THE DEVELOPMENT OF LIGHT EMITTING DIODE (LED)-BASED AS A BABY-FRIENDLY DEVICE FOR TREATMENT OF NEONATAL JAUNDICE

by

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Thesis submitted in fulfillment of the requirements
for the degree of
Master of Science

September 2018

ACKNOWLEDGEMENT

Bismillahirrahmanirrahim. Alhamdulillah.

I would first like to express my biggest gratitude to my supervisor, Professor Md Roslan Hashim of the School of Physics, PPSF USM Penang and my co-supervisor Professor Zabidi Azhar Mohd Hussin, previously from the School of Medical Sciences, PPSP Hospital USM Kelantan for their continuous support, expert guidance, care, and concern. Such supervision, motivation, and input have enabled and steered me in the right direction throughout my study. I would also like to thank Professor Zabidi's Neurology & Psychiatry (Pediatric Neurology) grant, (304/PPSP/652205/K134) for the financial assistance in completing this research project.

I am grateful to Mr. Muhammad Anis from the Engineering Lab, PPSF for the assistance and sharing of his know-how of developing my prototypes and power supply adapter. I would like to thank my colleagues in the Research Office Pediatric Department, PPSP Hospital USM Kelantan, Nurul Ilyana, Farhana, Fatihah, Diana, and Shahida for their company during my lab work there.

Finally, my profound gratitude goes to my parents Puan Noraizan and Encik Zainudin, and especially to my husband Mohd Faiz for their unfailing moral support, encouragement and believe in me throughout my years of study, as well as during the researching process and writing this thesis. This successful thesis completion would not have been possible without them.

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LIST OF ABBREVIATIONS

CFT	Compact fluorescent tube
LED	Light emitting diode
USM	Universiti Sains Malaysia
TSB	Total serum bilirubin
PT	Phototherapy
HPLC	High-performance liquid chromatography
CPG	Clinical Practice Guidelines
ABO	(blood) A, B and O
G6PD	Glucose 6 phosphate dehydrogenase
GDG	Guideline Development Group
DVET	Double-volume exchange transfusion
SVET	Single-volume exchange transfusion
NICU	Neonatal Intensive Care Unit
UK	United Kingdom
MHRA	(UK) Medicines and Healthcare products Regulatory Agency
IEC	International Electrotechnical Commission
IC	Integrated circuit
DC	Direct current
NIST	National Institute of Standards and Technology

SPSS	Statistical Package for the Social Sciences
SE	Standard error
DNA	Deoxyribonucleic acid

LIST OF SYMBOLS

I_T	Total current
P	Power consumption
V	Voltage

PEMBANGUNAN YANG BERASASKAN DIOD PEMANCAR CAHAYA (LED) SEBAGAI PERANTI MESRA BAYI UNTUK MERAWAT JAUNDIS NEONATAL

ABSTRAK

Enam puluh peratus bayi yang baru lahir terdedah kepada jaundis semasa dua minggu pertama kehidupan mereka, adalah disebabkan fungsi hati yang belum matang untuk menampung dan memproses pengeluaran bilirubin. Rawatan fototerapi terbukti dan diketahui secara meluas boleh merawat hiperbilirubinemia. Sumber cahaya yang biasa digunakan dalam peranti fototerapi konvensional adalah tiub pendarfluor biru khas, tiub pendarfluor padat (CFT), lampu sorot halogen dan selimut gentian optik. Walau bagaimanapun, peranti konvensional memerlukan ruang yang luas, mahal serta melibatkan kos untuk penyelenggaraan berkala. Oleh itu, BiliBaju yang berasaskan diod pemancar cahaya (LED) diperkenalkan bagi mengurangkan kos, mudah alih, dan sebagai alat fototerapi yang mesra bayi, di samping tidak menjejaskan keberkesanan dalam merawat penyakit jaundis. Sebuah prototaip di reka dengan ciri-ciri yang teguh dan kebolehpercayaan yang tinggi. Beberapa eksperiman dilakukan secara *in vitro*, kerana untuk mendapatkan hasil kajian secara terus dan cepat. Sampel serum yang telah didedahkan kepada sumber diod pemancar cahaya, kemudian dianalisis di makmal Patologi Kimia, Hospital USM. Pada 12 V voltan operasi, sinaran spektrum BiliBaju adalah 54.14 $\mu W/cm^2/nm$, dan panjang gelombang sumber cahaya BiliBaju seragam pada 458.49 nm. Jumlah sampel serum bilirubin yang berbeza dalam saiz tiub ujian yang sama menunjukkan jumlah yang lebih rendah 500 μL bertindak balas dengan lebih cepat berbanding dengan serum bilirubin 1500 μL, pada $r = -.822$, p

<0.01 untuk 500 μL dan $r = -.800$, $p <0.01$ untuk sampel 1500 μL. Selain itu, tidak terdapat perbezaan keertian dalam tindak balas pengurangan serum bilirubin untuk keadaan kerja yang berlainan seperti di dalam bilik gelap atau di bilik pencahayaan biasa, kerana korelasi Pearson antara ruang gelap $r = -.812$, pada $p <0.01$, dan normal keadaan pencahayaan, $r = -.808$, pada $p <0.01$. Di samping itu, kaedah penyampaian cahaya antara keadaan rata atau berbungkus sepenuhnya, terdapat tindak balas perlahan dalam keadaan rata dan terbuka berbanding dengan sampel yang dibalut sepenuhnya. Hasil korelasi Pearson antara sampel yang dibungkus sepenuhnya oleh sumber cahaya pada $r = -.814$, pada $p <0.01$, manakala sampel yang hanya terdedah kepada sinar cahaya dari keadaan rata berkorelasi pada $r = -.793$, pada $p <0.01$. Dari hasil uji kaji ini menunjukkan ada potensi yang amat baik oleh BiliBaju yang berasaskan diod pemancar cahaya (LED) sebagai penyelesaian terbaik untuk rawatan penyakit kuning neonatal.

