THE ROLE OF INTRAVENOUS IMMUNOGLOBULINS IN DECREASING THE NEED FOR EXCHANGE TRANSFUSION IN NEONATAL HYPERBILIRUBINEMIA

Thesis

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ABE	Acute Bilirubin Encephalopathy
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BA	Biliary Atresia
BAER	Brain Stem Auditory Evoked Responses
BCR	B Cell Receptor
BIND	Bilirubin Induced Neurological Dysfunction
CBC	Transcutaneous Bilirubinometry
CBC	Complete Blood Count direct antibody test (DAT)
CHT	Congenital Hypothyroidism
cMOAT	Canalicular Multispecific Organic Anion Transporter
CMV	Cytomegalovirus
CNSHA	Chronic Nonspherocytic Hemolytic Anemia
CO	Carbon Monoxide
COPD	Chronic obstructive pulmonary disease
DAT	Direct Antibody Test
2,3-DPG	2,3-Diphosphoglycerate
ER	Endoplasmic Reticulum
ERCP	Endoscopic Retrograde Cholangiopancreatography
ETCO	End-tidal Carbon Monoxide in Breath
FAB	Fragment, Antigen Binding
FC	Fragment, Crystallizable
G6PD	Glucose-6- Phsphate-Dehydrogenase Deficiency
GGT	G-Glutamyltransferase
GSTs	Glutathione S-Transferases
HDN	Hemolytic Disease of the Newborn
HDN	Hepatoiminodiacetic Acid
HE	Hereditary Elliptocytosis
HIDA	Hepatoiminodiacetic Acid
HPV	Human Papillomavirus
IgA	Immunoglobulin A
IgD	Immunoglobulin D

IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITP	Immune-mediated Thrombocytopenia
IUGR	Inrauterine Growth Retardation
IVIG	Intravenous Immunoglobulins
LED	Light-Emitting Diode
MRI	Magnetic Resonant Imaging
PK	Pyruvate Kinase
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, M-Protein, and
PPARs	Peroxisme-Prolifitated Activated Receptors
PTC	Percutaneous Transhepatic Cholangiography
PUBS	Percutaneous Umbilical Blood Sampling
RDS	Respiratory Distress Syndrome
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TCP	Transcutaneous Bilirubinometry
TSB	Total Serum Bilirubin
UDPGA)	Uridine-Diphosphoglucuronate
UGT	Uridine-Diphosphoglucuronate Glucuronosyltransferase
UGT1A1	Uridinediphosphoglucuronosyl Transferase 1A1

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Dedication

To my Grandfather' soul, I wish he is still with us

To my parents, who gave me every thing I have

To my husband, Abdullah who is behind all my achievements

To my son, whom I am waiting soon and give me a new meaning of life

APSTRACT

Exchange transfusion is not without risk; its complications include apnea, pulmonary hemorrhage, thrombocytopenia, coagulopathyies, hypoglycemia, hypocalcaemia, electrolyte imbalance, vasospasm, thrombosis, hypertension, arrhythmias, sepsis and necrotizing enterocolitis.

In isoimmune hemolytic diseases of the newborn, antibodies (Anti-A, anti-B, anti- D) coated erythrocytes are mainly eliminated through, antibody dependant cellular cytotoxic effect by Fc receptor bearing cells of the reticuloendothelial system.

In newborn infants, isoimmune hemolysis can be reduced or prevented and toxic bilirubin concentration can be avoided by means of reticuloendothelial Fc receptor blockage which means that the immunoglobulin act by occupying the Fc receptors of the the reticuloenothelial cells.

Keywords,,
THE ROLE OF INTRAVENOUS IMMUNOGLOBULINS IN DECREASING THE NEED FOR EXCHANGE TRANSFUSION.

INTRODUCTION AND AIM OF WORK

Neonatal Jaundice is one of the commonly seen neonatal problems, as it affects 60% of full term infants and 80% of preterm infants in the first 3 days of birth. Although transient, the condition account for up to 75% of hospital readmission in the first week after birth ***(Kristin Melton et al., 1999)***.

Neonatal Jaundice secondary to isoimmune haemolytic anemia (Rh – ABO incompatibility) is a cause of high serum bilirubin level due to haemolysis of RBC's secoundary to transplacental passage of antibodies. This lead to increased risk of acute bilirubin encephalopathy and kernicterus ***(Borgard et al., 2006)***.

Exchange transfusion is sometimes needed beside the conventional therapy (phototherapy) as it corrects anemia associated with hemolysis and is effective in removing sensitized red blood cells before they are hemolyzed. It also removes about 60% of bilirubin from the plasma, resulting in a clearance of about 30% to 40% of total bilirubin as it equilibrates with the extravascular tissues. Exchange transfusion is not without risk. It carries a 5% risk of major morbidity and the risks associated with blood exposure, Infants receiving exchange transfusion have increased risks of infection, NEC acidosis, hypocalcaemia, hypoglycemia, electrolyte abnormalities, and air embolism ***(Kristin Melton et al., 1999)***.

