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Review Article

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Guideline for the Indication of Red Cell Transfusion: Why Hemoglobin Concentration Alone Is Unreliable

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Introduction

Anemia defined by hemoglobin concentrations ([Hb]) is used predominantly as the main threshold for transfusions of packed red blood cells (RBC) in clinical practice. However, ongoing controversy exists regarding [Hb] as a threshold since Hb is only a rough estimate of oxygen delivery. Despite the majority of existing guidelines do not even list a hemoglobin trigger as an indication for transfusion (See Table 3 in [1]), clinical practice is determined more by the numbers derived from transfusion strategy trials- against the general knowledge that [Hb] alone is inadequate for determining a trigger for RBC transfusion. This is due to the also well-known fact that as a concentration value, Hb g/dL, is influenced by volume status that can lead to hemoconcentration or hemodilution. Moreover, other patient variables such as assessment of patient volume status, symptoms, vital signs, bleeding, and co-morbidities are listed as supplementary decision factors. However, there is no gold standard for the measurement and interpretation of any of the listed factors nor is there convincing evidence to what extend a comorbidity is of relevance. This might be the reason that clinical practice of transfusion management worldwide mainly is oriented on that [Hb] number resulting in inappropriate dosing, i.e. overtransfusion [2-6] in 20% to 50% and probably in underdosing [7] as well.

Even in clinical trials for "transfusion strategies", with a few exceptions (i.e. the FOCUS trial, [8]), practicability succeeds over precision. Protocol derived transfusion frequently is indicated by a [Hb] number in the absence of a variable that is easy and quickly at hand. Thus "liberal" strategy is aiming at a[Hb] of 7 to 10g/dl as opposed to "restrictive" in a corridor of 6 to 9g/dl, notwithstanding that [Hb] solely is not a reliable target as a solid base for a clinical strategy.

In this article we raise the question, if this is an acceptable procedure or if we should intensify our search for a more precise basis for the decision to transfuse or not. We will demonstrate that [Hb] as a sole treatment decision is unacceptable.

Reasons why [Hb] should not be used alone: Intravascular volume and relative anemia

Imprecision of [Hb] due to fluid imbalance

As a concentration, [Hb] is dependent on intravascular volume. Unfortunately, there is no gold standard for assessment of intravascular volume. This is a major problem for the transfusion indication since intravascular volume is deviating exactly in transfusion relevant situations- perioperatively and during critical illness. Among others, the reasons are dehydration, fasting, oliguria,

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hypotension, inadequate fluid therapy, acute kidney injury [9], fluid shifts to the interstitium in the size of 34.1 ± 11.1 mL/min [10] and cardiovascular malfunctions [11].

The size of the error provoked by unmonitored fluid therapy is estimated by a [Hb] decrease of 1 g/dl in adults by 500 ml of fluid. In healthy volunteers, fluid intake [12] orally or infusion of crystalloid solutions resulted in a reduced [Hb] of > 0.5 g/dL for at least 7h [13]. Existing calculations regarding the size of error range from fluid loading induced [Hb] variations can span from 8% [14] to 30% [15] depending on the patient and/or the underlying disease. To conclude, without a reliable method of measurement of intravascular volume, our present modes of calculation and or estimation regarding perioperative volume effects are insufficient [16] and may have a detrimental outcome [17].

Although various monitoring methods of i.e. urine output, HR, BP (sometime orthostatically measured), CVP, respiratory variation in BP by invasive or non-invasive measures, exist, they seem not to be able to correct the deviations of intravascular volume. Due to this "relative anemia" [18], over transfusion results [19], especially during the postoperative period and massive hemorrhage [20-22]. In contrast, treatment with furosemide can reduce the likelihood for RBC transfusions (OR 0.196; p = 0.005) with a reduction of the rate of RBC transfusion by half (62.5% to 31.3%; p = 0.009) [23].

