ASSOCIATED FACTORS LEADING TO EXCHANGE BLOOD TRANSFUSION AMONG SEVERE NEONATAL JAUNDICE IN KELANTAN 2015-2017

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2015-2017

By

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Bismillahirrahmanirrahim,

In the name of ALLAH, the Most Beneficent and the Most Merciful. Salutations upon His messenger Muhammad S.A.W (peace be upon him), his family and his companions. With help and success granted by ALLAH, I have finished and completed this research project on time.

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LIST OF SYMBOLS

$>$ More than

$<$ Less than

$=$ Equal to

$\geq$ More than and equal to

$\leq$ Less than and equal to

α Alpha

β Beta

% Percentage

Δ Precision / Delta

LIST OF ABBREVIATIONS

AAP   American Academy of Pediatrics

ABO   ABO blood group

CI   Confidence interval

DOSM   Department of Statistic Malaysia

HREC   Human Research and Ethics Committee

IgG   Immunoglobulin G

IgG   Immunoglobulin M

JKNK   *Jabatan Kesihatan Negeri Kelantan*

MOH   Ministry of Health

MREC   Medical Research Ethics Committee

NICE   National Institute for Health and Clinical Excellence

NMRR   National Medical Research Registry

RBC   Red blood cell

Rh   Rhesus

UGT1A1   Uridine Diphospho-Glucuronosyl Transferase 1A1

WHO   World Health Organization

ABSTRAK

FAKTOR-FAKTOR BERKAITAN YANG MENJURUS KE ARAH TRANSFUSI PERTUKARAN DARAH DALAM KALANGAN NEONATAL JAUNDIS TAHAP TERUK DI KELANTAN 2015-2017

Latar Belakang: Jaundis merupakan masalah yang sering dialami semasa tempoh neonatal. Jika tidak dipantau, kadar jaundis bakal meningkat ke tahap teruk. Jaundis neonatal tahap teruk dalam tempoh yang lama boleh menyebabkan gejala saraf yang melarat, termasuklah kernikterus. Transfusi pertukaran darah merupakan modaliti yang paling efektif bagi menurunkan tahap kepekatan serum bilirubin dengan cepat.

Objektif: Kajian ini dilakukan bertujuan untuk mengenalpasti kadar dan faktor-faktor yang berkaitan yang menjurus ke transfusi pertukaran darah dalam kalangan neonatal jaundis tahap teruk di Kelantan dari tahun 2015 hingga 2017.

Metodologi: Kajian ini menggunakan kaedah hirisan lintang terhadap neonatal jaundis tahap teruk di Kelantan sepanjang Januari 2015 hingga Disember 2017 menggunakan data sekunder dari Borang Pemantauan dan Pengurusan Neonatal Jaundis dari Unit Kesihatan Ibu dan Anak, Jabatan Kesihatan Negeri Kelantan. Data diperolehi dari pelbagai format termasuk Microsoft Excel dan borang Salinan keras yang telah diimbas.

Keputusan: Daripada 228 neonatal yang dimasukkan ke wad kerana jaundis tahap teruk, 45 neonatal (17%) memerlukan prosedur transfusi pertukaran darah. Kadar neonatal jaundis tahap teruk yang menjalani transfusi pertukaran darah semakin meningkat dari tahun 2015 hingga tahun 2017, iaitu sekitar 17.0% hingga 23.7%.

Faktor-faktor berkaitan yang signifikan adalah infeksi neonatal (AOR 6.423, 95% CI=2.148,19.205; p:0.001), berat lahir rendah (AOR 3.552, 95% CI=1.564,8.065; p:0.002), inkompatibiliti ABO (AOR 3.714, 95% CI=1.435,9.611; p:0.007) dan ibu berdarah kumpulan O (AOR 2.651, 95% CI=1.270,5.534; p:0.009). Purata jumlah serum bilirubin tertinggi dalam kalangan neonatal yang menjalani tarnsfusi pertukaran darah adalah 439.1 (51.02) mmol/L.

Kesimpulan: Kadar transfusi pertukaran darah masih tinggi di Kelantan. Faktor- faktor yang berkaitan transfusi pertukaran darah dalam kalangan neonatal jaundis teruk adalah infeksi, berat lahir rendah, inkompatibiliti ABO dan ibu berdarah kumpulan O. Pengetahuan tentang faktor-faktor yang berkaitan ini dapat membantu dalam menambah baik strategi untuk mencegah jaundis tahap teruk sekaligus mencegah prosedur transfusi pertukaran darah dan komplikasi yang berkaitan.

