2019 (COVID-19), the identification of appropriate transfusion thresholds has garnered increasing interest [6, 7]. Many studies have been conducted to determine appropriate transfusion thresholds; however, only few have focused on hematologic disorders that require chronic transfusion therapy. This review aimed to outline how appropriate thresholds can be set for red blood cell (RBC) transfusion based on up-to-date study results.

BASICS OF RBC TRANSFUSION

The goal of RBC transfusion is to improve the oxygen supply [8]. Accordingly, in principle, blood transfusion is not necessary if the oxygen supply to tissues is appropriate, even if the hemoglobin (Hb) level is low. However, no method is available to directly assess or measure the adequacy of the oxygen supply to tissues. Surrogate markers for Hb levels are usually used to determine whether blood transfusion is required in practical settings. Nevertheless, the necessity of blood transfusion must be evaluated based on the patient's clinical conditions, rather than the use of laboratory parameters alone [8].

TRADITIONAL APPROACH FOR ASSESSING TRANSFUSION THRESHOLD

For several years, the decision to transfuse RBCs in daily clinical practice was based on the traditional "10/30 rule" (Hb level of 10 g/dL or hematocrit of 30%). Originally, this rule was established to improve surgical outcomes in high-risk patients undergoing anesthesia but has been commonly used in clinical settings without in-depth consideration [9]. As concerns over the impact of blood transfusion-related side effects and blood transfusion on long-term clinical manifestations have been raised, more questions regarding such transfusion practices have also been raised.

The strategy based on the existing "10/30 rule" is called the "liberal transfusion strategy (Hb 9–10 g/dL)," and the strategy based on a lower RBC transfusion threshold (Hb 7–8 g/dL) is called the "restrictive transfusion strategy." Several studies have been conducted in this regard. For example, Holst *et al.* [10] determined the effects of two Hb thresholds on patient outcomes among patients with septic shock in the intensive care unit (ICU) who underwent transfusion at an Hb threshold of 7 g/dL compared with those who underwent transfusion at an Hb threshold of 9 g/dL. Based on the results, patients who were treated at the restrictive transfusion threshold and those who were treated at the liberal transfusion threshold had similar mortality, suggesting that restrictive transfusion strategies are useful. Notably, similar results were found in diverse patient groups, and a recent meta-analysis also reported these results [11]. In the study, 48 trials conducted with 21,433 patients were analyzed and the following clinical manifestations were reported: orthopedic surgery, cardiac surgery, vascular surgery, critical care, acute blood loss, acute coronary syndrome, cancer, leukemia, and other hematologic malignancies. According to the study, transfusion at the restrictive transfusion threshold decreased the proportion of patients exposed to transfusion by 41%; however, no study suggested that restrictive transfusion strategies significantly affected 30-day mortality or outcomes [11].

Based on these results, many studies, including the American Association for Blood Bank (AABB) clinical practice guidelines, recommend transfusion based on an Hb level of 7 g/dL, except for patients with clinically evident cardiovascular problems [12, 13]. Recent indicators for the appropriateness of transfusion implemented by the Health Insurance Review and Assessment Service consider Hb levels of <7 g/dL as the level at which transfusion is appropriate.

CHRONIC TRANSFUSION-DEPENDENT ANEMIA

Despite the availability of evidence, only few studies have been conducted on malignant/non-malignant hematologic disorders that require chronic transfusion therapy. The aforementioned meta-analysis reported that the lack of evidence on hematologic malignancies, including chronic bone marrow failure, was a limitation. Furthermore, the AABB guidelines do not provide any recommendations for chronic transfusion-dependent anemia due to a lack of evidence [11, 12, 14].

