

Clinical Commentary: The Transfusion Trigger – The Search For A Quantitative Holy Grail

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The decision to transfuse blood before or during an operation has begun to be called the “transfusion trigger.” For many years, a fixed value of blood hemoglobin concentration was used as the main “trigger” (usually 10 g/dl) in a pre-operative patient. It was based on little scientific data and took little account of the patient’s condition. Further, Belk and Sunderman [1] and others showed that assays of blood hemoglobin were unstandardized and the results were often inaccurate.

In 1988, an NIH Consensus Conference reconsidered the de facto standard criterion for peri-operative blood transfusions and added a consideration of the patient’s clinical condition [2], but even this recommendation was based on limited data. The revised guidelines state that most patients will not need preoperative blood transfusion if the blood hemoglobin level is ≥ 10 g/dl, but probably will require transfusion if the level is ≥ 7 g/dl. The guidelines stress that the decision to transfuse also depends on clinical criteria such as the duration of anemia, the patient’s intravascular volume, the probable extent and continuation of blood loss, the probability of massive blood loss, and various coexisting medical factors. These factors must be balanced against the small but real hazards of receiving blood. Only after these conditions have been considered can a decision be reached as to if, how much, and when the blood should be given.

When a person has been injured and has lost a significant amount of blood, there is little question

that sooner or later the patient will need to be transfused. However, the decision to transfuse can be complicated by the clinical condition of the patient. A clinical decision is required to determine if blood is to be transfused, when it is to be given, how much to give, the patient’s response to the blood loss, and the anticipation of further loss of blood and its quantity, weighing the need for blood against the small hazards of blood transfusion.

Blood transfusion has only one goal—to increase the oxygen carrying capacity of the body. As Weiskopf [3] states, “We transfuse red cells to treat or prevent *imminent* inadequate delivery of oxygen to tissues, with consequent tissue hypoxia.” Three types of clinical decisions exist with a surgical patient. The first is pre- or peri-operative transfusion, ie, getting the patient in the best possible condition for surgery. This is dependent on the condition of the patient prior to surgery both medically and surgically. The second is intra-operative transfusion, ie, maintaining the patient’s condition during surgery. This depends on the amount of blood lost during surgery, the other fluids and drugs that are given, and the patient’s response to the anesthetic and the surgery. The last is post-operative transfusion, ie, keeping the patient stable after surgery. This is dependent on the condition of the patient at the end of surgery, the loss of blood from oozing after surgery, and the other fluids that are given. Each of these conditions involves a somewhat different set of criteria to assess the need for transfusion. In this commentary, we shall deal only with the first decision—pre-operative transfusion.

One of the most pervasive rules in transfusion medicine has been (and to a certain extent still is)

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that a patient should be transfused prior to surgery if the blood hemoglobin concentration is determined <10 g/dl (ie, hematocrit <30%). If the value is 9.9 g/dl, a transfusion often was given, but 10.1 g/dl meant no transfusion, even though these three values might all represent the same hemoglobin concentration, depending on the analytical method and its reproducibility. This practice has been passed from surgical resident to resident with little or no confirming study. A few voices have cried in the wilderness, saying “consider the patient, the disease, the symptoms, and the hazards of transfusion,” but not many listened. As one of my surgery professors once exclaimed, “When I want strawberry juice, I want it now and don’t bother me with a lot of malarkey.” How did this attitude become ingrained in the thinking of the medical community?

To understand this attitude, one must examine the roots of transfusion medicine in the United States at the beginning of the 20th Century. The first recorded blood transfusion in America was performed by Dr. Alexis Carrel in 1908 for a newborn who was suffering from “melena neonatorum” [4]. This disease was commonly thought at that time to be caused by an intestinal infection, rather than by vitamin K deficiency. The patient’s father, a young surgeon in New York City, felt that since the infant was losing blood, a transfusion might help. Moreover, he suggested that, since Dr. Carrel had been performing blood vessel anastomoses on animals, he might be able to perform a direct anastomosis between the infant and a donor (the father), allowing blood to be transfused. The operation was performed and the child was cured [4]. In this case, the transfusion was indicated and effective and the amount of blood transfused was appropriate, even though the cause of the disease was not known at that time.