KATA KUNCI: jaundis tahap teruk, neonatal, transfusi pertukaran darah

ABSTRACT

**ASSOCIATED FACTORS LEADING TO EXCHANGE BLOOD
TRANSFUSION AMONG SEVERE NEONATAL JAUNDICE IN KELANTAN
2015-2017**

Background: Neonatal jaundice is a common disorder during the neonatal period. Jaundice may lead to worsening condition if it is not well monitored which steer up to severe jaundice level. Long-term results of severe neonatal jaundice may lead to devastating neurologic sequelae, including bilirubin encephalopathy and kernicterus. Exchange blood transfusion (ET) has remained the most effective and expeditious modality to rapidly lowering serum bilirubin concentration.

Objective: This study aims to determine the proportion and factors associated with exchange blood transfusion procedure among severe jaundice neonates in Kelantan from 2015 to 2017.

Methodology: This study applied the cross-sectional design on severe jaundice neonates in Kelantan between January 2015 and December 2017 using secondary data from Monitoring and Management Neonatal/ Neonatal Jaundice Forms from Maternal and Child Health unit, Kelantan Health State Department. Data obtained from sources including Microsoft Excel files and scanned hardcopy forms.

Result: Out of 228 neonates who were admitted for severe jaundice, 45 neonates (17%) required ET procedure. The proportion of severe neonatal jaundice underwent ET are increasing in trend by 2015 to 2017 with 17.0%, 16.3% and 23.7% respectively. The significant associated factors to ET were infection of neonates (Adjusted Odd Ratio

6.423, 95% CI=2.148,19.205; p=0.001), low birth weight (AOR 3.552, 95% Confidence Interval=1.564,8.065; p=0.002), ABO blood group incompatibility (AOR 3.714, 95% CI=1.435,9.611; p=0.007) and mother with blood group O (AOR 2.651, 95% CI=1.270,5.534; p=0.009). The mean of highest total serum bilirubin detected among exchange transfused neonates was 439.1 (51.02) mmol/L.

Conclusion: Exchange blood transfusion in Kelantan still high. Associated factors leading to exchange blood transfusion among severe neonatal jaundice were infection in neonates, low birth weight, ABO incompatibility and mothers with blood group O. Recognition of these associated factors is useful for improvisation of strategy in preventing severe neonatal jaundice as well as exchange blood transfusion procedure and complication related interventions.

KEY WORDS: severe jaundice, neonates, exchange blood transfusion

CHAPTER ONE

INTRODUCTION

1.1　Introduction

Jaundice is a state which result from raise of total serum bilirubin level in blood. The condition is clinically detected when total serum bilirubin > 85mmol/L (5mg/dL). It is a common disorder during neonatal period in more than half term neonates and almost all of pre-term neonates that require medical attention (Ministry of Health Malaysia, 2015; Rennie *et al.*, 2010). After birth, normally neonates will face the transitional period which may cause physiological jaundice. It happens due to multiple associated factors and when it became severe, it is considered as pathophysiological jaundice (Bhutani *et al.*, 2015)

Jaundice indicate the accumulation of bilirubin that manifest through the skin, sclerae, and other tissues. Once produced, bilirubin is normally unconjugated, where it is reversibly but tightly bound to albumin and then excreted via the liver (Cohen *et al.*, 2010). Then the bilirubin is absorbed into the blood circulation through the enterohepatic circulation which then increase the burden of bilirubin in the liver. By contrast, in adult, conjugated bilirubin is reduced rapidly by the infection via action of bacteria colonization to urobilinogens (Maisels, 2006).

Neonates with total serum bilirubin exceeding 340mmol/L (20mg/dL) will be classified as severe neonatal jaundice. Severe neonatal jaundice may lead to

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kernicterus, a condition of excessive hyperbilirubinemia that cause neurologic syndrome and permanent brain damage if prolonged, and acute bilirubin encephalopathy, an acute condition of neurological manifestation in early weeks of life of the neonates by load of bilirubin in the brain (Korejo *et al.*, 2010; Stevenson *et al.*, 2012).

If the bilirubin level rise continuously in spite of phototherapy with threat of kernicterus or acute bilirubin encephalopathy then exchange blood transfusion is the choice of treatment together with intravenous immunoglobulin (IVIG) depending on local practices (Begum *et al.*, 2012). Indication for performing exchange blood transfusion are based on consideration of risk of kernicterus and benefit, as well as the adverse events from the exchange blood transfusion intervention.

