A RANDOMIZED CLINICAL TRIAL ON HEMOGLOBIN DOSE AND PATIENT MATCHING

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CONTENTS

1. SCIENTIFIC BACKGROUND

Red blood cell concentrates (RBC) is the most frequently transfused blood component. The transfusion trigger for the product varies between different countries and different centres [1], as does the dosage (number of units) transfused under similar conditions [2]. Many centres experience a blood shortage periodically, and this may threaten patient safety and postpone planned operations [3]. The usual assumption used in the clinical practice is that a single unit of red blood cells transfused to an adult should result in an increment in circulating hemoglobin of 1 g/dl [4]. This practice is, however, based on an estimate on the basis of units, or at best volume.

Furthermore, there is an existing difference depending on which type of RBCs is transfused; whole blood, filtrated RBCs, buffy coat removed RBCs or filtrated and buffy coat removed RBCs. This will decrease the hemoglobin levels in the unit by approximately 10 %, 10 % and 20 % respectively.

Many have discussed the advantage of standardizing the units of RBCs [5-7].

Two different concepts are proposed; one is to standardise the unit, the other is to adjust the hemoglobin dose according to the patient's blood volume, called hemoglobin dosing. Unfortunately, the total hemoglobin content of the units does not represent a homogeneity [5], and the blood volume of the patients vary as well [8]. Högman & Knutson performed a red cell apheresis study, demonstrating it was possible to collect either one or two units of RBCs without exceeding 13 percent of any donor's blood volume, provided the collected volume of blood in each unit was less than the current standard [5]. Applying a standard at 45g of RBC Hb per unit was found to permit the collection of maximum RBC Hb and plasma in the evaluated population of Scandinavian donors (standardised units). Hemoglobin dosing requires information on the hemoglobin content of each unit to be transfused, as well as the patients' height, weight and actual and desired hemoglobin levels.

In a study from Turkey, Arslan et al showed that matching the hemoglobin dose to the individual needs of the patient may reduce the total usage of red cell concentrates by approximately 30 % [9]. Calculating the patients' total need of hemoglobin to achieve the targeted hemoglobin level made this possible. The hemoglobin dose was defined as hemoglobin concentration in the donor multiplied with donation volume. However the success rate was closely linked to patients' weight; increased weight correlated with unwanted outcome. In this study the total amount of transfused RBCs was reduced to 72 from the original 104 units required.

Holme et al have recently published data indicating that currently used formulas for estimation of a person's red cell volume (RCV) by weight and height are decades old and were based on the use of (51)Cr isotopes and on a sample population, which may not be reflective of today's population [10]. Their study demonstrated that (99m) Tc is a reproducible and precise method for determination of a person's RCV and that current formulas may significantly overestimate the RCV of today's population. This is likely the result of a shift in population characteristics over the past four decades as reflected by an increased mean body mass index (from 25 to 28 kg/m^2), which has not resulted in a proportionally increased RCV.

Although measuring of hemoglobin in the unit would represent the gold standard for the actually hemoglobin content in the unit, other methods can also be used. Preliminary data from Canada, Scotland and Norway have detected a close correlation between the hemoglobin content in the unit and the weight of the unit (Reikvam, Heddle, Prowse, Devine, Hervig, unpublished). This will allow us to simplify the methods used in the departments of immunology and transfusion medicine. By just measuring the weight of each unit, we can easily correlate and calculate the actually hemoglobin content in each unit.

Studies have also indicated that the quality of the blood probably will be reduced with the storage time in the blood bank [11, 12]. In future studies we will also be able to correlate the hemoglobin increment to the age (days from donations) of the unit. This will bring information to the postulated theory of reduced function and survival of older RBCs versus newer RBCs [11, 12]. The blood volume have traditionally been calculated after standard formulas (e.g. Dubois and Dubois), but recent studies have suggested use of other formulas, which are probably more relevant for the population today [10].

On the basis of this existing data, we have performed a pilot study to assess the feasibility of a multicentre study on hemoglobin dose and patient matching (Reikvam, Heddle, Roodie, Prowse, and Hervig, submitted). Patients administered for day-treatment with transfusion with RBCs at different centers in Norway, Scotland and Canada, were included in the study. Their hemoglobin concentration was measured before and after transfusion.

We found that the hemoglobin content in RBC units showed considerable heterogeneousity. By correlating the hemoglobin increment with the patients' weight or blood volume we found no significant correlation. However, when correlating the total hemoglobin dose given with the hemoglobin increment, we found a significant correlation. Furthermore, an even stronger correlation was found when the hemoglobin increment was correlated to hemoglobin dose divided with the patients' estimated blood volume (Reikvam, Heddle, Roodie, Prowse, and Hervig, submitted). Our study has made a contribution to the question about feasibility of hemoglobin dosage.

As a result of variation in transfused blood volume and the blood donors' hemoglobin concentration, besides the differences in the RBC preparation, the hemoglobin content in the final unit is far from standardized.
New and better technologies in combination with new findings and experience have made it possible to achieve a higher degree of standardization. However, we still need further and larger studies on this area to make a conclusion about the feasibility and the clinical impact of the method. Therefore we want to go on with a randomized clinical trial on hemoglobin dose and patient matching to bring further information about the question about feasibility and possibility of hemoglobin dosage and standardization of the RBCs.