In the following years, transfusions became more common, but since almost all were performed by direct blood vessel anastomosis of a donor to the patient (a few did use the multiple syringe technique) transfusion was usually performed with reluctance and then only administering a moderate amount of blood. Transfusion was performed until the patient felt better or the donor felt worse. Salem [5] stated that, at the turn of the 20th Century, a blood

hemoglobin level <30% of normal was considered unsafe because it left no margin for anesthetic errors. In 1899, Fish [6] endorsed the idea of not subjecting patients to an anesthetic if the blood hemoglobin level was <50% of normal. No clinical studies were cited as a basis for the recommendations. At that time, ether anesthesia was reputed to be toxic in anemic individuals. Da Costa and Kalteyer [7] reported that anesthesia with ether was attended by a slight rise of blood hemoglobin level, but a decrease in the color index.

In 1936, Cook County Hospital in Chicago started the first hospital blood bank where blood could be drawn, stored for a short period, and then transfused [8]. This provided a longer period in which to consider the indications for transfusion and it made more blood available for transfusion. No longer did the surgeon have to wait while a donor was located, tested, prepared, and bled. A few hospitals followed this lead and established their own blood banks.

The value of transfusion became increasingly recognized by physicians and surgeons. In 1936, Bock [9] in a review of blood transfusion, speaking of bleeding duodenal ulcers, stated: “If the hemorrhage is severe, with rapid fall of hemoglobin to 50 or below [sic], with pulse rate 120 or more, even though the blood pressure may remain at a normal level, transfusion should be undertaken without delay.”

The advent of World War II in 1941 created an urgent need for blood transfusions. Now blood and plasma could be drawn prior to need, stored, and transfused as needed (again based primarily on the patient’s symptoms or perceived loss). Although subsequent research [10] showed that various infectious organisms were present in both the plasma and blood, physicians felt that blood transfusion was safe and effective; blood transfusion certainly decreased the mortality of wounded soldiers during the war. The limiting factor in its use was not the fear of infection, but the limited availability of blood.

At the end of World War II, when surgeons came home from the battlefield, they expected and demanded the availability of blood transfusion and used it to extend the frontiers of surgery. However, in non-traumatic situations, the question arose as

to if or when patients should be transfused prior to surgery. Since larger amounts of blood could be administered as needed, there was an evident need to establish criteria for how much should be given.

The first report in the American medical literature of a quantitative indication for blood transfusion was published in 1942 by John Lundy [11], a pioneering MD anesthesiologist at the Mayo Clinic, who stated "I believe that patients who have marked anemia (hemoglobin of less than 50 percent) are greatly benefitted and make a better recovery if their value for hemoglobin can be increased to 50 or 60 percent immediately after operation than they would if some days passed before this increase were achieved. I believe that healing is promoted thereby." No data were presented to support this premise. When discussing the transfusion of anemic patients, Adams and Lundy [12] stated: "When the concentration of hemoglobin is less than 8 to 10 grams per 100 cubic centimeters of whole blood, it is wise to give a blood transfusion before operation." Again, no data were presented for this conclusion.

In a study reported in 1972, Kowalyshyn et al [13] mailed a questionnaire to the anesthesia departments of hospitals in the USA, surveying the practice of requiring a minimum hemoglobin level for elective surgery. Of the 1,903 surveyed hospitals, 66% responded. A vast majority (88%) required a hemoglobin level ≥ 9 gm/dl, of which 44% required a hemoglobin level ≥ 10 g/dL before surgery; only 7.4% had no minimum requirement. This survey confirmed the wide acceptance of a blood hemoglobin level of 9 or 10 g/dl as a minimum requirement for elective surgery [13].

At the middle of the 20th Century, blood hemoglobin concentration was generally considered a more important indicator of the patient's condition than the symptoms. Blood hemoglobin levels were commonly reported as a ratio of percent normal, often called the "color index," as well as an "iron index," "volume index," or "saturation index," in addition to the units "g/dl" or "g/100 ml" and "% hemoglobin." These units all had different ranges of normal values, which required the clinicians to remember the different ranges to interpret the results of hemoglobin assays performed at different hospitals.

In order to use the blood hemoglobin level as the sole criterion for transfusion, the value must be accurate. But there were great inaccuracies in the results of hemoglobin determinations. In 1947, Belk and Sunderman [1] sent a series of chemical solutions to be analyzed by clinical laboratories in Pennsylvania. Two hemoglobin solutions were included in this survey. Of 92 participating laboratories, only 14 reported hemoglobin concentrations within the accepted range for the sample containing 9.8 ± 0.3 g/dl; the reported range of values was 5 to 15.5 g/dl. Only 12 laboratories reported hemoglobin concentrations that were within the accepted range for the sample containing 15.1 ± 0.5 g/dl; the reported range of values was 12.5 to 18 g/dl.