Although exchange blood transfusion is known as a safe technique, it is still not a risk-free procedure, and may lead to death (Philip *et al.*, 2003). Infants post exchange blood transfusion should be observed for some possible complications of the procedure. Most common complications are thrombocytopenia, hyperkalaemia, hypocalcaemia, hypoglycaemia, hyponatraemia, septicaemia, acidosis, air embolus, necrotising enterocolitis, anaemia and hyperglycaemia (Begum *et al.*, 2012).

Exchange transfusion as the treatment of severe neonatal jaundice and its sequelae post a significant burden to health care for several reasons due to increasing incidence of severe neonatal jaundice, hospital admissions requirement, morbidity from complications, mortality, cost-consuming and, emotional and physical exhaustion especially to postnatal mothers.

The incidence of neonatal hyperbilirubinemia in lower-middle income countries such as African region and Southeast Asian is high, where it was estimated at 186.5 and

107.1 per 10,000 live births respectively (Bhutani *et al.*, 2013; Sakha and Gharehbaghi, 2010; Steiner *et al.*, 2007). In Malaysia, percentage of jaundice out of the total live births in Ministry of Health facilities in Peninsular Malaysia, Sabah and Sarawak are 23.9%, 21.2% and 23%, respectively (Ministry of Health Malaysia, 2002). Higher number of severe neonatal jaundice cases lead to higher chance for those babies to underwent exchange transfusion.

Neonatal jaundice remains the main reason for hospital readmission of newborns. Most neonates need hospital admission for strict monitoring while severe cases needed treatment requiring hospital admission including exchange transfusion. This happens due to increase awareness in the prevention of bilirubin encephalopathy and kernicterus by early detection and prompt treatment (Bhutani *et al.*, 2004).

There are several risks identified including the procedure itself, human error and the blood products used for transfusion. Potential problems of the procedure include electrolytes imbalance, sepsis, cardiac disorders, inadequate replacement of blood, air embolus and necrotising enterocolitis (Bujandric and Grujic, 2016; Sakha and Gharehbaghi, 2010). In Malaysia, 0.29% of severe neonatal jaundice underwent exchange blood transfusion procedure in 2002 (Ministry of Health Malaysia, 2002) and predispose them to the treatment risks, but the trend cannot be established since no other report was found.

Severe neonatal jaundice also carries high burden of mortality by its complication and even high mortality risk through exchange blood transfusion procedure. The mortality rates related to exchange blood transfusion procedure among term neonates vary, which ranged 0.1-24% (Bhutani *et al.*, 2004; Sakha and Gharehbaghi, 2010).

Treating severe jaundice neonate including exchange transfusion is very costly and burdensome to the patient and family. It becomes burden to the family in view of long ward admission stay, but the anxiety and psychological tension of mothers due to their concerns for newborn's health, their spouses and other children who were alone at home, was even more intolerable than the physical exhaustion (Rahbari *et al.*, 2014).

Apart from that, the cost of care for exchange transfusion is high due to hospitalization of neonates and disrupts the normal daily life of a family, especially to those residing far from hospital and lower socioeconomic group (Bhutani and Johnson, 2003).

1.2   Study rationale

The number of severe neonatal jaundice cases in Malaysia still high especially cases from Sabah and Sarawak. Most of them are neonates that require readmission in hospital within the first week of life. Exchange blood transfusion can sustain rapid reduction of bilirubin, so it is a prompt treatment to be selected in many cases of severe jaundice in the neonatal period (Bjerre *et al.*, 2008).

All jaundice newborns are facing possibilities of many complications such as encephalopathy, long term sequela and kernicterus if their jaundice is not being well monitored or inappropriately managed (Korejo *et al.*, 2010). These burdens may be experienced by the surviving jaundice neonates as well as their family.

The potential harms of exchange transfusion treatment need to be highlighted. The exchange blood transfusion intervention may result in complications and errors during the work process such as catheter related infection, blockage of the catheter, changes in the blood flow to organs and electrolytes imbalance (Sakha and Gharehbaghi, 2010).

The exchange blood transfusion procedure is relatively safe and all the possible fallacies may be preventable when it is conducted by expert, knowledgeable practitioners under high careful consideration. In spite of that, the procedure conveys risk for both morbidity and mortality.

Cost of care for kernicterus cases is high because of lifelong damage with possibility of permanent disability of surviving infants and need long term treatment and management. It will be a socio-economic burden to the parents and family as well as high demand and commitment for social and medical support.

Exchange blood transfusion can be prevented by knowing the contributing factors for exchange transfusion in severe neonatal jaundice as it will be valuable in monitoring and surveillance system for clinical necessary and public health interventions for better provision in health care service in Malaysia.