THE DEVELOPMENT OF LIGHT EMITTING DIODE (LED)-BASED AS A BABY-FRIENDLY DEVICE FOR TREATMENT OF NEONATAL JAUNDICE

ABSTRACT

Sixty percent of newborns are jaundiced in their first two weeks of life for their liver is immature and unable to cope with the production of bilirubin. Phototherapy treatment is proven and widely known to treat hyperbilirubinemia. The common light sources used in conventional phototherapy device are special blue fluorescent tubes, compact fluorescent tubes (CFT), halogen spotlights and fibre optic blankets. However, the conventional device is capacious, expensive and cost involved in periodical maintenance. Hence, the idea of BiliBaju which based on LED is to develop a low cost, mobile, and baby-friendly phototherapy device, and promising the same or better effectiveness in treating neonatal jaundiced. A prototype is designed with robust features and high reliability. Several experiments were done *in vitro*, for *in vitro* offer fast screening result. Samples were exposed to the LEDs light source, then were analyzed in Chemical Pathology laboratory, Hospital USM. At 12 V of its operating voltage, the spectral irradiance of the BiliBaju is 54.14 $\mu W/cm^2/nm$, and the wavelength of the BiliBaju light source was uniform at 458.49 nm. A different volume of serum bilirubin samples in the same test tube size shows the lower volume of 500 μL reacts faster compared to 1500 μL serum bilirubin, at $r = -.822$, $p<0.01$ for 500 μL and $r = -.800$, $p<0.01$ for sample 1500 μL. Moreover, there is no significant difference in the reduction reaction of serum bilirubin for the different working condition as in a dark room and in the normal lighting room, as Pearson correlation between darkroom

r= -.812, at p<0.01, and normal lighting conditions, r= -.808, at p<0.01. In addition, the method of light delivery between open flat or fully wrapped condition, there is a slower reaction in open flat condition compared to fully wrapped samples. The results of the Pearson correlation between the sample that is being fully wrapped by the light source at r= -.814, at p<0.01, while the sample that only being exposed to light rays from a plane source correlate at r= -.793 at p<0.01. In the experiments, the prototype showed a promising method of upgrading the current phototherapy system and offering faster treatment for neonatal jaundice.

CHAPTER 1

INTRODUCTION

1.1 Background of study

All expectant parents hope that their babies will be healthy, yet sometimes a problem arises. The main reason is that the baby has to make many physical adjustments outside their mother's womb. Not all babies have the same illness condition but some diagnoses are common to newborn, such as anemia, apnea, hydrocephalus, sepsis and the most common one is jaundice. Sixty percent of newborn – term or preterm baby are jaundiced in their first two weeks of life.

Phototherapy treatment is the most common and proved to be effective to treat jaundice. Phototherapy is the use of visible light predominantly 450 nm to 490 nm for the treatment of jaundice in newborns. Only these wavelengths in that blue-green region able to penetrate the tissues are absorbed by bilirubin [1] can have a phototherapeutic effect. Newborn infants produce more bilirubin compared to any other age group, but their metabolisms in secreting the unconjugated bilirubin are low. The energy emitted from the light will change the structure of bilirubin, converting it into molecules that soluble in water and can be excreted in urine [2]. The important mechanism in delivery phototherapy is the irradiance stability of the light source. Light emitting diodes (LEDs) technology has rapidly improved in the past few decades. The revolutions of the blue LED contributes to a huge range of applications, including in medical applications. Thus, the phototherapy device with LED as their light source proved that the effectiveness in treating jaundice is better than other light sources.

1.2 Understanding the medical terms for procedures and treatments

In this study, there are several medical fundamental terms that kept repeating and the understanding of these terms and the procedures involved are essential. Blood is the key to the research where blood is made up of two parts that are cells and fluids where fluids are consists of plasma and serum. Cells are divided into red blood cells, white blood cells, and platelets.

Two important elements in bilirubin are direct bilirubin (conjugated) and indirect bilirubin (unconjugated) which equal to the total bilirubin. The determination of the total, direct and indirect bilirubin are the frequent method used in clinical blood laboratory tests for the values normally indicate the reading of the severity of jaundice level. Only the reading of the total bilirubin and direct bilirubin is provided by the equipment that used to do the bilirubin test. Therefore, the data of the indirect bilirubin are obtained by deducting the direct bilirubin reading from the total bilirubin reading. However, data interpretations in the results sections, only total bilirubin data, and graphs, namely total serum bilirubin (TSB) with SI units µmol/L, are shown as the TSB is widely used in the clinical test as a standard chemistry screen [6]. By analysing the fluid from the blood sample drawn, TSB can be determined by spectrophotometric methods [3]. The commonly used device is High-performance liquid chromatography (HPLC).

Bilirubinemia is the condition where an increased amount of bilirubin in the blood is detected where the bilirubin is normally present in relatively small amounts. Bilirubinemia also used to describe the excessive amount of erythrocytes or any problem with the mechanism of excretion in the bile, namely pathologic condition problem. Elevated to a certain level of bilirubin pigment in the blood is called hyperbilirubinemia, meaning that baby is now diagnosed with jaundice.

1.3 Problem statements

Presently, the common light sources that available in phototherapy devices are special blue fluorescent tubes, compact fluorescent tubes (CFT), and halogen spotlights and fibre optic blankets. Apart from the design and their effectiveness, these devices have many disadvantages, including high heat production and unstable broad wavelength of its light output. They also have the limitations in terms of their light intensities and portability.

Neonatal jaundice will be treated in an incubator for hours, which requires both baby and family, especially mothers, to stay in hospitals and to be separated from her baby especially when not in visiting hours. This eventually will disturb the breastfeeding cycle and the bonding between babies and mothers. Some babies might even have nipple confusion, as nurses are fed milk via cup or syringe when the mother is not at the hospital. More severe jaundice cases will take longer time treatment and more time will be spent in the hospitals for the family.

