Pilot, randomized trial of the use of pediatric size phlebotomy tubes in adult critically ill patients to reduce red blood cell transfusions

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Protocol Title:	Pilot, randomized trial of the use of pediatric size phlebotomy tubes in adult critically ill patients to reduce red blood cell transfusions
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Study Coordinator:	None
Population:	Adult, intensive care unit patients, newly admitted to the ICU. N=200
Number of Sites:	Single site / Memorial Hermann Hospital / Medical ICU, Transplant ICU
Intervention:	Pediatric size phlebotomy tubes
Comparison:	Adult size phlebotomy tubes
Outcomes:	Primary: Time to red blood cell transfusion or hemoglobin less than 7 g/dL Main secondary: Rate of change in hemoglobin (g/dL per patient per day)
Study Duration:	6-12 months
Subject Duration:	Duration of ICU stay, up to 30 days

1. BACKGROUND AND RATIONALE

Anemia and red blood cells (RBC) transfusions are common in critically ill patients.[1,2] One factor associated with the development of anemia[3,4] and RBC transfusions[5,6] in these patients is the volume of diagnostic phlebotomy. Therefore, a more efficient use of blood drawn for diagnostic testing has the potential to reduce transfusions.

Even though blood conserving strategies could be beneficial, there are no randomized controlled trials (RCTs) assessing their efficacy in reducing RBC transfusions in adults. A blood conserving arterial line system reduced the RBC transfusion volume in an RCT of very low birth weight infants.[7] However, the results of this trial might not be applicable to adults as their larger circulating blood volume might limit the benefit of any blood conserving intervention.[8]

The use of pediatric size phlebotomy tubes has been proposed to reduce anemia and RBC transfusions in adults. Adult phlebotomy volumes exceed pediatric ones for the same tests.[9] However, the absence of high quality data supporting their efficacy compounded by the loss of automation in the processing of pediatric tubes prevents their routine use. Two RCTs assessed their effect on the change in hemoglobin in adults. The first trial showed no benefit, but the intervention was limited to basic metabolic profile tubes and the study was conducted in a general Internal Medicine population.[8] The second trial, performed in the Intensive Care Unit (ICU) setting, demonstrated a reduction in the decline of

hemoglobin, but used a co-intervention.[10] None of these studies analyzed the change in hemoglobin as a function of time at risk.

An RCT is needed to evaluate the hypothesis that the use of pediatric size phlebotomy tubes reduces RBC transfusions in adult ICU patients compared with the use of adult size tubes. However, its design is complicated by the lack of knowledge regarding the expected effect size and overall feasibility of this intervention. Thus, we will perform a pilot RCT that will allow us to investigate these issues.

2. OBJECTIVES

2.1 Primary

Estimate the effect size of using pediatric phlebotomy tubes in ICU patients on RBC transfusions compared with the use of adult phlebotomy tubes during their ICU stay

2.2 Secondary

- Determine the rate of recruitment of participants
- Evaluate the feasibility of implementing phlebotomies using pediatric size tubes in an adult ICU
- Establish the rate of change of hemoglobin in the intervention and control groups
- Identify the ICU admission hemoglobin range that best predicts benefit from pediatric phlebotomy tubes

3. METHODS

3.1 Trial design

Randomized controlled trial

3.2 Participants

Inclusion (all of the following)

- Age ≥ 18 years old
- New admission to the medical or transplant ICU at Memorial Hermann Hospital in Houston
- ICU admission hemoglobin level of at least 7 g/dL. The ICU admission hemoglobin will be the most recent hemoglobin value available at the time of screening for inclusion in the study.
- Randomization is expected within 12 hour of admission to the ICU

Exclusion (any of the following)

Conditions that affect the generation or loss of RBCs

- Clinical bleeding. Defined as menstrual bleeding, bleeding leading to a change in the frequency of hemoglobin monitoring or to an order for a medication, transfusion, procedure, or consultation intended to prevent or treat bleeding.
- Known hemolytic disorder (e.g. sickle cell disease, hereditary spherocytosis, autoimmune hemolytic anemia)
- Bone marrow disorder (e.g. aplastic anemia, marrow infiltration disorder, chemotherapy within the last 8 weeks)

Randomization to adult size phlebotomy tubes is not recommended

- Jehovah's Witnesses

Collection of blood tests is not possible or desired

- Patient is comfort care measures only

Inability to complete the desired time of follow up

- Refractory shock: mean arterial blood pressure below 60 mmHg despite maximal doses of 3 vasopressors. Maximal dose of vasopressors are as follows: Norepinephrine 70 mcg/min; vasopressin 0.04 units/min; epinephrine 35 mcg/min; dopamine 20 mcg/kg/min; phenylephrine 350 mcg/min
- Severe acidosis: pH below 7 in more than one arterial blood gas within 24 hours of ICU admission in the absence of diabetic ketoacidosis