Literature search found no study reported on proportion of exchange blood transfused neonatal jaundice in Malaysia and the factors associated with it. Hence, we would like to study the proportion and factors associated with exchange blood transfused neonatal jaundice in Kelantan from 2015 to 2017.

1.3   Research questions

1.   What is the proportion of exchange blood transfusion among severe neonatal jaundice in Kelantan?

2.   What are the factors associated with severe neonatal jaundice leading to exchange blood transfusion in Kelantan?

1.4 Objectives

1.4.1 General Objectives

To study the proportion and factors associated with exchange blood transfusion among severe neonatal jaundice in Kelantan from 2015 to 2017.

1.4.2 Specific Objectives

1. To determine proportion of exchange blood transfusion among severe neonatal jaundice in Kelantan from 2015-2017.

2. To determine the factors associated with exchange blood transfusion among severe neonatal jaundice in Kelantan from 2015- 2017.

1.5 Hypothesis

Exchange blood transfusion among severe neonatal jaundice in Kelantan is associated significantly with maternal and neonatal factors.

1.6 Study outcomes

There are three main study endpoints in this study. The first one is to identify the trend of proportion of exchange blood transfusion among severe neonatal jaundice in Kelantan from 2015-2017. The proportion will be the outcome instead of prevalence in view of the study population only among the severe neonatal jaundice and not referring to all newborn babies in Kelantan.

The second outcome is the maternal factors associated with exchange blood transfused neonatal jaundice in Kelantan from 2015- 2017. According to literature review and availability of secondary data, the maternal factors studied include age of mother, number of parity, place of delivery, mother with blood group O, ABO incompatibility and rhesus incompatibility.

The third outcome will be neonatal factors associated with exchange blood transfused neonatal jaundice in Kelantan from 2015- 2017, which are infections in neonatal period, prematurity of birth, low birth weight, birth trauma, inadequate breastfeeding and G6PD deficiency.

CHAPTER TWO

LITERATURE REVIEW

2.1 Physiological Jaundice

The term physiologic jaundice describes the normal occurrence of jaundice in neonates due to increase of breakdown of erythrocytes in the existence of a low capacity for uptake. This may result from faulty transport of bilirubin into hepatocyte and ineffective of bilirubin conjugating enzyme leading to bilirubin overload. Jaundice also cause by low bilirubin gut reabsorption due to low nutrient intake and thus reduce intestinal movement in the early days of life (M. Jeffrey Maisels, 2000).

The level of bilirubin in umbilical cord serum is 17-51µmol/l under normal condition but may rises up to 85µmol/l/24hrs. Bilirubin level usually peaks by the third day at 85-102µmol/l and decreasing to below 34µmol/l between fifth and seventh day of life (Rennie and Robertson, 2012).

2.2 Pathological Jaundice

Appearance of jaundice within 24hours, increase in serum bilirubin beyond 85µmol/l/24hrs, serum bilirubin more than 255µmol/l, direct bilirubin greater than 34µmol/l at any time, presence of clinical jaundice beyond two weeks and conjugated bilirubin would be categorized under pathological jaundice. Neonates without any recognized risk factors rarely have total serum bilirubin level above 205µmol/l. So, as

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the risk factors number increases, the potential to develop significant bilirubin levels also increases (Rennie and Robertson, 2012; Rennie *et al.*, 2010)

2.3   Severe Neonatal Jaundice and Its Complication

When serum bilirubin levels exceed more than 340mmol/L, the neonates are categorized as severe neonatal jaundice. This condition may worsen to kernicterus or acute bilirubin encephalopathy and death may occur while infants who survive may get lifelong neurodevelopmental sequelae. Kernicterus has at least one tenth of mortality and more than half of long term morbidity (Ministry of Health Malaysia, 2009; Olusanya *et al.*, 2015).

Kernicterus is one of the concerned possible of long term sequel condition with neurological involvement, identified by choreoathetosis, cerebral palsy, paralysis of palpebra, loss of hearing and intellectual deficits. Kernicterus, in most of the time be used to describe the chronic neurologic consequence, while bilirubin encephalopathy refer to the acute phase of neurological condition manifest in the first weeks of life (Shapiro, 2003). Acute bilirubin encephalopathy occurs with the symptoms of hypertonia of the body muscles and arching, cervical dystonia, opisthotonos and high-pitched cry (Kaplan *et al.*, 2011)