The idea of the Bilibaju is to bring jaundice treatment to be more effective as the conventional blue light source, where the light will only cover the baby's torso at once. The Bilibaju offered a low-cost, and portable device to deliver phototherapy while treating jaundice effectively. BiliBaju chooses light emitting diode (LED) as the light source for the LEDs are the latest and reliable light source for phototherapy treatment [4]. The durability, small in size and shape, and power efficiency of the LEDs making it possible to design and create a BiliBaju prototype.

With the same characteristic and properties as the conventional device available in hospitals, to deliver phototherapy, this portable device would help in lowering bilirubin count in newborn, while in the care of their own parents. The cost of BiliBaju is very economical and will help local hospitals to save more on the device, maintenance, spaces and also labour work. The device safety and the effectiveness of treating jaundice will be anticipated throughout the project.

Hence will reduce prolonged jaundice cases, and hospitals are then available for any severe cases. Mother-to-baby bonding also is not affected, especially during the mother's confinement period, thus both physically and emotionally mother and newborn are well taken care of.

1.4 Objectives of the research

1. To design a clinical device named BiliBaju towards performing phototherapy treatment in the hospital or at home.
2. To study the physical characteristics of the commercial blue LED as the light source of the BiliBaju device with the references of the conventional phototherapy system.
3. To identify the physical features of the BiliBaju prototype.
4. To study the reactivity of bilirubin during light exposure to the blue LED light of the BiliBaju prototype in different working conditions.

1.5 Scope of research

The scope studies will cover the fundamental of blue LEDs, the effectiveness of commercial and low-cost blue LED strips which are ready-made and commercially available in normal hardware stores. Next is, the usage of LEDs as a light source for phototherapy to treat neonatal jaundice.

Once a robust BiliBaju prototype is made, all characteristics and properties of the blue LED light are recorded. *In vitro* experiment is conducted by exposed the bilirubin serum sample to the BiliBaju prototype in different working conditions. Preliminary results from the *in vitro* test will be discussed.

1.6 Thesis outlines

This thesis is comprised of Chapter 1 as an introduction. Several important terms are discussed for a better understanding of the medical terms mentioned in the research. This chapter also explains the background study of blue LEDs and phototherapy as well as the objectives of the thesis. Chapter 2 will focus on the literature reviews about the fundamental mechanisms in neonatal jaundice and phototherapy treatment. Dosage, history of phototherapy treatment, chemical interactions during phototherapy and the light source of the device performing phototherapy. The costs of treating neonatal jaundice also are discussed in this chapter and the benefit of using blue LED as a phototherapy light source. Chapter 3 will explain the ideas and the development in constructing the prototypes. Next, the experimental setups, procedures, and methods that used during *in vitro* experiments and measurements. In this chapter also describes the light detector device and software used to determine the characteristics of the LED light source. Results and discussions are in Chapter 4, where results are divided into two parts. Part one will describe the physical features of the BiliBaju prototype, mainly the comparisons of the LED light source used by the BiliBaju to the conventional phototherapy system. The efficiency of the prototype in lowering down the bilirubin in the serum sample and the results of *in vitro* experiments are discussed in part two. Analysis and discussions follow, as to explain the reason and correlation of the experiments. Finally the summary of the study and suggestions for further research in Chapter 5.

CHAPTER 2

THEORY AND LITERATURE REVIEWS

2.1 Neonatal jaundice

Jaundice is the condition where the yellow colour appears on the neonates' skin and eyes. The colour symptoms start around the head and the face followed to the shoulders and arms until the rest of the neonates' body including the legs and feet. During pregnancy, bilirubin is removed by the placenta but after birth, the newborn's liver will not be able to keep up with the bilirubin formed due to young age [5] which will lead to the unconjugated bilirubin leaks into the bloodstream and settles on the skin. Conjugated bilirubin is excreted in urines and stools. This will also correspond to the increasing rate of unconjugated bilirubin in neonates. Bilirubin that has been conjugated by the liver is also called direct bilirubin (conjugated) and the increasing of the direct bilirubin is caused by a blockage in the liver. Indirect bilirubin (unconjugated) is normally circulated with plasma protein due to its lipid-soluble forms [6]. Conjugated bilirubin is soluble in water while unconjugated bilirubin is not soluble in water due to its intramolecular hydrogen bonding. Newborn infants produce more bilirubin, which is relatively 2 to 3 times higher than an adult [7]. As the result of excessive bilirubin or formations that are also known as hyperbilirubinemia, 2/3 of most healthy newborn and preterm newborn will become clinically jaundiced [8] in their first weeks of life. In a survey done by the Ministry of Health Malaysia in 1998, approximately 75% of newborns had jaundice [9] in their early stage of life.

Bilirubin is highly sensitive to visible light where bilirubin is a substance that absorbs the light and will undergo both oxidation [10] and isomerization [11] in serum when exposed to visible light. Phototherapy is the most common treatment used by hospitals worldwide to treat neonatal jaundice [12, 13]. The effectiveness of phototherapy has been documented in many domestic and international publications [14-16]. The goal of the phototherapy treatment is to reduce the bilirubin reading by photodegradation.

Neonates with a total serum bilirubin (TSB) of greater than 205 μmol/L for term newborn and 171 μmol/L for preterm newborn are considered as having jaundice [17]. They will be advised to undergo phototherapy. An intensive phototherapy is required if the TSB level does not show any decline after 4-6 hours of normal phototherapy [18]. Blood exchange transfusion will be recommended if the TSB reading achieves less or equals to 342 μmol/L [19] for preterm or sick infant, and 428 μmol/L [20] in healthy infants respectively considering the weight, gestational age and risk factors of the infants. The phototherapy treatment which they received previously will be considered as a failure of phototherapy. Table 2.1 shows the level of bilirubin on Clinical Practice Guidelines (CPG) for the management of neonatal jaundice used in Malaysia [21].

During a blood exchange transfusion, the whole blood including the red blood cells and the plasma is modified [20] to be compatible with the infants and cross-matched to the mother. Hyperbilirubinemia must be treated as it is known as a potentially toxic substance that might affect neurological development [20]. The most serious consequence from severe hyperbilirubinemia is kernicterus [22] besides cerebral palsy, brain damage and mental retardation [19], and vision and hearing problems [23] and deafness [24] in the long term, especially when the bilirubin achieved a very high level, whereby the effects on the central nervous system is fatal.