Imprecision of [Hb] due to physiological effects

Various interindividual facts such as age, gender, race, sodium content and hydration status, smoking and physical activity affect plasma volume and hemoglobin content. During blood loss, the volumes of plasma and hemoglobin do not change in parallel [24]. Although female might have a higher tolerance for anemia for unknown reason [25], normal female [Hb] is lower due to sex hormone dependent effects on erythropoiesis in men and women [26]. However, the relative loss of blood is greater in female patients [27] since they tend to have smaller body surface area and a smaller total blood volume [28]. Age increases the prevalence of anemia in elderly men and women (6.1% and 10.5%) due to compromised hematopoietic reserve in the presence of hematopoietic stress induced by an underlying disorder (e.g. infections, surgery, trauma) [29]. With the age induced chronic organ dysfunction of kidney, liver and heart, the intravascular volume increases resulting in an age dependent "established anemia of the elderly". Without a reliable measurement of intravascular volume, this anemia hardly is to distinguish from true anemia due to chronic inflammation, chronic organ failure, chronic gastrointestinal blood loss and nutrient-deficiencies. However, the elderly population are common recipients of transfusions: According to the REDSIII-trial, transfusion incidence has a bimodal distribution with incidence peaks at 2 to 5 and 70 to 89 years, especially in subjects with concomitant organ dysfunctions such as heart failure, kidney and liver dysfunction [30] and iatrogenic therapy with diuretics or steroids. In addition to these effects on the imbalance of hemoglobin content and plasma volume, circadian changes of cortisol and somatotropin release and diuresis [31] occur with time of day and changes [Hb] within the same subject by 0.3-0.5 g/dl [32].

Imprecision of [Hb] due to preanalytical error

Body posture at the time of blood probe withdrawal shifts fluids by gravitation to the lower parts of the body. Thereby, blood viscosity and plasma content are altered by extravasation of fluid from the intravascular compartment with concentration of blood cells in the sitting or upright position. Since usually the venous or arterial line for probe sampling is located on the upper half of the body, a decrease in comparison to the mean systemic [Hb] by up to 0.3 or 0.7 g/dl occurs [33,34]. Ear lobe probes have been shown to overestimate [Hb] by as much as 2g/dl. Fingertip probes are poorly reproducible when different fingers of the same subject are analysed. Capillary blood is associated with poor sensitivity (41.3% for females and 18.6% for males) for anemia detection [35]. Further pre-analytical errors are incorrect filling, admixture with skin disinfection fluid or tissue fluid, air bubbles, moisture, storage or delayed measurement.

Is the measurement method of hemoglobin precise?

As recently described [36], accuracy and precision of common [Hb]- analysers is <6%, the reproducibility for the same probe < 4% [37]. Current analysers (Sysmex, ABX) are deviating by 1.5 to 3.1% (0.3-0.8 g/dl) [38] as opposed to photometers with multiple wave lengths (by 0.1g/dl) (i.e. ABL series from Radiometer or Siemens by 0.2-0.3g/dl. Point-of-care methodology (Hemocue or HemoControl [EKF Diagnostics, GmbH, Barleben, Germany] and non-invasive spectrophotometry (NIS) techniques (occlusion spectroscopy (NBM 200; Or Sense Co., Petah-Tikya, Israel), multi-wavelength pulse CO-oximetry (Pronto-7; Masimo Co, Irvine, CA, USA), transcutaneous reflection spectroscopy (HemoSpect; MBR Optical Systems GmbH & Co. Wuppertal, Germany) are associated with an analytical error in the range of 0,1 to 0,5g/dl, in one study up to 5.9g/dl (36). According to the manufacturer's information, the following devices are associated with those maximal errors: Pronto 7®, Masimo (Irvine, California, USA) 1.0 g/dl (1.08-0.82; max. 1.5 g/dl, the higher [Hb] rises); Radical 7®, Masimo (Irvine, California, USA)-1.0 g/dl (max. 1.5g/dl, the higher [Hb] rises); NBM 200®, OrSense (Petah-Tikva, Israel)-0.86 g/dl (CI-1.59 to +1.78); [Hb]201+®, Hemocue (Angelholm, Sweden)-<0.5 g/dl [39-41]. In conclusion, the clinical decision making for or against packed red cell transfusion requires not only the [Hb] values but also the method used and the analytical error.