In July 2004 the American Academy of Pediatrics (AAP) published guidelines suggesting a possible increased incidence of kernicterus, and recommended bilirubin level testing in neonates prior to hospital discharge. The guideline also described risk factors for bilirubin-encephalopathy and suggested treatment options such as adequate rehydration, prompt elimination of meconium, and phototherapy and/or exchange

transfusion, as needed. Correct and early diagnosis of hyperbilirubinemia could lead

to a reduction in neonatal indirect hyperbilirubinemia-related morbidity rate.
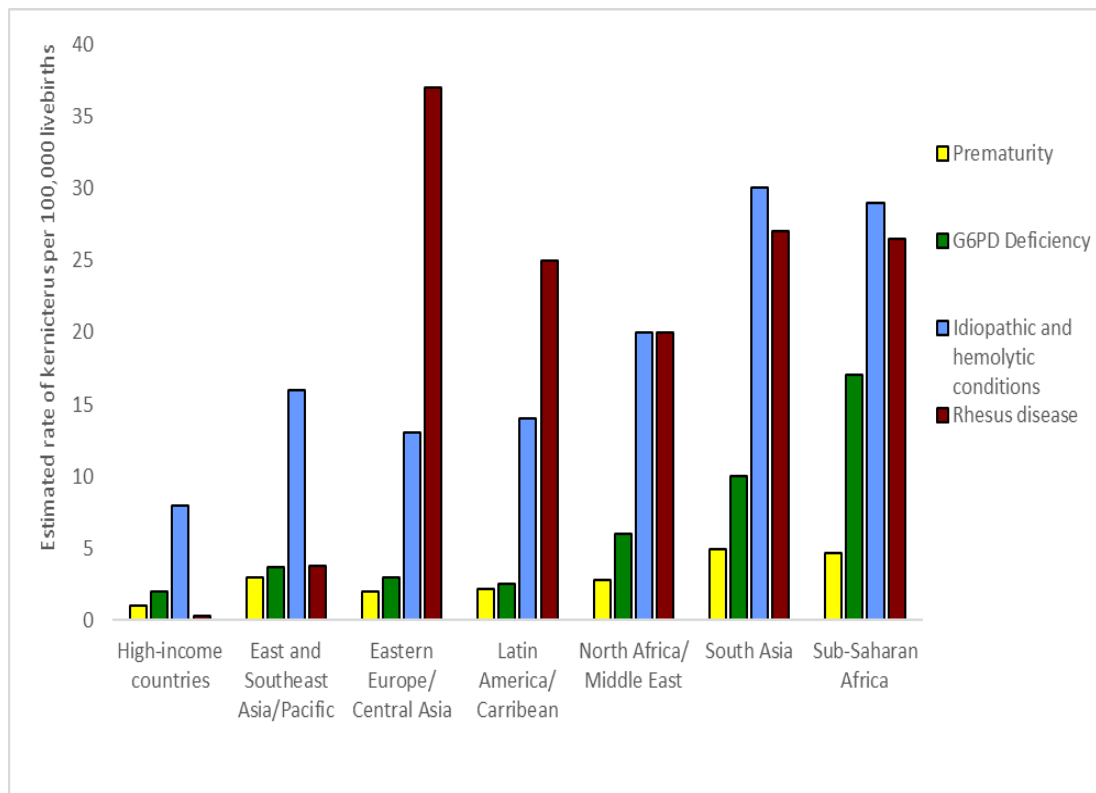
Figure 2.1: Estimated rates of kernicterus worldwide according to the causes.

The data in the figure above assigned to the causes of kernicterus. The yellow bars

represent the prematurity cause, G6PD deficiency represented by the green bars,

idiopathic and hemolytic conditions by blue bars and rhesus disease by red bars. From

here, we can see that rhesus disease is the leading cause in low-middle income country

while in generally, hemolytic and idiopathic conditions are the main cause (Bhutani *et*

al., 2013). Although exchange blood transfusion is meant for preventing kernicterus,

Bhutani and colleagues (2013) showed the occurrence of kernicterus is still high as

showed by this graph.

2.4 Exchange Blood Transfusion and Its Complication

The ultimate aim of the severe neonatal jaundice management is to reduce the serum bilirubin level rapidly to prevent mortality or disabilities. The two treatment of choices that are commonly used all over the world are phototherapy, either single phototherapy or intensive phototherapy, and exchange blood transfusion. Exchange blood transfusion procedure is still widely use in underdeveloped and developing countries (Maisels and McDonagh, 2008). It happens because exchange blood transfusion is the most rapid modality to reduce the serum bilirubin level and bring down the risk of kernicterus in severe neonatal jaundice cases (Owa and Ogunlesi, 2009).