Table 2.1 TSB levels for phototherapy & exchange transfusion in babies ≥ 35 weeks gestation [21]

Age	LOW-RISK		MEDIUM RISK		HIGH RISK	
	> 38 weeks and healthy		**> 38 weeks with risk factors or 35 - 37 weeks + 6 days, and healthy**		**35-37 weeks + 6 days with risk factors**	
Hours of life	Conventional PT - TSB (μmol/L)	Exchange transfusion - TSB (μmol/L)	Conventional PT - TSB (μmol/L)	Exchange transfusion - TSB (μmol/L)	Conventional PT - TSB (μmol/L)	Exchange transfusion - TSB (μmol/L)
< 24*						
24	154	325	120	291	86	257
48	205	376	171	325	137	291
72	257	410	2015	359	171	316
96	291	428	239	385	188	325
> 96	308	428	257	385	205	325

*Jaundice appearing within 24 hours of life is abnormal and needs further evaluation

Intensive phototherapy is initiated when the TSB level increased above 51 μmol/L from the conventional level or TSB level kept increasing by 8.5 μmol/L per hour.

The cause of hyperbilirubinemia in the newborns comes from many factors. The most usual case is isoimmune hemolytic anemia that is normally due to ABO incompatibility [17]. Rhesus incompatibility [25], Glucose 6 phosphate dehydrogenase (G6PD) deficiency [26, 27], prematurity, the presence of sepsis and asphyxia, maternal diabetes are other causes [28, 29] also contribute to hyperbilirubinemia. These factors are also known for developing severe hyperbilirubinemia thus screening test to identify for any of these risks are essential before phototherapy is prescribed.

2.2 Dose of phototherapy

In the current procedures in hospitals, capillary blood sampling will be taken from the jaundiced neonate in 6 hours interval after treated with phototherapy treatment. This is because the most significant fall in bilirubin reading is in the first 4 to 6 hours after phototherapy [30]. Phototherapy will be continued until the level of bilirubin drop to 187 μmol/L for term neonate.

There are several important keys in determining the effective dose of phototherapy to ensure the decline in serum bilirubin and these factors are always being discussed and have been proven to be effective by many researchers in their publications. Figure 2.1 shows the diagram of the important mechanisms in delivering phototherapy.

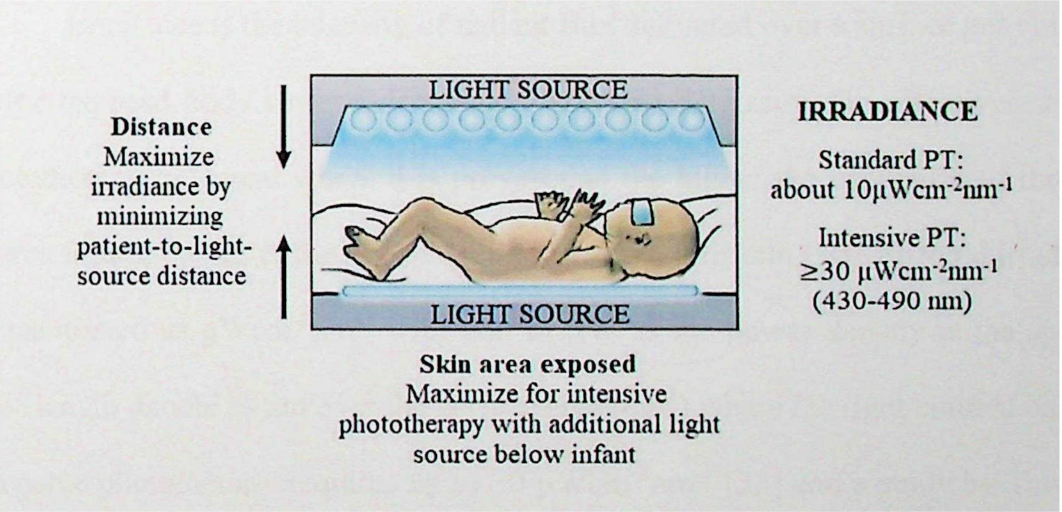

Figure 2.1 Simplified figure of phototherapy doses to ensure the efficacy of the treatment [5]. The patient is treated in an incubator.

2.2.1 Wavelength of the light source

The most effective range of spectral qualities of the phototherapy light source is in the narrow range of blue-green region, 430 nm – 490 nm with a peak at 460 nm ± 10 nm [31]. At this spectral range, the light source is well penetrable into the infant's skin to give a phototherapeutic effect on the unconjugated bilirubin. The unconjugated bilirubin also absorbs the light maximally in this visible light range [32]. The chemical reactions between the bilirubin and the light source will be discussed in the upcoming subtopic. There is a misconception on ultraviolet radiation during phototherapy but the phototherapy systems that used nowadays on infant does not produce significant ultraviolet radiation as it has been filtered to remove the harmful radiation (< 350 nm) [33].

2.2.2 Intensity of light source

Irradiance is the intensity of radiant flux delivered over a surface per unit area of the exposed body surface. Irradiance will also determine the effectiveness of a phototherapy treatment where it is proven that the higher the irradiance of the light source shines, the faster the rate of decline in serum bilirubin [30]. Spectral irradiance is quantitated as $\mu Wcm^{-2}nm^{-1}$ with unit of μW as the power density at the specific wavelength denote as nm over the surface area (cm^2) where the light emitted on [34]. Intensive phototherapy requires up to 30 $\mu Wcm^{-2}nm^{-1}$ [32] and a study by Tan K.L. also suggest the most effective spectral irradiance ensuring the decline in serum bilirubin is approximately 40 $\mu Wcm^{-2}nm^{-1}$ [30].