Is the problem clinically relevant?

Since in many critical ill and transfusion dependent subjects neither intravascular volume, co-morbidities and medications nor the size of measurement inaccuracy is known, [Hb] should no longer be used as a sole transfusion trigger. That is why most of existing guidelines do not list a hemoglobin trigger as an indication for transfusion. With convincing evidence, guidelines request to transfuse as restrictive as possible. However, in the absence of ischemic symptoms, [Hb] is the only easily accessible and established and quantifiable variable for the estimation of potential ischemia risk to walk the narrow path between being too liberal and provocation ischemic tissue damage.

The lack of a gold standard measurement of intravascular volume together with the nonexistence of an easy-to-use non-invasive measurement of tissue oxygenation and perfusion, requires trust in the clinical experience of physicians.

However, the question remains how misleading clinical orientation on [Hb] could be. Can the patient brought to severe organ damage if all information about a patient's comorbidities, intravascular volume, organ perfusion, and active bleeding is inexistent and [Hb] remains the only value to guide consideration of transfusion? In an attempt to quantify the maximum error, the sum of all possible error's accounts to max. 11.8 g/dl (Table 1). Although this maximal size of false estimation surprises, the possibility is minor that all influences unidirectionally are erroneous. Thus, the uncertainty for the clinician remains as long as a size of under- or overestimation of the [Hb] is unknown.

Clinical relevance is given if treatment decisions depend on thresholds. For transfusion, liberal and restrictive transfusion triggers from controlled trials are given as [Hb] thresholds with a recommendation to act. However, the accuracy of a test depends on the ability of [Hb] to separate the group being tested into those with and those without the risk of ischemia, and it is quantified by the area under the ROC curve [42]. While this approach has been used for years to assess the accuracy of diagnostic tools [43], its main limitation is that it transforms the biological nature of a continuous variable into an artificially dichotomous (i.e., "transfuse or not") statistical index that does not always accurately reflect the decision-making process applied to clinical management. The smaller, however, the separation area is chosen, i.e. the liberal and restrictive transfusion threshold, the predictive value of the estimation of [Hb] alone gets to what is done by flipping a coin. Applied to some of the controlled trials of transfusion strategy, the shrinkage of a predefined per protocol distinction between liberal and restrictive groups demonstrates the problem if only Hb is used for group division . The area of distance between liberal and restrictive transfusion is reduced (Fig 1a) to an even smaller area of separation when a small error size is added to the intention to treat transfusion thresholds (Fig 1b). Thus, for low predictable value, the decision to transfuse cannot be based on [Hb] alone. It generally should be combined by additional information.

The difficult search for a better specific decision-making tool

Due to the factors mentioned above, there is growing recognition among researchers that [Hb] as a single parameter for RBC transfusions is inefficient at best [44]. The use of a common parameter such as [Hb] as an investigational transfusion threshold offers the advantage of ease of use and is usual in daily practice. However, it bears a risk when the dependence on intravascular volume and measurement accuracy is not understood. One of several possibilities is the continuous tracking of the [Hb] changes during a procedure or a hospital stay. This method named "delta [Hb]" intended originally to demonstrate a greater tolerance capacity induced by chronic anemia. Several studies could demonstrate that the tolerance capacity for acute anemia inversely is related to the baseline [Hb] [45]. Larger delta [Hb] values were strongly associated with risk of perioperative complication [46,47], independent of the nadir [Hb]. For accuracy of this method, normovolemia is required since acute blood loss without volume substitution is not indicated by a greater delta [Hb] (see also Recommendation 10 of the actual resuscitation guideline in trauma [48]).