Dr. Louis Diamond was the first physician who used umbilical vein for exchange blood transfusion procedure in 1946 at the Boston Lying-in Hospital (Philip *et al.*, 2003). The detail purpose of the exchange blood transfusion is to swiftly reduce the levels of serum bilirubin that is likely to be toxicants, replacing defective red blood cells, remove anti rhesus immunoglobulin antibodies and also to remove the wastes of haemolysis in erythroblastosis fetalis, ABO incompatibility and GP6D deficiency (Horacio, 2016).

In spite of complications from the disease, the treatments especially exchange blood transfusion has its own complication such as biochemical and haematological abnormalities (Malla *et al.*, 2015). Behjati *et al.* (2009) reported possibilities of electrolytes imbalance such as hypernatremia, hyponatremia, hypoglycaemia and hypocalcaemia as unfavourable events during exchange transfusion. According to study by Patra *et al.* (2004) during 1992-2002, the most frequent adverse events of exchange transfusion were thrombocytopenia, metabolic acidosis and hypocalcaemia.

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During the process of umbilical catheterization throughout exchange blood transfusion, associated possible may arise complications possible arise for instance air embolism, limb gangrene, blood transfusion reactions and cardiac arrhythmias. It also had risk of transmission of infectious diseases like HIV, hepatitis, syphilis and malaria (Owa and Ogunlesi, 2009). Although exchange blood transfusion is effective and safe procedure in preventing kernicterus, the mortality risk may be high up to 5% (Ives, 2015).

2.5   Global and national burden of neonatal jaundice

Based on global burden study of neonatal jaundice, severe neonatal jaundice affects impact half a million of term neonates annually with 100,000 neonates death while more than half of them survive with moderate to severe sequele disabilities (Bhutani *et al.*, 2013; Lawn *et al.*, 2014). Three quarter of the severe jaundiced neonates were from South Asia and sub-Saharan Africa (Bhutani *et al.*, 2013). Asian neonates were found having higher risk of severe neonatal jaundice compared to white or mixed race (Setia *et al.*, 2002).

The Ministry of Health Malaysia has revealed the incidence of neonatal jaundice in Malaysia, over the years 1993 till 1997; the average percentage of neonatal jaundice out of the total live births in government facilities were 23.9%, 21.2% and 23% in Peninsular Malaysia, Sabah and Sarawak, respectively. Of these, one third of them received phototherapy, 0.29% of them required for exchange blood transfusion and 1.29% received both phototherapy and exchange transfusion, while 0.032% developed kernicterus among cases of neonatal jaundice (Ministry of Health Malaysia, 2002). In Kelantan, the number of severe neonatal jaundice was also increasing in trend; in 2013

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the prevalence was 3.12 per 1,000 live births which increased to 3.29 per 1,000 live births in 2015 (Ministry of Health Malaysia, 2015).

Higher number of severe neonatal jaundice cases lead to higher chance of exchange blood transfusion treatment as it is an immediate treatment for severe neonatal jaundice and prevention of kernicterus (Steiner *et al.*, 2007). Although exchange blood transfusion is meant for preventing kernicterus, Bhutani *et al.* (2013) showed the occurrence of kernicterus is still high in certain region in the world by global burden of diseases classification with leading contributors from South Asia and sub-Saharan Africa.

According to National Institute for Health and Clinical Excellence Neonatal Jaundice Costing Report 2010, estimated cost of care for neonates with kernicterus is 5.5 million pound sterling which is equivalent to RM 30 million per case lifetime. This estimated cost included physical, social and medical care costs of kernicterus sufferers as well as their carers as it is a long-standing disability neurological complication with manifestations of cerebral palsy and need for lifelong care.

Many studies from all over the world has established the relationship between maternal and neonatal factors of jaundice leading to exchange transfusion. Both mother and neonatal factors influence the treatment of choice for severe neonatal jaundice.

2.6   Proportion of exchange blood transfused neonatal jaundice.

According to a study done in Lagos, Nigeria, proportion of neonatal jaundice cases that required exchange blood transfusion was 1.9% (95% CI: 1.5–2.3) out of 5262 infants with severe jaundice enrolled (Olusanya *et al.*, 2009) while another study done

in Nigeria by Owa and Ogunlesi (2009) found that 5.3% neonates had exchange blood transfusion (90 cases) out of 1686 babies warded in the neonatal unit. Out of 258 severe cases of neonatal jaundice in Canada, 57 infants (22.1%) underwent an exchange transfusion, from 2002- 2004 (Sgro *et al.*, 2006). Out of one thousand newborns were admitted to hospital with diagnosis of neonatal jaundice, 176 exchange blood transfusion procedures were performed (10.13%) in Children's Hospital, Tabriz, Iran (Sakha and Gharehbaghi, 2010).