2.2.3 Distance between light source and infant

The effectiveness of the phototherapy is also determined by the distance from the light source to the body surface exposed by the infant [35]. It is inversely proportional [8] hence the closer the light source irradiates the body surface that is exposed to the light source, the rate of serum bilirubin declined is higher. The relationship is the irradiance is higher inversely to the distance between the baby and the light source which will improve in treatment time [36]. However, note that if the light source produces heat at the same time, the distance of the light source to the infant needs to be monitored safely so that it is not harmful to the neonate by overheating them [37] or cause hyperthermia to the infants undergoing phototherapy treatment. Besides, it may lead to the insensible water loss in the infants for the warming effect from the radiant heat to the infants' skin [13]. The energy conversion from light to radiant heat and chemical energy that happens in the infants' body will cause water loss. Thus, by using LED as the light source for phototherapy, it can be presumed that it is more effective and safe for LED produce less heat while bringing the light source closer to the body surface [38].

2.2.4 Area of body surface exposed

The surface area that a newborn's body was irradiated by the light source during phototherapy treatment must be delivered in the maximal area as possible [20]. The clarifications on these are the greater the surface body area that was exposed to the blue-green phototherapy light source, the greater the decline in serum bilirubin [35]. The efficacy is improved significantly up 30% to 40% in the first 4 to 6 hours decrement in serum bilirubin when more body surface area is exposed during phototherapy [39]. Most phototherapy systems support high spectral irradiance at the center of the light source, but the spectral irradiance is slightly reduced at the periphery of the light. This will normally be solved by adding two or more light sources on the phototherapy system [32].

2.3 History of phototherapy

The story begins at the Premature Unit at Rochford General Hospital in Essex, England. Sister Jean Ward believed that the combination of fresh air and warm sunshine would help with the revitalization of health rather than sit in the overheated baby incubator. On sunny days, Sister Ward would wheel the infants to the courtyard and return the infants in the nursery before the consultants or any doctors came for ward rounds. One particular day in 1956 during the ward rounds, Sister Ward showed the consultants and physicians an undressed infant with the full exposed abdomen. The infants' skin was totally pale yellow, but the triangle shape had much darker yellow than the rest of the infants' body. Dr. R. H. Dobbs [40] asked if she had painted the baby with iodine or flavine but apparently she had not. Sister Ward only held a jaundiced infant where the yellow colour on the infants' body had faded except for the area that was covered by the corner of a sheet [32]. Picture of Sister Ward with one of the infants of the hospital in figure 2.2. A few weeks later in the warm summer season, a biochemist left a tube of blood sample of a jaundiced infant by the window at the laboratory. The bilirubin result of the sample was reported to be dramatically dropped, although the blood sample was initially from an infant who had severe hyperbilirubinemia. These observations are put into considerations of the significance of sunlight on the degradation of bilirubin from hyperbilirubinemia. Other aspects that were taken into consideration was the source of light was not an ultraviolet ray, but it was visible light predominantly in the region of blue-green that are most effective. It was also reported that only the reading of unconjugated bilirubin was affected and converted by the light, hence the reduction in hyperbilirubinemia cases after being exposed to the sunlight may reduce the probability of exchange transfusion especially for a preterm infant [40].

Figure 2.2 Sister Jean Ward with one of the infants that received earlier phototherapy at Rochford General Hospital in 1956 [40]

2.4 Chemical interactions during phototherapy

Basic understanding during phototherapy, bilirubin that presents in the capillaries and subcutaneous tissues and interstitial spaces of the skin are converted [32] into water-soluble isomers that can be excreted by the body without glucuronidation or undergo further metabolism by the liver. In this process, urinary and gastrointestinal elimination [13] is an important mechanism to reduce the load of converting bilirubin. Bilirubin that is exposed to the light undergoes relatively rapid photochemical [16, 41] and photo-oxidation [42] reactions.

There are two isomeric forms of bilirubin during photochemical reactions that are configurational isomerization or also known as photo-isomerization and formation of structural isomerization. These two isomeric formations of bilirubin are highly wavelength-dependent and less lipophilic [5] compared to normal bilirubin that they are easily defecated into the bile [43] and waste is eliminated through urines and stools. However, configurational isomerization (photo-isomerization) is reversible while the structural isomerization process is irreversible. Thus, some of the photo-isomerization products will be reverted back to its natural bilirubin forms, but the systems will eventually achieve an equilibrium [33].

Figure 2.3 shows an illustration of an efficient absorption of light through the skin in the blue range of 460 nm – 490 nm. The initial changes started with the production of lumirubin and in the meantime, the process of photo-isomerization to certain degradation products and intermediate product, followed by the formation of biliverdin [44], and photo-oxidation process [45]. The study [46] considered that the rapid clearance of lumirubin from bile analysis proves that structural isomerization plays a major conversion in eliminating the yellow bilirubin pigment.

The photo-oxidation process occurs rather slowly compared to the configuration and structural isomerization. This process also has the minimal contribution to eliminate those yellow pigments during phototherapy. Photo-oxidation process produces colourless photo-oxidation products during the absorption of light by the bilirubin that generates excited-state of bilirubin molecules [47] and combined with oxygen. The photoproducts including mono- and di- pyrroles [44, 46], a colourless volatile liquid was released upon the reaction. The photo-oxidation products are non-toxic and predominantly excretable isomers in the urines. These converted bilirubin isomers will have different structural shapes than its native bilirubin isomers, besides being more polar [48] and can be eliminated by the liver into the bile without any special conjugation or transport for elimination [49].