Other

- Surgical admission diagnosis
- Pregnancy
- Current prisoner

3.3 Allocation

All patients admitted to the medical or transplant ICU will be screened for eligibility. Group assignment will be done using the randomization module in the Research electronic data capture (RedCap). Randomization will be stratified by ICU admission hemoglobin level (7 to 9.49 g/dL, 9.5 to 11.99 g/dL, and 12 g/dL or greater). Patients will be randomized using permuted blocks of 4 or 6 and a 1 to 1 ratio, into one of two groups: the pediatric size phlebotomy tubes group or the adult size phlebotomy tubes group.

3.4 Interventions

Pre-intervention period (1 month)

The first objective of this period is to standardize the pediatric tubes phlebotomy process. Study procedures will be presented to the ICU nurses by email, printed material, and lectures. Information will include the type of pediatric tube and the blood volume needed for each test, and the importance to collect only the total estimated blood volume according to the tests that need to be performed. Pocket size cards that include the suggested volume of blood to be drawn for each pediatric tube will be provided. No guidance regarding the phlebotomy process when using adult size tubes will be given so that it reflects usual practice. The volume of fluid

drawn to clear the intravenous line will be returned to the patient in a sterile fashion in both groups whenever possible. The frequency and type of blood tests performed will follow usual practice.

The second objective of the pre-intervention period is to provide RBC transfusions recommendations to the ICU physicians. This will be accomplished by email and during any of the regular Critical Care Division meetings. An RBC transfusion will be recommended if the hemoglobin is less than 7 g/dL or if there is bleeding with associated hemodynamic instability regardless of the hemoglobin level. It will be dependent upon the ICU physician to make the final determination regarding the need of any transfusions.

Intervention period (5-11 months)

Blood tests will be collected using pediatric and adult phlebotomy tubes in the experimental and control groups, respectively (Table 1). Arterial blood gases, blood cultures, and lactate levels will be collected using the same tubes in both groups. The exposure period will be from randomization until the hemoglobin is less than 7 g/dL, an RBC transfusion order is placed, the patient is discharged from the ICU (time of an acceptance note) or dies (time of death), clinical bleeding or surgery occur, comfort care measures only are initiated, or the patient stays in the ICU for more than 30 consecutive days.

3.5 Outcomes

Primary

The primary outcome will be the time from randomization to hemoglobin less than 7 g/dL or RBC transfusion order.

Secondary

The main secondary outcome will be the rate of change in hemoglobin (g/dL/patient/day) in the ICU. This will be calculated as the most recent hemoglobin prior to randomization minus the last hemoglobin prior to ICU discharge, death, RBC transfusion, clinical bleeding, surgery, or change of clinical status to comfort measures, divided by the number of days (rounded to the nearest 0.5) between these two values (crude estimate). If the longitudinal measures of hemoglobin levels deviate substantially from a linear trajectory, we will use a growth model to capture the best fitting function of time (see Analysis Plan for details) and generate a predicted rate of change.

Other secondary outcomes will be the proportion of participants receiving an RBC transfusion while in the ICU, the proportion of patients with at least one inadequate blood sample for laboratory analysis, and the ICU mortality. An inadequate blood sample is defined as any blood sample that requires recollection.

The patient's admission height and weight will be used to estimate the total blood volume of each patient based on Nadler's equation.[11] The total daily phlebotomy volume per participant will be calculated based on the number of blood tests per patient per day and the minimal blood volume for analysis of each test.

3.6 Blinding

The primary outcome assessors will be blinded to the intervention assignments. Study participants, nurses, and physicians will not be blinded.

3.7 Analysis plan

Baseline variables (e.g. gender, race, age) between groups will be examined for clinically significant differences that may have occurred by chance. If a clinically significant difference is noted, both unadjusted and adjusted analyses will be performed.

Intent-to-treat analyses will be used. The primary outcome will be assessed using time to event analysis with the Cox proportional hazard model including treatment group and ICU admission hemoglobin level group (stratifying variable). Censoring events will be death, ICU discharge, clinical bleeding, surgery, initiation of comfort care measures, and end of the study. We will report the hazard ratio and 95% confidence interval (CI).

