A COMPARATIVE STUDY OF SINGLE PHOTOTHERAPY PLUS WHITE CURTAINS AND SINGLE PHOTOTHERAPY IN TERM NEWBORNS WITH HYPERBILIRUBINAEMIA

by

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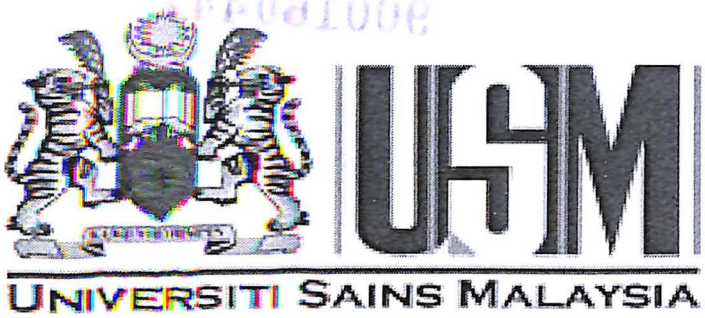

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TO

MY FAMILY

MY WIFE:

Ir. AFRISIANA ISKANDAR PUTRI

OUR CHILDREN:

ZOYA MARIE ADYASA

AUDREY DEVINA ADYASA

LUKAS ALDEN ADYASA

ACHIEVEMENTS and PUBLICATION

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This study has been presented during the

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ABBREVIATIONS

NADPH	Nicotinamide Adenine Dinucleotide Phosphate-Oxidase
UDPGT	Uridyl Diphosphate Glucuronyl Transferase
RBC	Red Blood Cell
G6PD	Glucose 6 Phosphate Dehydrogenase
ET	Exchange Tranfusion

ABSTRACT

English

Objective

To determine whether the addition of low-cost reflecting curtain to a standard phototherapy unit could increase effectiveness of phototherapy for neonatal jaundice.

Design

Randomized controlled clinical trial.

Setting

Level one nursery of the Hospital Universiti Sains Malaysia, Kelantan , Malaysia.

Patients

Term newborns with uncomplicated neonatal jaundice presenting in the first week of life.

Intervention

Phototherapy with white curtains hanging from the sides of phototherapy unit (study group, n=50) was compared with single phototherapy without curtains (control group, n=47).

Main outcome measures

The primary outcome was the mean difference in total serum bilirubin measured at baseline and after 4 hours of phototherapy. The secondary outcome was the duration of phototherapy.

Results

The mean (standard deviation) decrease in total serum bilirubin levels after 4 hours of phototherapy was significantly ($p<0.001$) higher in the study group [27.62 (25.24) μml/L] than in the control group [4.04 (24.27) μml/L]. Cox proportional hazard regression analysis indicated that the median duration of phototherapy was significantly shorter in the study group (12 hours) than in the control group (34 hours; χ^2 change 45.2; $p<0.001$; hazards ratio 0.20; 95% confidence interval 0.12 to 0.32). No difference in adverse events was noted in terms of hyperthermia or hypothermia, weight loss, rash, loose stools or feeding intolerance.

Conclusion

Hanging white curtains around phototherapy units significantly increase the efficacy of phototherapy in the treatment of neonatal jaundice without evidence of increased adverse effects.

Bahasa Malaysia

Tujuan

Untuk menentukan sama ada penggunaan langsir putih yang murah pada unit fototerapi yang biasa digunakan boleh meningkatkan keberkesanan rawatan jaundis neonatal.

Model

Bahan kes diambil secara rambang (randomized controlled clinical trial).

Tempat

Unit rawatan rapi neonatal dan nursery Hospital Universiti Sains Malaysia, Kelantan. Malaysia.

Pesakit

Bayi yang lahir cukup bulan dan tanpa komplikasi yang mengalami jaundis neonatal pada minggu pertama kelahiran.

Kaedah

Kajian dijalankan dengan membandingkan antara fototerapi dengan langsir putih (kumpulan kajian, n=50) dan tanpa langsir (kumpulan control,n=47).

Hasil Kajian

Keputusan pertama adalah membezakan purata paras bilirubin dalam darah pada bayi yang diambil pada awal penggunaan fototerapi dimulakan dan selepas 4 jam penggunaan fototerapi. Keputusan kedua adalah jangka masa penggunaan fototerapi.