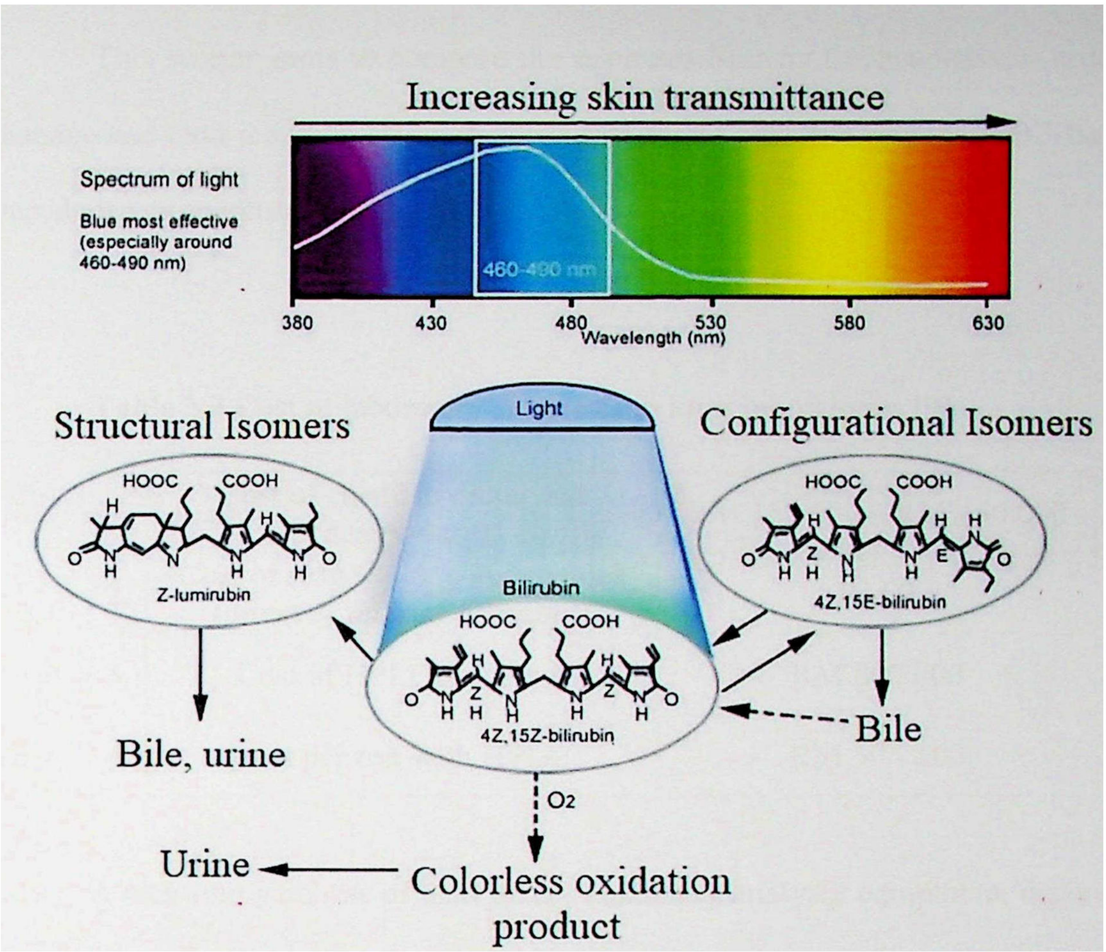

Figure 2.3 Absorption by the light in the range 460 nm – 490 nm generates the changes in isomers [47]

2.5 Costing

In this section, all the total costs involved in providing the phototherapy treatment by the hospitals in Malaysia are evaluated. The costs are provided by the Health Technology Assessment Unit of Medical Development Division from the Ministry of Health Malaysia in the year 2002. The cost discussed was only on equipment and other consumables used in local hospitals. However, costs such as building, personnel, and labour, or maintenance, for example, were not included in the calculation. Table 2.2 shows the cost in local laboratories to diagnose a blood sample of a patient with jaundice.

This section aims to compare the expenses bear by the hospitals in order to manage and treat jaundice cases, thus to identify the probable savings if BiliBaju is introduced as an alternative to treat neonatal with jaundice.

Table 2.2 Cost of laboratory diagnosis in local laboratories [9]

1.	Cost of chemistry analyser (heavy-duty)	RM 150 000 – RM 450 000
2.	Cost of reagents & consumables (direct & indirect bilirubin)	RM 2
3.	Cost of HPLC Analyser	RM 200 000
4.	Cost per test with HPLC	RM 50 - 100

A one-time purchase of heavy-duty chemistry analyser equipment, depending on the version and model year, ranges from RM 150k to RM 450k. Blood sampling is then analysed by the chemistry analyser with respective reagents for both direct and indirect bilirubin that will cost RM 2 per sample. Separation of blood either for drug screening, therapeutic drug monitoring, toxicology in blood or even for the bilirubin fractionation test using an HPLC Analyser machine, which is also a one-time purchase cost around RM 200k. Depending on the reagent used for multi-purpose blood separation the cost involved per test using this equipment is RM 50 to RM 100.

Once a neonate is confirmed to be hospitalised for hyperbilirubinemia, the baby will be treated with the phototherapy machine. In Malaysia, there is a common brand of phototherapy devices used in hospitals.

Table 2.3 shows several common brands of phototherapy devices used in local hospitals and the comparison of costs on a daily basis per baby for a phototherapy treatment.

The difference between each device is mostly the power source and the capability of delivering phototherapy. By adding the equipment price, and its light source makes the total costs for each equipment. Double photolight and wooden photolight use blue light as their light source while Medela intensive phototherapy uses blue fibre tubes. Air Shield High-Intensity photolight and Biliblanket, use halogen bulbs where halogen bulbs are widely known for generating more heat as compared to other light sources such as incandescent light. It can be observed that double photolight and Medela intensive photolight are in the same price range, RM 4,800 and RM 4,900 respectively, and both devices use the same set of light source.

Since the costs and the number of lights are not the same for the light source set, thus the calculation of total costs per day is affected. Wooden photolight is capable to occupy four babies at once though the cost of the light source set is expensive. Therefore, the total cost is divided per baby making the price lower. Air shield high-intensity photolight is another device that offers a reasonable cost at RM 1.31 per day, compared to double photolight and BiliBlanket at RM 5.03 and RM 5.20 respectively. Medela intensive phototherapy has the most expensive cost, which is at RM 7.30 per baby. These costs comprised for daily basis cost per baby of jaundice treatment.

