ANEMIA IN CRITICALLY ILL PATIENTS; PREVALENCE AND PROGNOSTIC IMPLICATIONS

Thesis

Submitted for Fulfillment of Master Degree in **Intensive Care**

By

Kareem Mohamed Fawzy Mohamed Fawzy Ahmed Elkotby
(MBBCH)

Under Supervision of

Prof. Dr. Naglaa Mohammad Aly
Professor of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine –Ain Shams University

Prof. Dr. Manal Mohamed Kamal Shams Eldin
Professor of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine –Ain Shams University

Dr. Wael Sayed Ahmed Abd-Elghafar
Lecturer of Anesthesiology, Intensive Care and Pain Management
Faculty of Medicine –Ain Shams University

Faculty of Medicine
Ain Shams University
2020

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Naglaa Mohammad Aly****, Professor of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Prof. Dr. Manal Mohamed Kamal Shams Eldin****, Professor of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

I am deeply thankful to ***Dr. Wael Sayed Ahmed Abd-Elghafar****, Lecturer of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Kareem Mohamed Fawzy Mohamed Fawzy Ahmed Elkotby

List of Contents

List of Abbreviations

Abb.	Full term

2, 3 DPG: *2, 3 diphosphoglycerate*
ABC: *Anemia and blood transfusion in critical care trial*
ACE: *Angiotensin-converting enzyme*
ACS: *Acute coronary syndrome*
ADH: *Antidiuretic hormone*
ALI: *Acute lung injury*
ALT: *Alanine transaminase*
APACHE: *Acute physiology and chronic health evaluation*
ARDS: *Acute respiratory distress syndrome*
AST: *Aspartate aminotransferase*
ATICS *Audit of Transfusion in Intensive Care in Scotland*
ATP: *Adenosine tri-phosphate*
BOOST 2 *Brain Oxygen Optimization in Severe Traumatic Brain Injury*
BUN: *Blood urea nitrogen*
CABG: *Coronary artery bypass grafting*
CKD: *Chronic kidney disease*
COPD: *Chronic obstructive pulmonary disease*
CRIT: *Anemia and blood transfusion in the critically ill-current clinical practice in the United States*
CVS: *Cardiovascular system*
DAT: *Direct antiglobulin test*
DIC: *Disseminated intravascular coagulopathy*
DM: *Diabetes mellitus*
EAST: *Eastern Association for the Surgery of Trauma*
EGDT: *Early goal-directed therapy*
EPO: *Erythropoietin*
FDA: *Food and Drug Administration*

List of Abbreviations cont...

Abb.	Full term

Fe: *.....Iron*
Hb: *.....Hemoglobin*
HBOCs: *.....Hemoglobin-based oxygen carriers*
HCO_3 : *.....Bicarbonate*
HCT: *.....Hematocrit*
HELLP: *.....Heamolysis, elevated liver enzymes, low platelets count syndrome*
HEMPAS: *.....Hereditary erythroblastic multinuclearity with a positive acidified serum test*
HTN: *.....Hypertension*
HUS : *.....Hemolytic uremic syndrome*
ICU: *.....Intensive care unit*
IDA: *.....Iron deficiency anemia*
IHD: *.....Ischemic heart diseases*
IL-1: *.....Interleukin 1*
IL6: *.....Interleukin 6*
INR: *.....International normalized ratio*
K: *.....Potassium*
LCF: *.....Liver cell failure*
LDH: *.....Lactate dehydrogenase*
mcg/dl : *.....Micrograms per deciliter*
MCH: *.....Mean corpuscular heamoglobin*
MCHC: *.....The amount of hemoglobin relative to the size of the cell (hemoglobin concentration) per red blood cell*
MCV: *.....Mean corpuscular volume*
mEq/L: *.....Milliequivalent per liter*
MV: *.....Mechanically ventilated*
Na: *.....Sodium*
NSTEMI: *.....Non ST elevation myocardial infarction*
Pao_2: *.....Arterial oxygen pressure*
Pco_2: *.....Partial pressure of carbon dioxide.*

List of Abbreviations cont...

Abb.	Full term

PH: ..... *The power of hydrogen =the negative logarithm of the proton concentration*
PNH: ..... *Paroxysmal nocturnal hemoglobinuria*
PRBC: ..... *Packed red blood cells*
ProCESS: ..... *Protocolized Care for Early Septic Shock*
PT: ..... *Prothrombin time*
PTT: ..... *Partial thromboplastin time*
RBCs: ..... *Red blood cells*
RDW: ..... *Red cell distribution width*
RECESS: ..... *Red Cell Storage Duration study*
RHC ..... *Reticulocyte hemoglobin concentration*
Sao_2: ..... *Oxygen saturation of hemoglobin in arterial blood*
SCCM: ..... *Society of Critical Care Medicine*
STEMI: ..... *ST elevation myocardial infarction*
SVR: ..... *Systemic vascular resistance*
TACO: ..... *Transfusion-associated circulatory overload*
TIBC: ..... *Total iron binding capacity*
TNF: ..... *Tumor necrosis factor.*
TRALI: ..... *Transfusion related acute lung injury*
TRICC: ..... *Transfusion Requirements in Critical Care trial*
TRIM: ..... *Transfusion-related immunomodulation*
TTP: ..... *Thrombotic thrombocytopenic purpura*
WBCs: ..... *White blood cells*
WHO: ..... *World health organization*

List of Tables

List of Figures

INTRODUCTION

Anemia of critical illness is defined as anemia in the critically ill patient that cannot be explained by other causes and that is characterized by an inadequate response of endogenous erythropoietin in relation to the degree of hemoglobin deficiency present. It is a significant issue in critical care especially it is present in 97% of patients in the ICU at Day 8 and around 77% of patients are still anemic at hospital discharge [1,2].

