New Strategies of Blood Transfusion in Anemic Critically Ill Patients

An Essay

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List of Contents

List of Abbreviations

Abbre.	*Full term*
ACS	**:** Acute coronary syndrome.
AHTR	**:** Acute hemolytic transfusion reaction.
ANZSBT	**:** Australian New Zealand Society of Blood Transfusion
ARDS	**:** Acute respiratory distress syndrome.
BP	**:** Blood pressure.
CABG	**:** Coronary artery bypasses grafting.
CaO_2	**:** Arterial oxygen content.
CBF	**:** Cerebral blood flow.
CHF	**:** Congestive heart failure.
CMV	**:** Cytomegalovirus.
COPD	**:** Chronic obstructive pulmonary disease.
CPD	**:** Citrate phosphate dextrose.
DMT	**:** Divalent metal transporter.
DO_2	**:** Oxygen delivery.
EPO	**:** Erythropoietin.
ESAs	**:** Erythropoiesis stimulating agents.
Fab	**:** Antibody fragment.
Fe	**:** Iron.
FFP	**:** Fresh frozen plasma.
FNHTR	**:** Febrile nonhemolytic transfusion reaction.
GI	**:** Gastrointestinal.
GvHD	**:** Graft versus host disease.
Gy	**:** The gray unit of ionizing radiation dose in the International System of Units (SI).
Hb	**:** Hemoglobin.

HBOCs : Recombinant-based hemoglobin based oxygen carriers.
HIV : Human immune-deficiency virus.
HLA : Human leucocyte antigen.
HTLV : Human T-lymphotropic virus.
ICP : Intracranial pressure.
IF : Interferon.
IHD : Ischemic heart disease.
IL : Interleukin.
IRP : Iron regulatory protein.
LOS : Length of stay.
LPS : Lipopolysaccharides.
NO : Nitric oxide.
NSTEMI : Non ST segment elevation myocardial infarction.
NTBI : Non transferrin bound iron.
O_2ER : Oxygen extraction ratio.
PaO_2 : Partial pressure of oxygen in arterial blood
PRBCs : Packed red blood cells.
RBCs : Red blood cells.
rfvIIa : Recombinant activated factor VII.
RR : Respiratory rate.
SAGM : Saline (NaCl 0.9%) and adenine glucose mannitol.
SAH : Subarachnoid hemorrhage.
SaO_2 : Arterial oxygen saturation.
$ScVO_2$: Central venous oxygen saturation.
SpHb : Hemoglobin monitoring by Spectrophotometry.
STEMI : ST segment elevation myocardial infarction.
TA-GVHD : Transfusion-associated graft versus host disease.
TACO : Transfusion-associated circulatory overload.

TBI : Traumatic brain injury.
TfR : Transferrin receptors.
TNF : Tumor necrosis factor.
TRALI : Transfusion related acute lung injury.
TRIM : Transfusion related immunomodulation.
UK : United Kingdom.
USA : United States of America.
VAMP : Venous arterial blood management protection.
VAP : Ventilator associated pneumonia.
VO_2 : Oxygen uptake.
vWF : Von Willebrand factor .
WHO : World Health Organization.

List of Tables

List of Figures

Introduction

Anemia is a common finding in critically ill patients, approximately 95% of patients who have been in the intensive care unit (ICU) for 3 days or longer are anemic, with almost 50% of these patients receive a mean of 5 units of RBCs while in the ICU. Anemia results in a reduction in the oxygen-carrying capacity of the blood, which can increase morbidity, mortality, organ failure, and length of stay in the hospital. Although treating anemic patients with RBC transfusions appears logical, some research studies suggest that transfusions may not increase oxygen-carrying capacity and may actually be more harmful to patients than anemia itself ***(Collins, 2011).***

Most RBC products are derived by collection of 450-500 (±10%) ml of whole blood from volunteer donors and removal of the plasma by centrifugation. Red cells must only be stored in temperature-controlled, dedicated blood refrigerators and not in ward or domestic refrigerators. The most commonly available RBC product has a 42-day blood bank shelf life and hematocrit (HCT) 55-65%. One unit of RBC will raise the hemoglobin of an average-size adult by ~1g/dl or raise HCT by ~3 % ***(Weinstein, 2012).***

RBC transfusion is not routinely indicated for pharmacologically treatable anemia such as iron deficiency

anemia and vitamin B_{12} or folate deficiency anemia. RBCs are indicated for treatment of symptomatic anemia, for prophylaxis in life-threatening anemia, for restoration of oxygen-carrying capacity in case of hemorrhage. They are also indicated for exchange transfusion in sickle cell disease, severe parasitic infection (malaria, babesiosis), severe methemoglobinemia, and in severe hyperbilirubinemia of the newborn ***(Weinstein, 2012).***

The strategies to prevent unnecessary blood transfusion are recommended. Multiple studies support the use of restrictive transfusion strategies, avoidance of pooled blood products, minimizing blood loss due to phlebotomy, and the close monitoring of postoperative bleeding ***(McEvoy and Shander, 2013)***.