Keputusan

Paras (purata) bilirubin dalam darah menurun selepas 4 jam penggunaan fototerapi secara nyata sekali ($p<0.001$) lebih banyak dalam kumpulan kajian [27.62 (25.24) μml/L] berbanding dengan kumpulan kontrol [4.04 (24.27) μml/L]. Analisa cox proportional hazards regression menunjukkan bahawa jangka masa penggunaan fototerapi pada kumpulan kajian adalah lebih pendek iaitu 12 jam berbanding dengan kumpulan kontrol iaitu 34 jam; χ^2 change 45.2; $p<0.001$; hazards ratio 0.20; 95% confidence interval 0.21 to 0.32). Kajian ini tidak menunjukkan perbezaan dalam kesan sampingan fototerapi pada bayi seperti hipertermia atau hipotermia, penurunan berat badan, ruam pada kulit, cirit birit atau tidak hadam susu.

Kesimpulan

Penggunaan langsir putih pada unit fototerapi telah memberi kesan yang nyata dalam meningkatkan rawatan jaundis neonatal bayi baru lahir tanpa kesan sampingan.

INTRODUCTION

1. INTRODUCTION

1.1 BACKGROUND

Jaundice is defined as yellowish discoloration of the sclerae and /or skin which is due to increased serum levels of bilirubin. It has been described as early as 1000 years ago in a Chinese textbook (Thor WR Hansen, 2002).

Hyperbilirubinaemia is a very common condition in neonates affecting 60 - 80% of the newborn babies during the first week of life (Agrawal R, 2002). It is the commonest morbidity in the neonatal period and 5 - 10% of all newborns require a diagnostic work-up and therapeutic intervention for pathological jaundice (Agrawal et al., 2001).

Unconjugated bilirubin is a lipid soluble substance that can cross the blood brain barrier, accumulate in the basal nuclei (kernicterus) and lead to brain damage (bilirubin encephalopathy). The most severe sequelae include lifelong athetoid cerebral palsy, severe sensorineural hearing loss, dental dysplasia and death (Kliegman, 2000).

These sequelae can be prevented by adequate therapy. If bilirubin levels are increasing, treatment for jaundice involves treatment of the underlying causes, phototherapy and/or exchange transfusion (Boyd, 2004). Intravenous immunoglobulin is an added new therapy in treating isoimmune haemolytic jaundice (Alcock and Liley, 2002).

Phototherapy has been used widespread and is proven to be effective in lowering serum bilirubin levels. The efficacy of phototherapy depends on the type of light-source, the wavelength and intensity of the light and the area of skin exposed (Thor WR Hansen, 2002).

Special blue light bulbs are most commonly used and have been proven to be more effective than fiber-optic lights. Blue light has an optimal wave length for photo-isomerization of bilirubin. It is widely used throughout the world. Green light penetrates deeper into the skin but is not more effective than blue light and it makes the babies look sick. White light is also used. Decreasing the distance between infants and lamps can make it more effective (Thor WR Hansen, 2002).

Double phototherapy is more effective than single phototherapy. An increase in light intensity renders phototherapy more effective. Usually 2 or 3 phototherapy units are used to increase light intensity. If hanging low cost white curtains around the phototherapy unit could be shown to be more effective than single phototherapy only, that would be very significant, especially for developing countries, having only a limited number of phototherapy units (American Academy of Pediatrics, 2004).

Before elaborating further on phototherapy and potential modifications to improve its effectiveness, there will be a brief description of the epidemiology and etiology of neonatal jaundice. The bilirubin metabolism and the clinical assessment of jaundiced babies will also be discussed briefly.

1.2 EPIDEMIOLOGY of NEONATAL JAUNDICE

Some literature reviews mention that East Asians and native American infants have higher serum bilirubin levels than Caucasian infants (Maisels, 2000a)

East Asians have inherently higher serum bilirubin levels at birth than whites. In America, children of full East Asian parentage were more likely to be diagnosed with jaundice than were white infants. Jaundice is a problem of public health and clinical significance in countries like Malaysia (Sabeena Setia, 2002).

Potential reasons for this increased incidence in (southeast) Asians include the high incidence of G6PD deficiency and other red cell abnormalities in these populations. More recently is has been found that point mutations in the bilirubin diphosphate-glucuronosyl transferase (UGT1A1) gene, associated with Gilbert syndrome are common in East Asians (Maisels, 2000a) and also in a Malay population (Surini et al., 2006).