2. OBJECTIVES AND STUDY DESIGN

This is a randomized clinical study on hemoglobin dose and patient matching. The aim of the study is to evaluate whether the targeted hemoglobin increment (2 grams per decilitre) in the patient can be predicted from the hemoglobin dose/weight of the blood bag transfused. In the test group, the hemoglobin dose needed will be calculated, whereas in the control group, the prescribed number of red cell units will be transfused.

3. PATIENTS

Patients will be hospital in or out-patients, recruited by the investigator, who require transfusions of red cell concentrates and who fulfill the inclusion criteria.

a. Inclusion Criteria

- Patients receiving red cell transfusions or expected to receive one or more red cell transfusions
- Patients over 16 years of age
- Patients for whom height and weight information is available
- Patients who have consented to participate

b. Exclusion Criteria

- Patients who are hemodynamically unstable (ongoing bleeding or hemolysis)
- Patients with a known hemolytic anemia (congenital or acquired)

- Patients with a positive Direct Antiglobulin Test (DAT)
- Patients for whom informed consent has not been obtained
- Patients where the hemoglobin concentration increment target is above 2g/dl.
- Patients with auto- or alloantibodies against RBCs.

c. Patient Enrolment

Patients who meet the inclusion criteria will be invited to participate, and those who provide informed consent will be enrolled in the study. Patients will be randomized to standard transfusion or patient matched hemoglobin dosing transfusion based on the weight of the blood bag.

d. Patient Consent Procedure

The purpose and procedures of the study will be explained to prospective participants and their written consent obtained prior to their taking part in the study. The patients will also be informed that they have the right to withdraw from the study at any time, without giving a reason, and this will not affect their future treatment in any way.

4. TRANSFUSION PROCEDURE

Patients will be transfused according to local practice for their clinical condition and may receive more than one red cell unit, up to a maximum of three units per transfusion. Multiple units must be transfused consecutively with no disruption in the procedure.

Data may be collected on more than one transfusion procedure for each patient, to allow assessment of factors affecting hemoglobin increment between and within patients.

5. DATA COLLECTION

a. Baseline Data Collection

i. Patient Baseline Demographic Data

The following information will be collected for all participating patients:

- Age
- Gender
- Weight
- Height
- Primary diagnosis
- ABO and Rh (D) blood type

b. Pre-Transfusion Data Collection

i. Patient Data

Prior to transfusion the following data will be collected for the patient:-

- Indication for transfusion
- Hemoglobin level (within 24 hours prior to transfusion)

ii. Product Data

Prior to transfusion the following data will be collected for the red cell unit(s) to be transfused:

- ABO and Rh type
- Weight of the red cell unit(s)
- Age of the red cell unit(s)

c. Transfusion Data Collection

The following data will be recorded for each transfusion:

- Time transfusion started
- Time transfusion completed.
- Number of red cell units transfused (maximum 3 units)

d. Post Transfusion Data Collection

i. Patient Data

Patients will have a blood sample taken (preferably from the arm contralateral to the transfusion site) between 15 minutes and 8 hours post completion of transfusion. In the case of transfusion of multiple units, this sample will be taken after the final unit has been transfused. The following data will be recorded:

- Hemoglobin level

ii. Product Data

- Weight of each red cell unit transfused (if not performed prior to transfusion)

6. ADMINISTRATION

a. Sample size and Randomisation procedure

The patients will be randomized to two groups, the test group receiving a calculated hemoglobin dose and a control group receiving the prescribed number of red cell units. Based on experience, the average hemoglobin increment in the control group will be 1.62 g/dl with a standard deviation of 0.7. To be sure to detect a difference between 1.62 g/dl and 2.0 g/dl hemoglobin increment, 55 transfusion episodes must be included in each group. To allow for 10% missing data, we will include 61 episodes in each group.

The randomization itself is performed by a computer programme.

b. Indemnity Arrangements

This is a study using data collected during routine treatment of the patient, with the possible exception of one additional blood sample to be taken for hemoglobin determination between 15 minutes and 8 hours post-transfusion. Therefore, no indemnity/insurance arrangements in addition to those already in place at the participating centres are required.

c. Patient Confidentiality

Participating site will be allocated a unique site identifying code and all patients will be given an associated trial number on entry to the study. Thereafter they will be referred to by that number and by their initials on all documentation to preserve their confidentiality.

d. Patient Withdrawal Policy

Patients may withdraw from the study at any time without giving a reason.

e. Ethical Standards

The protocol will be approved by the appropriate Research Ethics Committee/Institutional Review Board for each of the centres that enrol patients in the trial, and, where appropriate, by local Research and Development Management. This trial will be performed in accordance with the requirements of the ICH Tripartite Guideline for Good Clinical Practice, which is consistent with the principles laid down in the Declaration of Helsinki as adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, the 35th WMA General Assembly, Venice, Italy, October 1983, the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

f. Publication

The results will be published in an international peer-reviewed journal and will be presented at national and international scientific meetings.

7. REFERENCES

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