Thus, the monitoring of intravascular volume could avoid interpretation errors of [Hb]. An actual feasibility trial demonstrated that [Hb] can be used after normovolemia is re-established in all subjects [49]. In a small Danish study in vascular surgery patients, intraoperative fluid therapy was guided by cardiac stroke volume measurement. Although not designed for an outcome but a feasibility trial, liberal red cell transfusion at an [Hb] of almost 10g/dl lead to better outcome than restrictive. Although measurement of normovolemia is elaborate and not applicable for all patients, it changes outcome in high-risk subjects. The use of blood volume monitoring reduces mortality by avoidance of TACO or volume overload as shown in a recent study [50]. However, as recently reviewed in Critical Care Guidelines for Septic and Cardiogenic Shock [51], methodology issues still are existent. Dynamic functional hemodynamic markers such as pulse pressure analysis or stroke volume variation [52] during positive pressure breathing and mean flow changes with passive leg raising (PLR) are highly predictive of volume responsiveness [53]. Continuous volume monitoring is superior to intermittent measurements of intravascular volume. Hypervolemia (11%), anemia (17%), and mortality (16%) by intermittent volume monitoring can be reduced by continuous techniques [54]. Non-invasive methods allow continuous monitoring of both stroke volume and [Hb] but are less accurate. The use of plethysmography indices (Sp [Hb]) and stroke volume variability (SVV) improved outcome by a reduction of mortality by 53%, complications by 14% and of length of stay by 30% in high-risk abdominal surgery [55,56]. Since the use of these monitoring techniques in high-risk patients is indisputable [57], it should be applied also for transfusion recipients.

Future transfusion guidance might derive from alternate methods. Tissue and organ viability depend on a variety of factors that are not limited to perfusion pressure and oxygen content. For example, investigators emphasized the importance of vascular tone modulation by blood rheology, autoregulation, and blood viscosity [58-62]. Other factors that might be involved include vessel integrity and the glycocalyx. Hence, measured tissue perfusion might be a better indicator of therapy impact. A few trials have used direct measurement of tissue oxygenation and hemodynamic functionality of red cells by near infrared spectrometry (NIRS) [49,63,64] alone or together with fractional tissue oxygen extraction (FTOE) [65,66] for skin, muscle, intestinal, and brain vasculature. However, the penetration depth of non-invasive NIRS techniques is limited. Furthermore, the application at the wrong anatomical site is a basic potential error of this methodology.

Conclusion

[Hb] should no longer be used as a sole transfusion trigger. Although it is well recognized that the potential for error and other

limitations of [Hb] as a single measurement is unacceptable, no alternative or guideline recommendation is present so far. [Hb] is dependent on correct sampling and accurate measurement. In the absence of ischemic symptoms, its use for a transfusion decision requires additional information about intravascular volume, base line [Hb], perfusion pressure and oxygen consumption at tissue levels. From these sources of information, to date, only a combination between continuous stroke volume and [Hb] monitoring allows reliable decision making in transfusion practice.

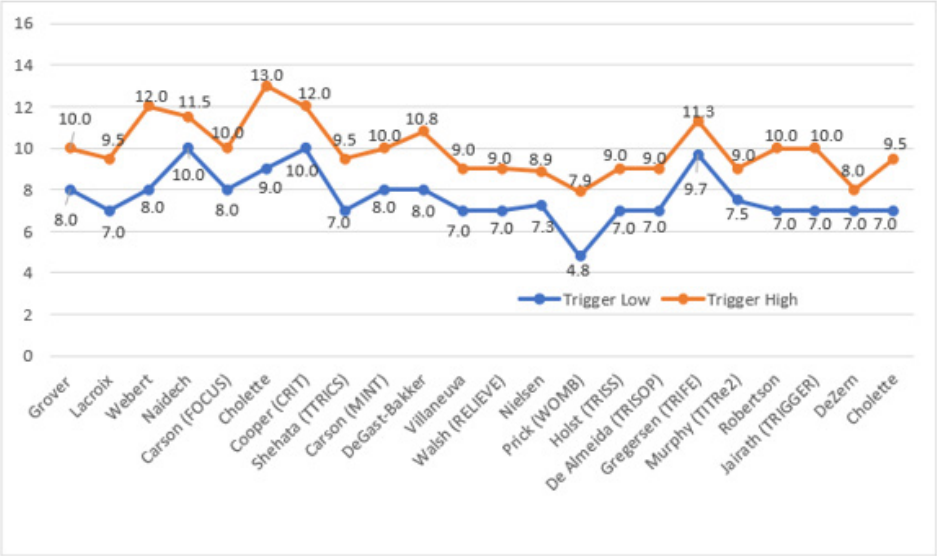

Figure 1a: A Per Protocol Transfusion Triggers Liberal vs. Restrictive in RCTs.
Chosen were RCTs that gave both the intended triggers as well as the actual realized mean hemoglobin level per group. The mean difference amounts 2.3 ± 0.76 g/dl. Red line and squares- liberal. Green line and diamonds- restrictive.