A workshop on hemoglobinometry was held in 1953 in Chicago, sponsored by the American Society of Clinical Pathologists [14]. The workshop assessed the accuracy of various methods for hemoglobin estimations, ranging from visual observation of a drop of blood absorbed onto filter paper using reflected light, to simple dilutions with water, acids, or thiocyanate. Methods for determining hemoglobin levels involved visual comparisons using a printed color card, a fixed glass standard, a wedge glass standard, and a DuBosq colorimeter, as well as photometric comparisons using an electronic colorimeter with glass filters, or a spectrophotometer. The workshop emphasized the need for periodic recalibration of hemoglobinometers, the need to establish reliable reference ranges in healthy subjects, and the need for extramural proficiency testing. The workshop concluded that oxyhemoglobin and cyanmethemoglobin assay methods were the most stable and reproducible. One conclusion, which now seems rather humorous, was: "A disadvantage in the routine use of cyanmethemoglobin is that {mouth} pipetting must be done with great care, since the reagent contains cyanide" [14].

Subsequent to this workshop, the College of American Pathologists developed a stable cyanmethemoglobin standard that could be purchased and used to standardize hemoglobinometry. The author remembers visiting the CAP office in Chicago, where a closet was filled with ampoules of cyanmethemoglobin standards that were available for purchase.

The blood hemoglobin level, although cherished by clinicians, was not reproducible in the 1950s, nor comparable from one institution to another. Yet great reliance was placed upon it. In 1959, Mann et al [15] showed that changes in hemoglobinometry significantly influenced transfusion therapy. In their hospital, a new hemoglobinometer was put into service and after standardization, the normal range of hemoglobin values increased 1 gm/dl. Following this, the amount of blood that was transfused decreased by 60 to 100 units per month, although other patient indices remained the same and the number of crossmatches was unchanged. In other situations, a defective autopipettor or contaminated Drabkin's reagent caused blood hemoglobin results to decrease temporarily, leading to transfusion of extra units of blood. According to Mann et al [15], most patients at the hospital either obviously needed blood or obviously did not. However, if the 80 physicians at their hospital each based one patient transfusion per month on the hemoglobin value, the change in transfusion rate would be explained. The introduction of external proficiency testing, the inspection of clinical laboratories, and advances in analytical techniques have improved the accuracy and precision of hemoglobinometry and decreased the influence of this factor in patient management.

Yet clinical reliance upon the 10 g/dl hemoglobin level was maintained by word of mouth. The number is easy to remember; it provides a positive indication on a patient's chart that blood transfusion is indicated, and we are a decimal society so the number 10 has great significance to us. Further, it is a high enough value to compensate for laboratory inaccuracies. Zander [16] stated: "This recommendation later appeared in virtually every textbook on anesthesiology written in the English language between 1941 and the 1980's."

In 1967, the 4th edition of Mollison's text on Blood Transfusion in Clinical Medicine [17] recommended transfusing up to a blood hemoglobin level of 10 g/dl: "There is evidence that when the PCV (packed cell volume) falls below about 30 per cent, corresponding to a haemoglobin concentration of about 10 g/100 ml, there is some interference with cardiac function – therefore, before surgery is undertaken the haemoglobin should be raised above

this level, even if only trivial haemorrhage is expected. Before major surgery, it seems desirable to raise the haemoglobin level to within the normal range; that is to say, above 12.5 g/100 ml in women and 13.5 g/100 ml in men."

In 1983, the 7th edition of Mollison's text [18] stated: "There is evidence from experimental animals that when the PCV falls to about 30% corresponding to a haemoglobin concentration of about 10 gm/dl, there is some depression of ventricular function." Mollison qualified this by a following statement: "It has been suggested that a PCV of 20% or more is acceptable in patients undergoing surgery in civilian practice." In 1993, the 9th edition of Mollison's text [19] stated: "It was for long considered that a pre-operation hemoglobin concentration of 100 g/L was the lowest value acceptable for safe elective surgery," and recommended medical criteria.