Table 2.3 Costs comprised of various types of phototherapy machines in local hospitals [9]

Type of light	Double photolight		Wooden photolight		Medela intensive photolight		Air shield high intensity photolight		Biliblanket		
	Equipment cost	Blue light	(4 babies each time)	Blue light	Equipment cost	Blue tubes	Equipment cost	Bulbs	Equipment cost	Halogen bulb	Blanket
Total cost (RM)	4800	1680	700	2900	4900	1680	1500	180	800	150	-
Number of lights/ tubes/ bulbs required	-	12	-	10	-	-	-	3	-	1	-
Cost of each light/ tube/ blanket (RM)	-	28	-	58	-	70	-	15	-	25	90
Number of times changed per year	-	5	-	-	-	-	-	4	-	-	-
Lifespan (years)	5	-	5	5	5	6	5	-	5	6	-
Cost per day (RM)	0.60	4.60	0.38	7.94	2.70	4.60	0.82	0.49	4.38	0.40	0.25
Total cost per baby per day (RM)	5.20		0.10	2.08	7.30		1.31		5.03		

Table 2.4 shows all the costs involved in the requirements of procedures of exchange transfusion. An exchange transfusion requires blood to be drawn and be replaced with healthy blood cells.

Table 2.4 Cost implications of exchange transfusion [9]

Equipment	Disposable blood exchange set	83.00
	Disposable Intravenous drip set (x 2)	2.40
	Face mask	0.20
	Disposable needles 23G & 21G (x 4)	1.40
	Blade x 2	1.20
	Gloves x 1 pair	1.40
	Bandage x 1 roll	0.50
	Plaster	0.40
	Staff Nurse	2.54
	Doctor	4.72
Blood Products	Fresh whole blood x 1 pint	100.00
Investigations	Blood tests before and after transfusion	40.00
Drugs	Drugs are given during exchange transfusion	41.00
	TOTAL (RM)	**278.76**

During the procedure of exchange transfusion, the Guideline Development Group (GDG) from the National Collaborating Centre for Women's and Children's Health (UK) recommends to perform double-volume exchange. The study compares the effect of the double-volume exchange transfusion (DVET) compared to alternative treatment methods, including DVET without treatment, DVET vs. simple transfusion and DVET vs. single-volume exchange transfusion (SVET). In addition, multiple phototherapy is advised during exchange transfusion to avoid a hyperbilirubinemia rebound. After exchange transfusion, the possibility of the rebound in serum bilirubin is rapid [30]. The procedure is quite challenging with limited blood donor and high infection popularity of transfusion-transmissible especially for low resource countries.

This is probably the last alternative to be done and is a life-saving procedure to save a neonate from severe hyperbilirubinemia [48]. Phototherapy may react slowly but constantly to reduce number of bilirubin [49] compared to exchange transfusion, however the rebound rate is lower. For every successful transfusion procedure, the patient is monitored for several days depending on the patients' condition and the type of blood transfusion diagnosed.

2.6 Current phototherapy devices

Neonatal Intensive Care Unit (NICU) in Hospital Universiti Sains Malaysia (Hospital USM) is the unit that provided phototherapy treatment for jaundiced neonates. Frequently used device in NICU is the phototherapy system unit from Draeger Company.as in figure 2.4, which normally be used with a bassinet or incubator depending on the treatment required by the baby. The unit emits blue wavelength spectrum with a peak of 460 nm [50]. Other technical details as shown in table 2.5. Besides the Draeger unit, Hospital USM also has a few units of Medela BiliBed, in figure 2.5, and a BiliBlanket. BiliBed emits blue light in the range of 425 – 475 nm [51]. BiliBed uses a single fluorescent tube thus this device is low energy consumption. BiliBed can support up to 10 kg baby's weight onto its frame. However, the BiliBed in Hospital USM is always malfunctioning for its spare parts are hardly available.

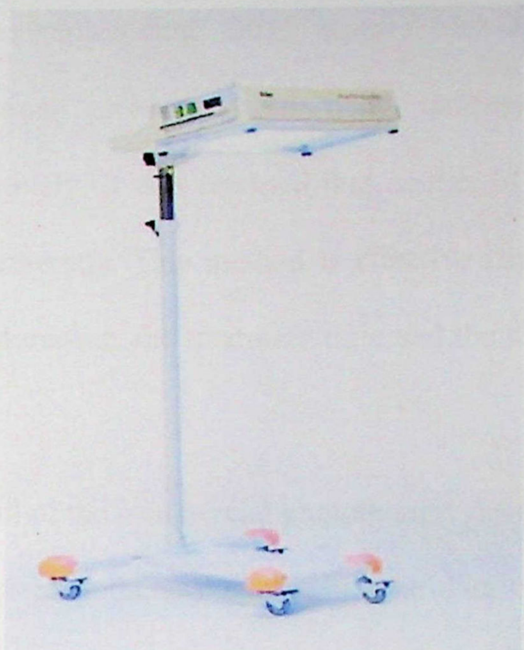

Figure 2.4 Draeger Phototherapy-4000 [50]