2.7   Maternal Factors Leading to Exchange Blood Transfusion Among Severe Neonatal Jaundice

Numerous studies found that mother give some influence towards the development of jaundice in the neonatal such as age of mother, number of parity, place of delivery chose by the mother, mode of delivery, mother with blood group O, breastfeeding attitude, herbal usage and underlying disease for instance Rhesus disease and diabetes mellitus.

2.7.1   Maternal age

The significant mean age of mothers associated with exchange transfused neonatal jaundice was 26 years in a Turkish study in 2010 (Davutoglu *et al.*, 2010), similar to a study by Behjati *et al.* (2009) with significantly mean of age of mothers was 26 years. This finding is bit different in a study in Nigeria by Olusanya *et al.* (2009) with mean age of mothers was 28 years.

2.7.2 Parity of mother

Primiparity factor was found by Menon, 2017 in South India as a significant factor associated with exchange transfused neonatal jaundice by 67.8% (OR: 2.17; 95% CI: 1.15, 4.11; p=0.019). A study done in Nigeria by Olusanya *et al.* (2009) found that 40.9% of the cases had exchange blood transfusion was primiparas mother.

2.7.3 Place of delivery

Babies who were delivered in non-hospital area or home delivery were at risk to underwent exchange blood transfusion *(Hameed et al., 2011)*, but a report in India found that high incidence of severe neonatal jaundice cases that underwent exchange blood transfusion were delivered in hospital setting, about 82.8% (p=0.120) (Malla *et al.*, 2015). According to Olusanya *et al.* (2009), less than half of severe neonates who underwent exchange blood transfusion were delivered in hospital facilities while a higher number of jaundiced neonates were attended by skilled health practitioners outside the health facilities.

2.7.4 Vaginal delivery

According to a study in UK and Ireland, they found that vaginal delivery was associated with babies who underwent exchange blood transfusion by 58.3% (p=0.05) compare to instrumental delivery and caesarean section delivery (Manning *et al.*, 2007). Vaginal delivery was found significant associated with exchange blood transfusion among severe jaundice babies by 63.6% (p=0.003) (Heydarian and Majdi, 2010). A study in North India discovered that normal spontaneous vaginal delivery (OR 5.5; 95% CI: 1.1, 27.4; p=0.037) as significant risk factor of neonates underwent exchange blood transfusion even for development of ABE (Kumar *et al.*, 2016).

2.7.5 Mother blood group O

Mother with blood group O was found as risk factors with 26% underwent exchange blood transfusion in Canada (Bujandric and Grujic, 2016) while a study Nepal contributes higher number, 65.5% of cases (p=0.200) (Malla *et al.*, 2015). A report from Iran revealed mother with blood group O was the most common cause of exchange blood transfusion because mothers have IgG antibodies that can pass through placenta and cause haemolytic events in A or B blood group offspring (Heydarian and Majdi, 2010).

2.7.6 Breastfeeding Jaundice

Studies in South Africa, Iran, UK and Ireland found that breastfeeding is a risk factor of severe NNJ babies readmitted for requiring exchange blood transfusion (Horn *et al.*, 2006; Manning *et al.*, 2007). A study done in Tehran, Iran found that breastfeeding jaundice was the second most prevalent underlying factor for severe hyperbilirubinemia underwent exchange transfusion by 35% with odd ratio 3.2 (Taheri *et al.*, 2014).

2.7.7 Herbal usage during pregnancy

According to a study done in Southeast Nigeria, mothers of two neonates born in hospital facilities (2.4%) and 25 mothers of those who were born outside the hospital facilities (35.2%) took herbal medications during pregnancy with statistically significant difference between them with p < 0.001 (Onyearugha *et al.*, 2011). Olusanya *et al.* (2009) in their study done in Lagos, Nigeria found that mother who consumed herbal medications during pregnancy had 2.43 times the odds compared to

those mothers who did not take herbal medications during pregnancy to have neonates with severe jaundice requiring exchange blood transfusion.

2.7.8 Rhesus incompatibility

Isoimmune haemolysis such as Rhesus disease is a common risk factor for severe neonatal jaundice underwent exchange blood transfusion as mentioned in studies in South Africa and Iraq (Ballot and Rugamba, 2016; Bhutani *et al.*, 2013; Hameed *et al.*, 2011). A study done in Vojvodina, Serbia in 2016 found that Rhesus disease was the highest risk factor with 38% (odd ratio=1.25) underwent exchange blood transfusion (Bujandric and Grujic, 2016).