In 1988, the National Institutes of Health held a Consensus Conference to establish if there was a standard value of what had come to be called the "transfusion trigger" [2]. Conference members paid due consideration to the hazards of transfusion, so the final decision would involve a risk/benefit ratio to the patient. The consensus was that patients with blood hemoglobin levels ≥ 100 g/L rarely need perioperative transfusion, while those with hemoglobin levels ≤ 70 g/l frequently require red blood cell transfusions. A major conclusion was: "Available evidence does not support the use of a single criterion for transfusion such as a hemoglobin concentration of less than 100 g/L. No single measure can replace good clinical judgment as the basis for decision making regarding perioperative transfusion." This appears logical, yet Zander [16] expressed a fear, echoed by others, that the clinical evaluation might be ignored and the new "magic number" would become 7 g/dl. Let us hope that this is not the case!

In 1996, a Task Force of the American Society of Anesthesiologists came to similar conclusions [20]: "Red blood cell transfusion should not be dictated by a single hemoglobin 'trigger' but instead should be based on the patient's risks of developing complications of inadequate oxygenation. Red blood cell transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dl

and is almost always indicated when it is less than 6 g/dl.”

In 1990, Salem-Schatz et al [21] conducted face-to-face interviews with 122 general surgeons, orthopedic surgeons, and anesthesiologists in three teaching hospitals in order to evaluate the influence of clinical and nonclinical factors on transfusion decision making. They found “widespread deficiencies in physicians’ knowledge of transfusion risks and indications.” When a series of cases was given to the participants, only 31% of those interviewed gave correct responses about the need to transfuse, and fewer than half correctly estimated the transfusion risks. Attending physicians generally had lower knowledge scores than residents, yet showed more confidence in their knowledge. The transfusion decisions of residents were influenced by the views of their attending physicians, resulting in orders for potentially inappropriate transfusions. Sixty-one percent of residents said that they had ordered transfusions that they considered unjustified at least once per month, based on recommendations of a senior physician. The authors noted that the residents received more formal training on the use of blood components than the attending staff [21].

Upon the urging of hospital inspection and accreditation agencies, hospitals developed criteria for the analysis of the clinical appropriateness of blood transfusions. Most of these included a target level of hemoglobin. Such a number is comforting, remains on the chart, and is not debatable; below a certain number, one transfuses. Although this may protect one from the scrutiny of the hospital transfusion committee, it leads to what Crosby [22] has called “the secretarial practice of blood transfusion.” He states: “Thoughtless prescription of blood transfusion is playing Russian Roulette with bottles of blood instead of a revolver. While the odds are in the physician’s favor that nothing will go wrong, the patient takes the risk.”

There are a few recent investigations on the indications for blood transfusion. In a study by Carson et al [23], two groups (40 patients each) with hip replacements and postoperative hemoglobin levels <10 g/dl were randomized in respect to their postoperative transfusion therapy. One group (“threshold group”) received 1 unit of red cells

immediately after surgery and were transfused to keep the blood hemoglobin level above 10 g/dl at all times. The other group (“symptomatic transfusion group”) were transfused only if they exhibited symptoms of hypoxia or the hemoglobin level was <8 g/dl. Although there were no significant differences in morbidity and mortality between the groups, the symptomatic transfusion protocol was associated with the transfusion of appreciably fewer units of red blood cells than were associated with the threshold transfusion study. The authors felt that their findings merited a larger, more definitive trial. A report by Valerie et al [24], with the provocative title: “The red cell transfusion trigger: has a sin of commission now become a sin of omission?” reminds us that the blood hemoglobin level may be indicative of anemia in a normovolemic patient, but in the hypovolemic patient, or the surgical patient who has received extra fluids, the blood hemoglobin level may be misleading. These papers both appeared in the same issue of *Transfusion*, along with an editorial by Weiskopf [3], who stated that the numbers of patients were inadequate to reach firm conclusions in either investigation. In the study of Carson et al [23], considering the observed differences in outcome, 1200-3600 patients would be required to derive meaningful statistics.

We all need criteria for giving a transfusion. At this time, the best criteria for perioperative evaluation of blood transfusion appear to be those of the NIH Consensus Conference Report [2]:

1. Hemoglobin value – probably no transfusion at ≥ 10 g/dl, probably transfusion at ≤ 7 g/dl.
2. The duration of anemia (chronic, acute).
3. The intravascular volume of the patient.
4. The probable extent of the surgical operation.
5. The probability of massive blood loss.
6. The presence of coexisting medical factors, such as:
impaired pulmonary function,
inadequate cardiac output,
myocardial ischemia,
cerebrovascular disease, or
peripheral circulatory disease.

The severity of these conditions should be balanced against the known hazards of transfusion.

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