We will assess whether the longitudinal measures of hemoglobin follow a linear trajectory. If they substantially deviate, we will employ multilevel mixed models including a quadratic term for time or splines to capture the non-linear change while accounting for within-subject correlation. We will generate predicted rates of change to compare between the study groups.

To compare the rate of change in hemoglobin (either crude or predicted) between the two study groups, a linear regression model will be used with treatment and ICU admission hemoglobin groups as covariates. Multiple regression analysis will be used to assess the relationship between the rate of change in hemoglobin as the dependent variable, and age, admission hemoglobin, acute physiology and chronic health evaluation (APACHE) II score, acute or chronic renal disease, sepsis admission diagnosis, use of medications that can cause bleeding, intervention group, and ICU admission hemoglobin group as independent variables. Proportions of RBC transfusion and proportions of at least one inadequate blood sample will be compared among the two groups using logistic regression models with treatment group and ICU admission hemoglobin level group as covariates.

Sample Size

It is estimated that the primary outcome will occur in about 20-40% of the participants in the control group.[1,2,6,12-14] A total of 200 patients (100 in each group) will be randomized in the study. This number of participants was chosen to allow completion of the study in a reasonable time frame while obtaining preliminary information to estimate an unbiased treatment effect. This sample size allows a reasonable width of the 95% CI for the rate of the primary outcome in each group (+/- 8%).

3.8 Study duration

It is estimated that about 6 to 12 months will be needed to complete this pilot study. This estimate takes into account the pre-intervention period (1 month). No more than 5 patients per

day and 25 patients per month will be active in the intervention group as per hospital laboratory restrictions.

4. DATA AND SAFETY MONITORING

The adverse events related to the use of pediatric phlebotomy tubes are not expected to be different than the ones that occur with adult tubes. Potential events include local complications at the site of blood collection, complications related to blood loss including anemia and RBC transfusions, and insufficient blood for analysis requiring recollection of blood. Previous studies in adults have not shown a difference in the number of insufficient samples between patients using adult or pediatric size tubes.[15,16]

Participants that receive the other group's intervention will remain in their assigned group for the duration of the trial. These protocol deviations as well as instances of inadequate blood samples will be recorded in the blood tests record forms by the investigators (Appendix).

5. QUALITY CONTROL AND ASSURANCE

One investigator will be blinded to the group assignments. This researcher will determine when the study completion criteria has been met for each participant, the primary outcome, and the transfusion related events.

6. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Before implementing this study, the protocol and any other required information, must be reviewed and approved by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the IRB before implementation. If an immediate change to the protocol is implemented for safety reasons by the investigator, the IRB must be informed immediately.

All patients admitted to the medical and transplant ICUs of Memorial Hermann Hospital will be screened for eligibility by reviewing the electronic medical record.

A waiver of informed consent and Health Insurance and Accountability Act (HIPAA) authorization are being sought. The study does not involve more than minimal risk, the waiver will not adversely affect the rights and welfare of the participants, and whenever appropriate, the participants will be provided with additional pertinent information after participation. The probability and magnitude of harm or discomfort anticipated with the use of pediatric phlebotomy tubes is not greater than those of blood collection using adult phlebotomy tubes. Blood is collected routinely in pediatric ICUs with the same tubes and processes that will be used in the experimental intervention group. Obtaining informed consent and HIPAA authorization could create bias related to the inclusion of

healthier participants that are not representative of the typical ICU population. This could yield meaningless results.

All records identifying the patient will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available. The medical record number will be the only patient identifier that will be recorded. Patient names or any other patient identifiers will not be supplied to third parties. A unique study specific number will be assigned to every participant. Records containing patient identifiers will be destroyed as soon as possible according to legal regulations.

7. DATA COLLECTION AND DATABASE MANAGEMENT

6.1 Data collection

The investigators will fill out the blood tests form to document the number of blood tests performed and the occurrence of insufficient samples or crossover between interventions. This will be done through review of the electronic medical record and interview of the nurses. This information and data obtained from the patient's electronic medical record will be entered directly in the RedCap database, a secure electronic database (Appendix).

6.2 Storage of data collection forms

The blood tests record forms will be stored in the locked research office.

6.3 Patient Identifiers

The patient's medical record number will be recorded on the blood tests record forms only. A study specific identifier will be given to each participant and will be used for identification in the electronic database.

6.4 Access to patient's information

Only study investigators will have access to the paper and electronic patient's information.

8. PUBLICATION PLAN

The results of the study will be submitted for publication in scientific journals and/or scientific meetings. If the results of the study are published, the patient's identity will remain confidential.

9. REFERENCES

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