There is a wide range of factors that affect neonatal bilirubin levels. They are listed in table 1.1.

Table 1.1 Important factors in the epidemiology of neonatal jaundice (Maisels, 2000a)

Associated factors	Effect on neonatal serum bilirubin levels		
	Increase	Decrease	No effect
Race	East Asians Native American Greek	African Caucasian	
Genetic of familial	Previous sibling with jaundice Variant promoter of mutation of UGT1A1 gene associated with Gilbert's syndrome		
Maternal	Older mothers Diabetes Hypertension Oral contraceptive use at time of conception First-trimester bleeding Decreased plasma zinc level	Smoking	
Drugs	Oxytocin Diazepam Epidural anesthesia Promethazine	Phenobarbital Meperidine Reserpine Aspirin Chloral hydrate Heroin Phenitoin Antipyrine Alcohol	Beta-adrenergic agents
Labour and delivery	Premature rupture of membrane Forceps delivery Vacuum delivery Breech delivery		Fetal distress Low apgar score
Infants	Low Birth weight Decreasing gestation Male gender Delayed cord clamping Delayed meconium passage Breast-feeding Caloric deprivation Weight loss Low serum zinc and Mg		
Drugs to infants	Chloral hydrate, pancuronium		
Others	Altitude		

1.3 ETIOLOGY

Indirect hyperbilirubinaemia in the first few days of life is caused by changes in bilirubin production and/or impaired conjugation or excretion of bilirubin. The most common causes of neonatal jaundice are listed in table 1.2.

Table 1.2 Causes of indirect hyperbilirubinaemia (Watchko, 2000)

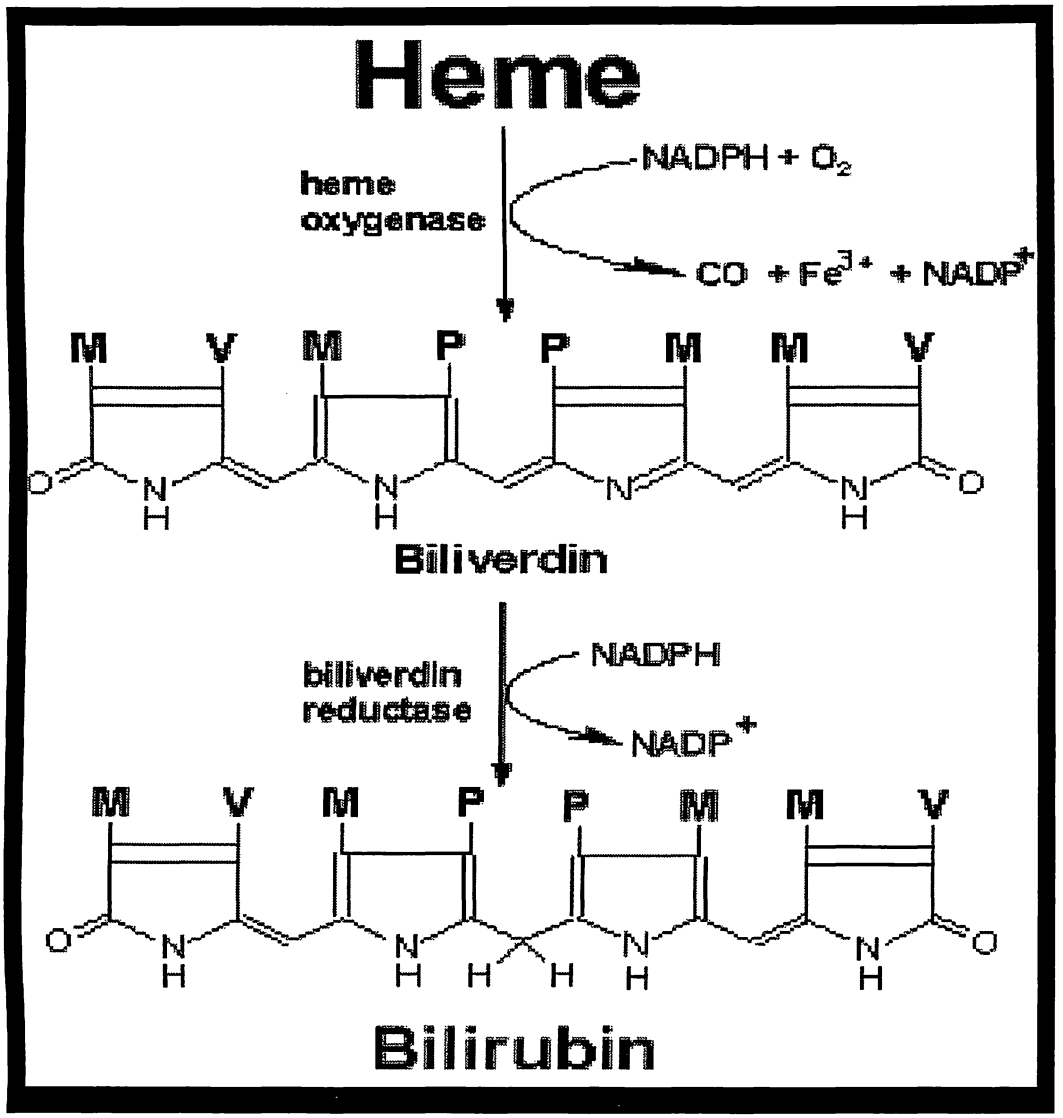
Increased bilirubin production or bilirubin load in the liver
Hemolytic disease Immune mediated Rh alloimmunization ABO or other blood group incompatibilities Hereditary Red cell membrane defect Spherocytosis Ellipcytosis Stomatocytosis Pyknocytosis Red blood cell enzyme defect Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency Hemoglobinophaties Alpha thalassemia and beta thalassemia Other causes of increased production Sepsis Disseminated intravascular coagulation Extravasation blood Hematomas Subapponeurotic hemorrhage Polycythemia Infant of diabetic mother
Impaired conjugation or decreased bilirubin clearance
Inadequate or poor feeding intake Prematurity Delayed or impaired lactogenesis Inadequate milk transfer Other feeding problem Inborn errors of metabolism Crigler-Najjar syndrome type 1 and type 2 Gilbert syndrome Tyrosinemia Hypermethioninemia Lucey-Driscoll syndrome Increased enterohepatic circulation Intestinal obstruction Meconium ileus Meconium plugging Cystic fibrosis Hormonal Hypothyroidism Hypopituitarism