Several studies have been conducted on this topic. In a study that assessed the quality of life (QoL) of 50 patients with myelodysplastic syndrome (MDS), decreased QoL was observed for patients with chronic anemia and low Hb levels [15]. In addition, Vijenthira *et al.* [16] evaluated the experience and preference of patients with MDS (N=447) in the U.S., U.K., and Canada and reported that patients experienced pre-transfusion fatigue and dyspnea and had decreased QoL. Large variations were noted in personal preference for transfusion thresholds; however, 62% and 20% of patients preferred to have transfusion when their Hb levels were 8.5 g/dL and 10.0 g/dL, respectively. This finding was significantly different from those of previous studies and guidelines. St Lezin *et al.* [17] measured the 6-min walk distance and fatigue/dyspnea-related QoL of 208 cancer patients (hematologic/oncology) who underwent outpatient-based transfusion. According to their results, a high Hb level improved both the walk test distance and fatigue score.

Few randomized controlled trials (RCTs) have been conducted with patients with chronic transfusion-dependent anemia, and notable results have recently become available. An RBC-Enhance study compared the outcomes of liberal vs. restrictive transfusion thresholds in 28 patients [with MDS, chronic myelomonocytic leukemia (CMML), and low blast acute myeloid leukemia (AML)] who underwent transfusion at three institutions. The results revealed that patients in the liberal arm had improved QoL, despite an increase in the transfusion volume [18]. Stanworth *et al.* [19] compared liberal and restrictive transfusion strategies in 38 patients with MDS (in the U.K., Australia, and New Zealand). In this study, a group of patients who underwent liberal transfusion strategies showed better compliance with transfusion thresholds and improved QoL. Morton *et al.* [20] compared restrictive transfusion strategies (Hg, 7 g/dL) to liberal transfusion strategies (Hb, 9 g/dL) in 43 patients with AML using a crossover design. Although the group of patients with liberal transfusion strategies had more transfusion volume (median, 6 vs. 9 units), they had improved QoL scores (median, 55 vs. 65). In addition, in the group of patients with liberal transfusion strategies, no transfusion was conducted based on symptoms, regardless of Hb target levels. However, in the group of patients with restrictive transfusion strategies, 14 transfusions were performed owing to the symptoms. Accordingly, restrictive transfusion strategies negatively affect the subjective symptoms experienced by patients.

TRANSFUSION FOR PATIENTS WITH HEMATOLOGIC DISORDERS

Unlike acute care conditions, a transfusion-related strategy should vary for diseases requiring chronic transfusion, such as MDS [21]. Most previous studies on transfusion thresholds were based on the 30-day mortality or morbidity [10-12, 14]. However, simple mortality and morbidity, as well as subjective symptoms experienced by patients on long-term treatment and QoL should be considered in patients with hematologic disorders requiring chronic transfusion, such as MDS. The British Society for Hematology guidelines suggest that the severity of anemia in patients with MDS is associated with QoL and an individual patient-centered symptom-based approach is necessary rather than Hb level. Accordingly, RBC transfusions should be conducted for patients with symptomatic anemia, and patient-centered factors should be considered. Further, iron chelation therapy should be considered, and active management is necessary in patients with MDS who frequently undergo transfusion [22].

The European LeukemiaNet recommends the following

transfusion goals: 1) improve QoL, 2) prevent anemia-related symptoms, and 3) prevent ischemic organ damage. To achieve these goals, decisions on transfusion should be made by considering the patient's symptoms and comorbidity rather than using a single Hb threshold. Nevertheless, generally, it is emphasized that patients with severe anemia (Hb <8 g/dL) or symptomatic anemia (Hb ≥8 g/dL) should undergo transfusion. In addition, iron chelation therapy should be considered in advance for patients who are transfusion-dependent or for those who will undergo allogeneic stem cell transplantation [23].

Despite its low prevalence in Korea, the usefulness of hypertransfusion therapy that deliberately maintains high hemoglobin levels in patients with hemoglobinopathy, such as sickle cell diseases, has been questioned [24]. Thus, restrictive transfusion strategies that are commonly used in patients with non-hematologic disorders should be cautiously considered for patients with hematologic disorders.

CONCLUSIONS

Transfusion sometimes induces side effects, and the transfusion itself affects patient outcomes. However, transfusion also saves many patients' lives and improves their QoL. Patient-centered decision-making is always needed to develop the best transfusion strategy. We anticipate the need for many studies on this topic in the future, and the implementation of evidence-based transfusion practices.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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