Anemia in Critical Illness

Definition of anemia

Anemia is a hemoglobin concentration in blood that is below the expected value, when age, gender, pregnancy and certain environmental factors; such as altitude, are taken into account. According to The World Health Organization (WHO), anemia is a hemoglobin <13 g/dl (hematocrit <39%) for adult males and <12 g/dl (hematocrit <36%) for adult nonpregnant females ***(McEvoy and Shander, 2013).*** It results in a reduction in red cell mass and a decrease in the oxygen-carrying capacity of the blood. The oxygen carrying capacity of blood is probably best determined by the mass of circulating red blood cells (RBCs). Since red cell mass is not easily measured in the clinical setting, the practical definition of anemia is based on the hemoglobin (Hb) concentration of whole blood. Under most circumstances the Hb concentration is a good indicator of the red cell mass, but changes in the plasma volume may lead to discrepancies ***(Walsh and Saleh, 2006).*** For example, an increase in the plasma volume will decrease the Hb concentration, which may be interpreted as worsening anemia, even though the red cell mass remains unchanged as occurring in pregnancy. During pregnancy, the red cell mass increases by almost 50% but the Hb concentration usually falls because the plasma volume increases by more than 50%, and in surgical and critically ill patients, fluctuations in the plasma volume often

occur due to intravenous fluid resuscitation and increased capillary leak [***(McLellan et al.,2003); (Walsh and Saleh, 2006)***]**.**

The prevalence of anemia of critical illness

The prevalence of anemia among critically ill patients is influenced by factors that include patient case mix, illness severity and pre-existing comorbidity.

Anemia at ICU admission

In an observational, multicenter, cohort study in Scotland, 25% of patients admitted to the ICU had a hemoglobin level < 9 g/dl. A cohort study of 3534 patients admitted to 146 Western European ICUs with varying case mix **(Table 1)** found that the mean hemoglobin concentration at ICU admission was 11.3 g/dl. Sixty-three per cent of patients had a hemoglobin concentration <12 g/dl on ICU admission and 29% of patients had an admission hemoglobin concentration <10 g/dl. The study found that 50% of those patients admitted to ICUs with a hemoglobin concentration <10 g/dl had no history of either acute bleeding or other documented causes of anemia. Approximately, 40% of the patients in the study were elective postoperative admissions to ICUs and the overall illness severity was therefore lower than is typical for some countries (mean APACHE II score 14.8; SD 7.9) ***(Walsh and Saleh, 2006)***.

A similarly designed study in the USA examined 4892 admissions to ICUs. In this study, the mean hemoglobin concentration at ICU admission was 11.0 g/dl. In the study, 20% of patients were postoperative, although it is unclear whether these were emergency or planned admissions, and the illness severity at ICU admission was higher than in the previous study (mean 19.7; SD 8.2). As in the previous study, 13% of patients had anemia as comorbidity on admission ***(Walsh and Saleh, 2006)***.

Table (1): Estimates of the prevalence of anemia at admission to intensive care

Variable	Prevalence
Patients with Hb <12 g/dl	60–70%
Patients with Hb <9 g/dl	20–30%
Patients with pre-existing anemia at ICU admission	13%

(Walsh and Saleh, 2006).

Anemia during stay in ICU

The prevalence and severity of anemia during ICU admission is closely linked with the transfusion practice used. The evolution of anemia among non-transfused, non-bleeding, critically ill patients is difficult to study both ethically and in practice ***(Walsh and Saleh, 2006)***.

Nguyen et al., (2003) found that among non-bleeding ICU patients who did not receive red cell transfusions, hemoglobin

concentrations decreased by a mean of 0.52 g/dl per day. On average, hemoglobin concentrations decreased by 0.66 g/dl /day for the first 3 days and by 0.12 g/dl per day thereafter**.**

This early rapid decrease in hemoglobin values was also found in a prospective observational single center cohort study of patients receiving more than 24 hours of intensive care. The mean hemoglobin concentration in a cohort of non-transfused patients decreased from 12 g/dl at admission to 11 g/dl by days 3–4, after which values reached a plateau among patients remaining in the study. The normal mean baseline hemoglobin concentration of this cohort suggested that these observations might not be generalized to all intensive care admissions, but confirmed the early rapid onset of anemia in many critically ill patients ***(Walsh and Saleh, 2006)***.

Another way of assessing the prevalence of anemia in ICU is to examine transfusion rates in conjunction with a measure of illness severity and the hemoglobin transfusion triggers used **(Table 2)** ***(Walsh and Saleh, 2006)***.