1.4 METABOLISM OF BILIRUBIN

Every human will continuously produce and form bilirubin and newborn infants produce relatively more bilirubin than any other age group. The bilirubin load of the newborn is 2 to 3 times higher than that of an adult (Laura A.Stokowski, 2006).

1.4.1 Bilirubin Production

Bilirubin production is the result from degradation of heme from the red blood cells (75% - 80%), muscle myoglobin and liver enzymes such as cytochrome and catalases (20% - 25%), through the intermediary step of biliverdin. The formation of bilirubin is shown step by step in figure 1.1. Bilirubin in the serum of humans occurs in the form of the 4Z,15Z isomer and is almost insoluble in water (Hansen, 2000).



Substituents: M=methyl, P=proprionic, V=vinyl

Figure 1.1 Formation of biliverdin and unconjugated bilirubin from heme. Reproduced from (Michael W. King, 2006) with permission

1.4.2 Transport of Bilirubin

The indirect bilirubin or unconjugated bilirubin is transported in the plasma, bound to albumin with a binding affinity of $10^7 - 10^8$ M^{-1} at the primary binding site, but there is also a secondary binding site on albumin where bilirubin is bound with lower affinity (Hansen, 2000).

Because of the high affinity of albumin for bilirubin, the equilibrium concentration of free or unbound bilirubin in the plasma is only in the low nanomolar range even in the presence of hyperbilirubinaemia. But when the concentration of bilirubin increases excessively, the primary binding site of albumin becomes saturated and free bilirubin concentration will increase markedly. The binding of bilirubin to albumin increases with postnatal age and is reduced in sick babies and also in the presence of exogenous or endogenous binding competitors. Besides binding to albumin, bilirubin can also bind to other proteins such as ά-fetoprotein, ligandin, lipoprotein, lysine and erythrocytes (Hansen, 2000).

1.4.3 Uptake, conjugation and Excretion of Bilirubin

After bilirubin-albumin binding, this bilirubin-albumin complex passes through the hepatic circulation and comes into contact with hepatocytes and bilirubin is transported into the cell. Within the hepatocyte around 60% of bilirubin is found in the cytosol and 25% in the microsomes (Hansen, 2000).