The cause of anemia in critically ill patients is multi-factorial including: sepsis, haemolysis (and disseminated intravascular coagulation), iatrogenic blood loss secondary to laboratory sampling, post-operative anemia, bone marrow suppression/failure, decreased production of erythropoietin, anaemia secondary to drugs/toxins, overt or occult blood loss, functional iron deficiency, poor nutrition and haemodilution [3].

The amount of blood collected for diagnostic purposes at intensive care units leads to significant anemia. a recently published study by Jackson Chornenki *et al.* [4] confirmed that the total volume of blood loss due to phlebotomies during the whole intensive care stay was 337 mL; the mean daily volume was 32 mL. This volume of blood loss due to phlebotomies was associated with the development of anemia.

Critically ill patients are exposed to blood loss that will inevitably participate in the onset or worsening of anemia, but also potentially to a true iron deficiency. A study in Australia and New Zealand reported that bleeding was the reason for transfusion in 46% of transfusion events [(5)]. Blood loss is rarely the only explanation for anemia. During resuscitation with colloid and crystalloid solutions hemodilution contributes to the rapid decrease in hemoglobin concentration seen early after ICU admission in many critically ill patients without altering red cell mass [(6)].

A major factor resulting in the development and persistence of anemia is reduced new red blood cell production (erythropoiesis) which occurs in the bone marrow and is controlled by erythropoietin hormone. This appears to result from a combination of inappropriately low circulating erythropoietin and hypo-reactive bone marrow. ICU patients develop an "anemia of inflammation" in part because of proinflammatory cytokines, with resultant impaired RBC proliferation related to dysregulated iron metabolism and a blunted erythropoietin response. Anemia of inflammation is characterized by high levels of hepcidin, ferritin, and IL-6 and low levels of iron, erythropoietin, transferrin, and erythroferrone, resulting in iron-restricted erythropoiesis [(7)].

Hemolysis may also cause anemia in critically ill patients. This may be associated with several pathologic conditions, including bacterial infections, malaria, trauma and

conditions in which mechanical forces can lead to RBCs rupture, such as surgical procedures, hemodialysis and blood transfusion. Hemolysis results in release of free plasma hemoglobin and heme, which are toxic to the vascular endothelium. Hypersplenism may also lead to excessive RBCs destruction. As hemolytic anemia occurs because of intrasplenic destruction of erythrocytes [(8)].

The pathophysiologic consequences of anemia in critically ill patients include inadequate tissue oxygenation and eventual ischemia of end organs. Inadequate tissue oxygenation results from either decreased oxygen delivery and/or increased tissue oxygen consumption. Oxygen delivery is a function of arterial oxygen content and cardiac output. Hemoglobin concentration and Oxygen saturation both affect arterial oxygen content [(9)]. Oxygen consumption is the rate at which tissues take up oxygen and is a function of oxygen delivery and the amount of oxygen that is extracted by tissues (i.e., the oxygen extraction ratio).

However, the efficacy of red blood cell transfusions in improving oxygen delivery capacity is not established, many studies have looked into the hemoglobin range that would yield most improvement in tissue oxygenation, while minimizing the harm of red blood cell transfusions. A recent systematic review and meta-analysis found that red blood cell transfusion in critically ill patients with a hemoglobin level of 7–8 g/dL or lower (restrictive strategy) was associated with reduced risk of

30-day mortality, length of hospital stay, number of transfusions, and reduced risk of stroke than in critically ill patients receiving red blood cell transfusions with a liberal strategy (hemoglobin trigger 9–10 g/dL) [(10)].

More than one third of patients in intensive care units (ICUs) require red blood cell (RBC) transfusion to maintain a target hemoglobin concentration of 7 g/dL. Moreover, in patients who stay in ICU longer than a week, the proportion of RBC transfusion exceeds 70%. Since anemia and RBC transfusion are associated with worse clinical outcomes in critically ill patients, it is important to prevent anemia and the need for RBC transfusion in critically ill patients, which may improve the quality and clinical outcomes of critical care [(11)].

Aim of the Work

The aim of this work is to evaluate the prevalence of anemia in critically ill patients and to assess the effect of anemia of critical illness on the patients' outcome.

Chapter I:

ANEMIA

Definition

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. It results in a reduction in red cell mass and a decrease in the oxygen-carrying capacity of the blood. The World Health Organization (WHO) defines anemia as a hemoglobin <13 g dl^{-1} (hematocrit <39%) for adult males and <12 g dl^{-1} (hematocrit <36%) for adult non-pregnant females [(12)].

Hemoglobin threshold

Normal Hb distributions vary with age, sex, and physiological status, e.g., during pregnancy. WHO Hb thresholds were used to classify individuals living at sea level as anemic (Table 1) [(12)].