A RANDOMISED CONTROLLED TRIAL OF SINGLE PHOTOTHERAPY WITH REFLECTING CURTAINS AND DOUBLE PHOTOTHERAPY IN TERM NEWBORNS WITH HYPERBILIRUBINEMIA

By

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TO

THE LOVE OF MY LIFE,

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MUHAMMAD AIMAN MUSTAFA KAMAL

AMIRUDDIN MUSTAFA KAMAL

MUHAMMAD AMIN MUSTAFA KAMAL

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ABBREVIATIONS

AAP	American Academy of Pediatrics
A&E Department	Accident & Emergency Department
CI	Confidence Interval
CRP	C-reactive protein
DP	Double Phototherapy
ET	Exchange Transfusion
GIT	Gastro-intestinal Tract
G6PD	Glucose 6 Phosphate Dehydrogenase
HIV	Human Immunodeficiency Virus
HUSM	Hospital Universiti Sains Malaysia
IV	Intra-venous
MOH	Ministry of Health
NICU	Neonatal Intensive Care Unit
NICE	The National Institute for Health and Clinical Excellence, United Kingdom
SD	Standard Deviation
SPRC	Single Phototherapy with Reflecting Curtains
SPSS	Statistical Package for the Social Sciences
s.w.t.	Subhanahu wa taala

ABSTRACT

English

Objective

To compare the efficacy of single phototherapy with reflecting curtains and double phototherapy in treating neonatal jaundice.

Design

Randomized controlled clinical trial.

Setting

NICU Hospital Universiti Sains Malaysia, Kelantan, Malaysia.

Patients

Term newborns with severe neonatal jaundice in the first 2 weeks of life.

Intervention

Single phototherapy with reflecting curtains (intervention group, n=63) was compared with double phototherapy (control group, n=54).

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 serum bilirubin after 4 hours of phototherapy in the intervention group was 24.16 (27.87) μmol/L and the control group was 21.11 (24.69) μmol/L (p 0.536), statistically not significant. Cox proportional hazards regression analysis indicated that there was no statistically significant difference in duration of phototherapy in both intervention (SPRC) and control (DP) (x^2 change 1.641; p 0.200; hazard ratio 0.784; 95% confidence interval 0.542 to 1.136). There were no other significant adverse events noted.

Conclusion

This study suggested that single phototherapy with reflecting curtains are equally effective as double phototherapy in treating severe neonatal hyperbilirubinaemia.

Bahasa Malaysia

Tujuan

Kajian ini adalah untuk membandingkan di antara satu unit fototerapi bersama kain langsir berpantulan berkesan atau lebih lagi berbanding dua unit fototerapi.

Model

Bahan kes diambil secara rawak (Randomized controlled trial)

Tempat

NICU, Hospital Universiti Sains Malaysia, Kelantan, Malaysia.

Pesakit

Setiap bayi yang lahir cukup bulan yang mengalami jaundis neonatal yang agak tinggi pada dua minggu kelahiran.

Kaedah

Kajian dilakukan dengan membandingkan diantara satu unit fototerapi bersama kain langsir berpantulan (kumpulan kajian, n=63) dengan dua unit fototerapi (kumpulan kawalan, n=54).

Hasil kajian

Keputusan utama adalah untuk melihat perbezaan pada purata paras bilirubin di dalam darah bayi yang diambil pada sebelum fototerapi dimulakan dan setelah empat jam penggunaan fototerapi. Keputusan kedua adalah jangka masa penggunaan fototerapi.

Keputusan

Paras purata bilirubin dalam darah menurun selepas 4 jam penggunaan fototerapi bagi kumpulan kajian adalah 24.16 (27.87) μmol/L dan kumpulan kawalan 21.11 (24.69) μmol/L (p 0.536). Dimana, ia adalah tidak bererti secara statistik. Analisa cox proportional hazards regression analysis menunjukkan tiada perbezaan secara statistik bagi tempoh penggunaan fototerapi pada kedua-dua kumpulan ini (x^2 change 1.641; p 0.200; hazard ratio 0.784; 95% confidence interval 0.542 to 1.136). Tidak ada kesan sampingan lain didapati setelah diuji.

Kesimpulan

Penggunaan kain langsir berpantulan pada unit fototerapi menjadikan satu unit fototerapi sama mantap dengan dua unit fototerapi dalam rawatan jaundis neonatal.