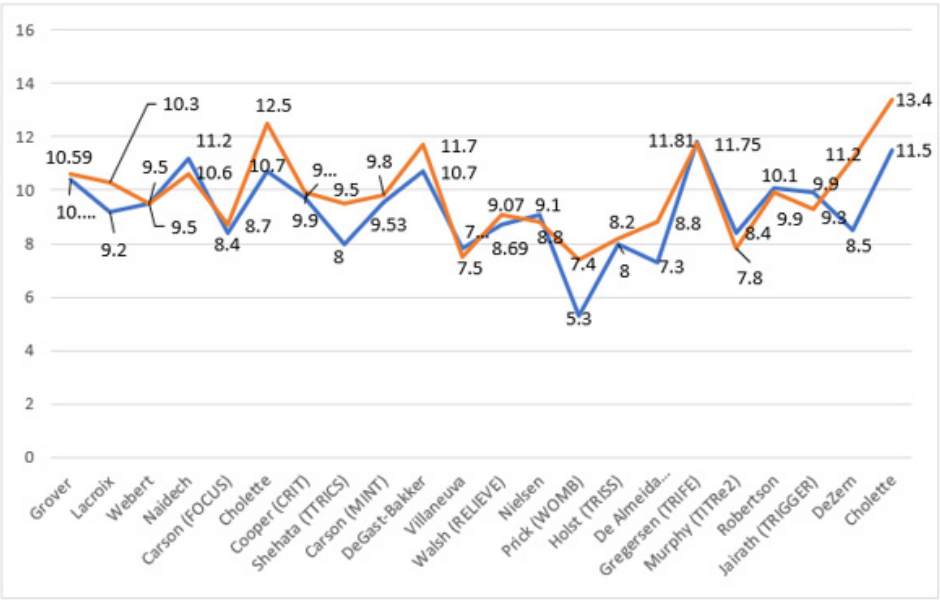

Figure 1b: Realized Transfusion Triggers corrected for Analytical and Methodological Errors.
A mean error of 0.5 g/dl was added to the [Hb] actually achieved (Hb targets).
from the same trials (Fig. 2b). The triggers interfere with each other.

Table 1: Error sizes with the use of hemoglobin concentration as transfusion trigger.

Category	Mechanism	Plasma Volume	Estimated size (g/dl) in [Hb] over- or underestimation
Deviations from normovolemia by changes in plasma volumes	Dehydration due to preoperative fasting, diarrhea from enteral feeding and laxatives, drainage losses, etc.	↓	+ 0.5 to 1.5
	Oliguria during hypotension and acute kidney injury	↑	- 0.5 to 1.0
	Volume resuscitation	↑	- 1.0 to 2.5
	Cardiac malfunction to failure	↑	- 1.0 to 2.5
Physiological inter-individual variation	Gender-associated relationship of blood volume to erythrocyte mass (in case of acute blood loss and volume replacement)	Male ↑ Female ↓	± 1.0 to 1.3
Intra-individual variations	Circadian hormones, diuretic therapy, chronic hypertension	↑↓	± 0.3-0.5 g/dl
	Body posture and blood vessel for testing	↑↓	± 0.3 or 0.7 g/dl
[Hb] measurement inaccuracy	Analyzers and photometers		± 0.1 to 0.3 g/dl
	POCT and co-oximeters		± 0.1 to 1.5 g/dl
	Preanalytical error, source of blood sample		± 0.5 to 2.0 g/dl

Inaccuracy of hemoglobin concentration measurements from various sources is listed. POCT-Point of Care Testing.

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Conflict of Interest

No conflict of interest.

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