In recent years, intravenous immunoglobulins (IVIG) have been successfully used in isoimmune haemolytic anemia (Rh-ABO incompatibility)***. (Milqelad A M et al., 2004)***.

Intravenous Immunoglobulins (**IVIG):** was found to decrease hemolysis leading to reduction in serum bilirubin level. The immunoglobulin could act by occupying the FC receptors of reticulo - endothelial cells preventing them from taking up and lysing antibody coated RBCs ***(Mundy, 2005)***.

AIM OF THE STUDY

The aim of this study is to prove or disprove the effect of intravenous Immunoglobulins (IVIG) on serum bilirubin aiming to decrease the need for exchange transfusion in cases of Rh and ABO incompatibility (hemolysis).

BILIRUBIN METABOLISM

Introduction

Bilirubin is a nonpolar, lipid-soluble, potentially toxic end product of the catabolism of heme containing proteins, the major source of which is the circulating hemoglobin. In the newborn infant the normal destruction of the circulating red blood cells in the reticuloendothelial system account for 70 ~ 80% of the daily production of bilirubin ***(Maisels M et al., 1999)***.

There are elaborate physiologic mechanisms for its detoxification and disposition. Understanding these mechanisms is necessary for interpretation of the clinical significance of high serum bilirubin concentrations.

Formation of Bilirubin

Bilirubin is formed by breakdown of heme present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase and tryptophan pyrrolase. Eighty percent of the daily bilirubin production (250 to 400 mg in adults) is derived from hemoglobin (**Chowdhury N and Chowdhury., J 2007**). The remaining 20 percent is being contributed by other hemoproteins and a rapidly turning-over small pool of free heme. Enhanced bilirubin formation is found in all conditions associated with increased red cell turnover such as intramedullary or intravascular hemolysis (eg, hemolytic, dyserythropoietic, and megaloblastic anemias).

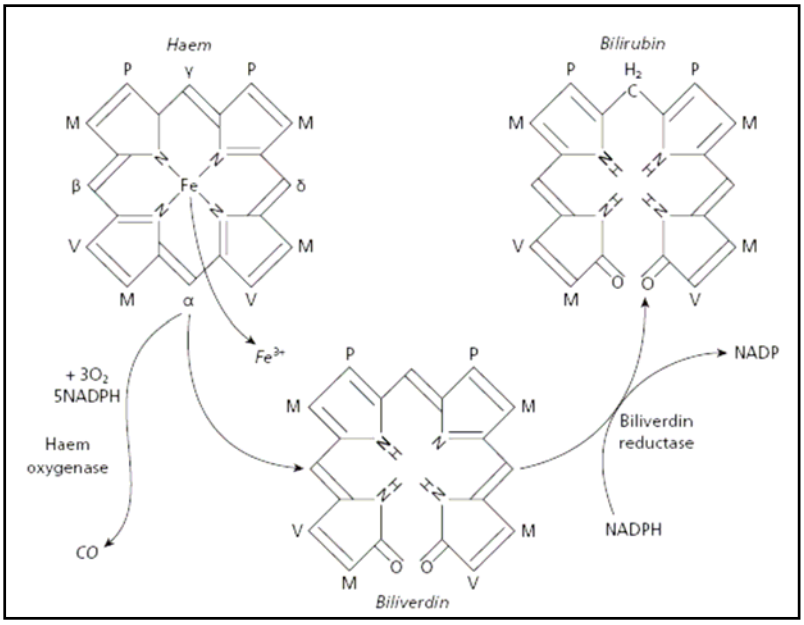

Figure (1): Enzyme-Catalysed Degradation Of Haem.
(Chowdhury N et al., 2007)

Breakdown of heme

Heme consists of a ring of four pyrroles joined by carbon bridges and a central iron atom (ferroprotoporphyrin IX). Bilirubin is generated by sequential catalytic degradation of heme mediated by two groups of enzymes; Heme oxygenase and Biliverdin reductase, heme oxygenase initiates the opening of the porphyrin ring of heme by catalyzing the oxidation of the alpha-carbon bridge. This leads to formation of the green pigment, biliverdin**,** which is then reduced by the biliverdin reductase to the orange-yellow pigment bilirubin IXa. Iron is released in this process, and the oxidized alpha-bridge carbon is eliminated as carbon monoxide **(CO).** Measurement of intrinsic CO production has been used to quantify bilirubin production Heme oxygenase is present in high concentrations in