INTRODUCTION

1. Introduction

1.1 Background

Neonatal hyperbilirubinaemia is very common in newborns. Almost 60% of term normal newborns will have jaundice during the first week of life (Kliegman, 2007). By definition, neonatal jaundice is yellowish discoloration of the sclerae and/or skin due to increased serum levels of bilirubin in the blood. It is divided into indirect hyperbilirubinaemia and direct hyperbilirubinaemia.

Indirect hyperbilirubinaemia often does not cause problems, but it can be severe enough to lead to kernicterus. Bilirubin is potentially toxic to the developing central nervous system and can cause kernicterus (Dennery, 2001). Indirect bilirubin or unconjugated bilirubin is lipid soluble, thus can cross the blood brain barrier entering the central nervous system. The amount of bilirubin entry into the brain is directly related with the incidence of bilirubin encephalopathy in animal models (Hansen, 2000). Many theories have been proposed for the mechanism of bilirubin causing kernicterus but the exact mechanism is still not confirmed. It was postulated that bilirubin deposited in brain cells cause kernicterus by disrupting neuronal metabolism and functions (Kliegman, 2007).

Studies on neonatal jaundice had been made since many centuries ago. Descriptions of yellow staining of the basal ganglia of the brain in jaundiced infants were first made by Orth (Figure 1.1) in 1875 (Hansen, 2000). But only in 1903,

Christian Schmorl (Figure 1.2) had linked the term 'kernicterus' to yellowish staining of basal ganglia in jaundiced infants (Hansen, 2000). Initially, kernicterus was used to describe the pathological finding of yellowish staining of basal ganglia. Nowadays, the term kernicterus was also used to describe clinical manifestations of those infants suffering from bilirubin encephalopathy.

Kernicterus is a neurologic syndrome resulting from the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei (Figure 1.3) (Kliegman, 2007). Kernicterus leads to devastating and permanent neuro-developmental handicaps (AAP, 2001). Long term sequalae such as severe choreoathetosis, gaze paresis, hearing loss and developmental delay may occur in those survivors of kernicterus (AAP, 2004).

According to 2004 American Academy of Pediatrics guidelines for the management of hyperbilirubinaemia in newborn, 3 clinical phases were identified. Lethargy, hypotonia and poor sucking manifest the early phase of acute bilirubin encephalopathy. The intermediate phase is characterized by moderate stupor, irritability and hypertonia (retrocollis or opisthotonus). The advanced phase is characterized by pronounced retrocollis/opisthotonus, shrill cry, anorexia, apnoea, fever, deep stupor to coma, sometimes seizures and death.

Babies in the early phase of acute bilirubin encephalopathy may have reversible central nervous system changes. Generally, for intermediate to advanced acute phase bilirubin encephalopathy, central nervous system changes are irreversible (Van Praagh, 1961 & Volpe JJ, 2008).

Bilirubin is neurotoxic, but the inter-individual variations in vulnerability are not fully understood (Hansen, 2010). Neonatal hyperbilirubinaemia and bilirubin encephalopathy has been extensively researched for many years. However, there is still no specific level of total serum bilirubin above which kernicterus can be predicted to happen (Maisels et al, 2008 & MOH, 2003). Factors that predisposed for bilirubin neurotoxicity are duration of exposure to bilirubin and the brain concentration of bilirubin (Kliegman, 2007). Few other factors are also involved in increasing the vulnerability such as acidosis, hyperosmolality, haemolysis, sepsis and ill condition of the baby (Maisels, 2005).

Because of the above mentioned potentially severe and permanent consequences of neonatal hyperbilirubinaemia, early and optimal treatment is very important. The aim of treatment in neonatal hyperbilirubinaemia is to lower the concentration of circulating bilirubin as fast as possible (Maisels et al, 2008). It can be achieved either using phototherapy or exchange transfusion. Phototherapy has been introduced since 1958, and many trials done previously have demonstrated its efficacy and safety (Brown et al, 1985). Exchange transfusion was introduced in the 20th century, after the discoveries of blood groups. Surprisingly, the first exchange transfusion was done to remove sensitized red blood cells in a patient with Erythroblastosis Fetalis (Hansen, 2000). However, since then; exchange transfusion had become a modality of treatment of severe neonatal hyperbilirubinaemia no matter what is the underlying pathology (Hansen, 2010).