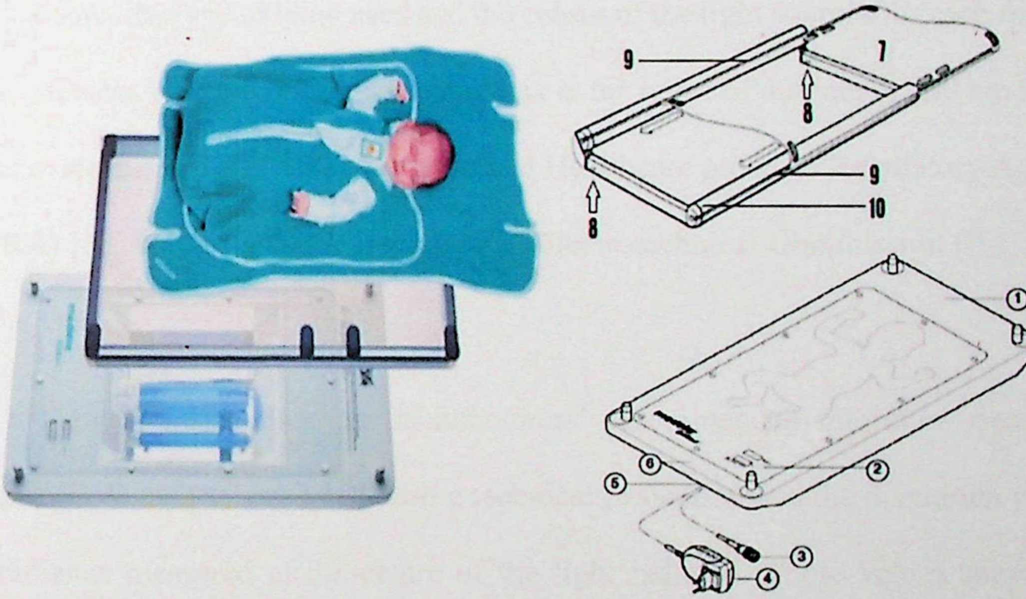

Figure 2.5 Medela BiliBed and illustrations of the parts[1] [51]

Hospital USM has come out with the idea of enhancing the treatment by using a white curtain hung around the incubator as reflectance materials [15] so that there is

[1] 1) Head of BiliBed 2) Hour meters 3) Start/Stop switch 4) 12 V DC power adapter 5) Socket 6) Foot end of BiliBed 7) Plastic cover 8) Button 9) Groove 10) Aluminium frame

no light wasted to the surrounding. Other aspects such as body hydration, skin problems, gastrointestinal problems, and body temperature were monitored periodically and repetitively. It was reported that neither of the patients developed hypothermia nor hyperthermia. This method is effective compared to an incubator without the curtains. Moreover, the treatment time and the period of hospitalization reportedly reduced.

Table 2.5 lists all of the commercial phototherapy devices that have been used in the UK hospitals for phototherapy treatment. The data compare many types of phototherapy devices that available before and present including the devices used in Hospital USM. These devices meet at least the minimum criteria discussed. The table also indicates the type of lamp used and the colour of the light sources for each device. All the devices stated that their wavelength is in the range of 400 nm to 550 nm based on the evaluations by the UK Medicines and Healthcare products Regulatory Agency (MHRA) [52] and follows the International Electrotechnical Commission (IEC) [53] standards.

Table 2.5 also lists the manufacturers' recommended minimum treatment distance ($mWcm^{-2}$) as measured during technical evaluation and the maximum values of irradiance measured at the centre of the light radiated. These values show that different devices have different minimum distances recommended by the manufacturers for phototherapy treatment. From the table, the distance between the lamp head and the neonate are further for halogen devices as halogen bulbs normally produce more heat. A standard distance from the incubator canopy or the lamp head to the neonate during phototherapy has been discussed at 40 cm [54] however, none of the devices are mentioned to be used at such distance.

Table 2.5 Commercial phototherapy device data available in UK hospitals [37]

Device	Colour of light	Lamp type	Manufacturer's minimum recommended distance between the lamp head and the neonate	Irradiance at manufacturer's recommended minimum treatment distance ($mWcm^{-2}$)	Can the device be used with a baby incubator ?
Draeger Phototherapy 4000 Unit	Blue & white options	6 pcs folded fluorescent tubes	30 cm	3.39 (4 blue tubes & 2 white tubes), 4.07 (6 blue tubes)	Yes
Draeger Heraeus Phototherapy Lamp	White	1 pcs gas discharge bulb	30 cm	5.03	Yes
Medela Phototherapy Lamp	Blue	4 pcs folded fluorescent tubes	25 cm	4.66	Yes
Medela BiliBed	Blue	1 pc folded fluorescent tube	On frame (~6 cm)	5.56	No
Ohmeda BiliBlanket Plus	Blue	1 pc halogen bulb	In contact	4.83	Yes
Datex-Ohmeda Spot Phototherapy Lamp	White	1 pc halogen bulb	50 cm	7.75	Yes
Hill-Rom Micro-Lite Phototherapy System	White	3 pcs halogen bulbs	42 cm	2.50	Yes
Natus neoBLUE LED Phototherapy System	Blue (yellow & red)	LEDs; 852 Blue, 320 Yellow, 13 Red	30 cm	2.29	Yes
Mediprema Cradle 360	Blue	16 pcs long fluorescent tubes	On gauze hammock (~20 cm)	5.25	No
Vickers 80	White	4 pcs long fluorescent tubes	None specified	0.83 @ 30 cm	Yes

A Draeger brand with its products; Phototherapy 4000 Unit and Heraeus Phototherapy Lamp are using blue and white light respectively. Medela Phototherapy Lamp and its BiliBed, as well as Ohmeda BiliBlanket, are using blue light as their light source, but the Medela brand is using a fluorescent tube while the BiliBlanket is using a halogen bulb. Datex-Ohmeda Spot Phototherapy Lamp and Hill-Rom Micro-Lite Phototherapy System choose white colour halogen lamp as their light source. Natus neoBLUE LED Phototherapy System is the latest devices with LEDs as their light source.

Vickers 80 is the oldest device used for phototherapy which is now discontinued, and from the table, it can be seen that this device has the lowest irradiance value at 0.83 $mWcm^{-2}$. Medela Phototherapy Lamp, both Draeger phototherapy devices and the Natus neoBLUE LED Phototherapy System are very flexible and suitable for neonates that require thermal monitoring and can be used with a bassinet or incubator. These devices are very user-friendly, very convenient for both neonates and nurses, and they oblige all the phototherapy doses required. The Mediprema Cradle 360 is the only device that provides full illumination for phototherapy treatment, but this device has no thermal control. Medela BiliBed and Ohmeda BiliBlanket are suitable for neonates that do not need thermal support and the irradiance provided is also very high. The highest irradiance is at 7.75 $mWcm^{-2}$ provided by the Datex-Ohmeda Spot Phototherapy Lamp which will significantly reduce the treatment time. However, this device only irradiates and cover a small area [55] with 50 cm recommended distance by the manufacturer. At a standard distance of 40 cm, the device may cause unwanted heating effect or hyperthermic to the neonates [55].