Exchange transfusion is effective because it reduces both circulating bilirubin and antibodies. Its efficacy has been used as a reference to measure the efficacy of phototherapy in treating neonatal hyperbilirubinaemia (Maisels, 2001 & Steiner et al, 2007). However, exchange transfusion takes a long time to prepare and it poses multiple risks, including HIV infection. These factors make that exchange transfusions are only used as a last resort to prevent kernicterus.

The main treatment of jaundice is still phototherapy. Many factors are involved in determining phototherapy efficacy. It is positively dependent on spectral qualities of the delivered light (wavelength range and peak), intensity of light (irradiance), exposed body surface area and duration of exposure (Vreman et al, 2004).

Previous studies had shown double phototherapy were more effective compared to single phototherapy in reducing serum bilirubin in neonatal jaundice. Sarici et al (2000) and Boonyarittipong et al (2008) had demonstrated the efficacy of double phototherapy compared to single phototherapy. The single phototherapy in both these study are consist of a conventional phototherapy without any curtain or white curtain hanged. However, increasing body temperature was statistically significant finding in double phototherapy group in Boonyarittipong et al study.

Multiple efforts have been made to improve the efficacy and reduce the costs of phototherapy. These included the use of white lights (Meslo et al, 2000) and the use of white reflecting curtains at the side of the phototherapy unit (Djokomuljanto et al, 2006). Reflecting curtains have been shown to be more effective than single

phototherapy but so far no comparison has been made between single phototherapy with curtains and double phototherapy.

Djokomuljanto (Djokomuljanto et al, 2006) had demonstrated that by hanging white curtains around phototherapy units significantly increases efficacy in the treatment of neonatal jaundice without evidence of increased adverse effects. However, it only compares single phototherapy with white curtain and conventional single phototherapy and the mean total serum bilirubin at start of phototherapy was lower (intervention group = 262.94 (61.51) μmol/l & control group = 264.76 (56.63) μmol/).

Sivanandhan (Sivanandhan et al, 2009) also had done randomized controlled trial comparing single phototherapy with sling to single phototherapy without sling. The sling been used in this study was only described as reflective material hung on the sides of a phototherapy unit. No further details of colour, and the type of material used were reported. He had showed no significant difference in the duration of phototherapy between the groups. The rate of decrease in serum bilirubin was higher in sling group (0.23 ± 0.49 mg/dL, mean ± SD) compared to non-sling group (0.03 ± 0.47 mg/dL) but it was not statistically significant with p-value 0.06. Babies with haemolytic diseases of newborn were not included in this study.

The aim of this study is to compare the effectiveness of single phototherapy with reflecting curtains with that of double phototherapy in treating neonatal jaundice. Reflecting curtains are used to increase the irradiance of single phototherapy to a similar or higher strength than double phototherapy.

Figure 1.1 Johannes Orth (1847 - 1932) (Hansen, 2000) reproduced with permission.

Figure 1.2 Christian Georg Schmorl (1861-1932) (Hansen, 2000) reproduced with permission.

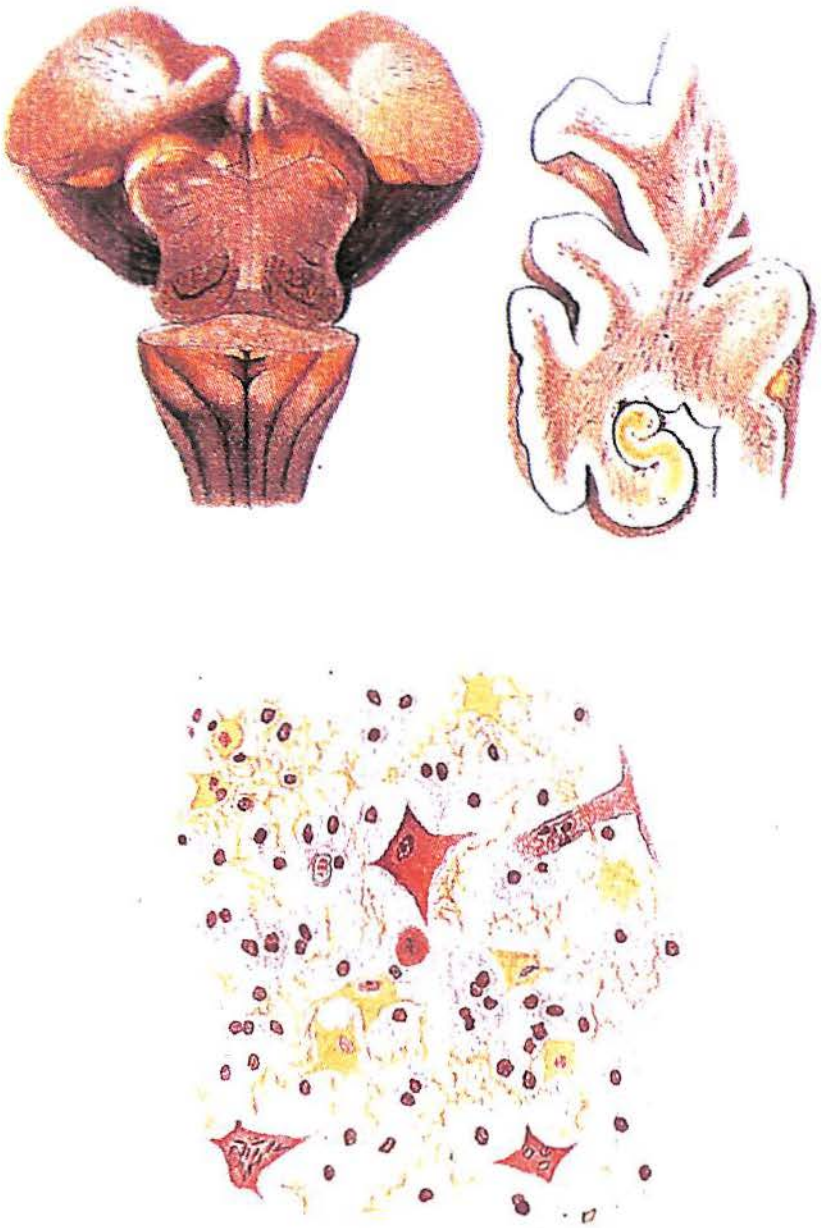

Figure 1.3 Colour figure from the 1904 publication by Schmorl, illustrating the findings that led him to linked the term kernicterus and jaundice of the basal ganglia (Hansen, 2000).

Hereunder, the bilirubin metabolism, the epidemiology, etiology and clinical assessment of neonatal jaundice are elaborated briefly after which a more detailed literature review of the treatment of neonatal jaundice is given.

1.2 Metabolism of Bilirubin

The neonatal period is a transition period from the foetal stage (where the placenta plays a major role in eliminating lipid-soluble bilirubin) to the adult stage (during which bilirubin is conjugated in the liver and this water-soluble bilirubin is excreted from hepatic cells into the biliary system and gastrointestinal tract) (Maisels et al, 2008). Neonatal hyperbilirubinaemia occurs when production of bilirubin exceeds the clearance of bilirubin from the body.

Red blood cells of the newborn have a shorter half-life compared to adults. The concentration of red blood cells in the circulation is also higher in newborns compared to adults (Kliegman, 2007).

Bilirubin is a breakdown product of the red cells in the blood. Red blood cells breakdown produces lipophyllic bilirubin, mostly bound to albumin. Bilirubin in the serum of human occurs in the form of 4Z, 15Z isomer and is almost completely insoluble in water (Lightner, 2001).

After uptake by the liver, it is converted into monoglucuronides and a diglucuronide (direct bilirubin) by the enzyme uridine-diphosphoglucuronosyl-transferase 1A1 (UGT1A1). The water-soluble glucuronides are excreted in bile

through canalicular multidrug-resistance associated transport protein (Maisels et al, 2008).

From bile, the conjugated bilirubin will be excreted into the gut. Bacterial action in the gut will convert conjugated bilirubin into urobilinogen. Urobilinogen is further metabolized into stercobilinogen and excreted through faeces. Some of the conjugated bilirubin may undergo de-conjugation into unconjugated bilirubin. This unconjugated bilirubin will be absorbed into the circulation via enterohepatic circulation. The bilirubin metabolism is illustrated in Figure 1.4.