2.7.9 Diabetic mother

Sh. Behjati *et al.,* (2009) and Bjerre *et al.,* (2008) stated that infant of diabetic mother was an indicator for severe neonatal jaundice requiring exchange blood transfusion. A study in Bangladesh in 2012 found that 46.7% of severe jaundice neonates who requiring exchange blood transfusion procedure were infant of diabetic mother (Begum *et al.*, 2012).

2.8 Neonatal Factors Leading to Exchange Blood Transfusion Among Severe Neonatal Jaundice

Lots of studies discussed neonatal risk factors such as male gender, ABO incompatibility and UGT1A1, or birth related component such as prematurity, birth weight, birth trauma and birth asphyxia, or co-existing factors such as infection, G6PD deficiency, excessive weight loss and inadequate breastfeeding.

2.8.1 Male gender

Male gender of neonates was found to be associated with exchange blood transfusion among severe jaundice neonates by 60.4% in a study in UK and Ireland (Manning *et al.*, 2007). Similar finding in a study done in Mashhad, Iran in 2010, male gender were detected as an associated factor with exchange blood transfusion by 63.6% (p=0.003) (Heydarian and Majdi, 2010). A study in Cairo showed that male to female ratio was 2:1 (Hashem *et al.*, 2009), similar with Bujandric and Grujic (2016) who revealed their study findings with the sex ratio males to females as 1.25:1, which reflected that male gender had higher chances for exchange blood transfusion.

2.8.2 ABO incompatibility

According to a study done in Iran among 346 neonates with hyperbilirubinemia, ABO incompatibility was the major risk factor for exchange blood transfusion, which contributes for about half of the severe neonatal jaundice cases (Behjati *et al.*, 2009). Similar result by study in Canada by Sgro *et al.* (2006), ABO incompatibility was found as the most significant factor of severe neonatal jaundice requiring exchange blood transfusion by 52%. A study done in Vojvodina, Serbia in 2016 found that ABO incompatibility was the second highest risk factors with 38% (150 infants) requiring exchange blood transfusion (Bujandric and Grujic, 2016).

2.8.3 Genetic (UGT1A1)

Genetic defect in the promoter or coding area of the UGT1A1 gene, was found as an associated factor leading to severe jaundice among Whites, Taiwanese and Japanese (Huang *et al.*, 2002). The prevailling variant in the UGT1A1 gene was the substitution of G to A at nucleotide 211. According to study by Huang *et al.* (2004) in Taiwan, the

significant risk factor identified was the variant UGT1A1 gene at nucleotide 211, and the variant OATP 2 gene at nucleotide 388 (p=0.043). But a study in Brazil in 2010 and a study in German in 2014 found that UGT1A1 gene promoter variants were not risk characteristic for jaundiced neonates underwent exchange transfusion (Mezzacappa *et al.*, 2010; Petersen *et al.*, 2014).

2.8.4   Preterm birth

Several studies reported gestational age to be significant risk factor of severe neonatal jaundice (Kuzniewicz *et al.*, 2014; Pius *et al.*, 2017). According to the Canadian Paediatric Society, gestational age of 35 to 36 weeks is an paramount period at risk for neonatal jaundice. Sakha and Gharehbaghi (2010) also reported that preterm birth which is defined as birth less than 37 weeks is associated with neonatal jaundice exchange blood transfusion. In study by Taheri *et al* in 2014, the main risk factor for exchange blood transfusion was neonates who were delivered with mean 35.2 weeks and half of neonates in study population were preterm.

2.8.5   Low birth weight

Okwundu *et al.* in 2013 reported that low birth weight less 2500 grams is the risk factor for exchange blood transfusion among severe neonatal jaundice in Canada. Low birthweight which defined as less 2500 grams is the main factor associated with severe jaundice in neonates demanding exchange blood transfusion in Nigeria by 44.4% while 11.1% of them were very low birth weight (Owa and Ogunlesi, 2009). In Kerala, South India, low birth weight was also the most common risk factors of exchange blood transfusion among severe neonatal jaundice by 80.6% (p = 0.0001) (Menon, 2017).

2.8.6 Birth trauma

A study in India showed that cephalohematoma was not a significant factor for severe jaundiced neonates requiring exchange transfusion and it was diagnosed only on 9.5% of them (Lavanya *et al.*, 2012). According to report in Taiwan, cephalohematoma also not a risk factor to develop severe hyperbilirubinemia till treated by exchange blood transfusion (p=0.071) (Huang *et al.*, 2004).

2.8.7 Birth asphyxia

Birth asphyxia was seen more commonly in neonates who developed jaundice underwent exchange blood transfusion with 29% of total neonates, (p = 0.0001) (Menon, 2017). According to study by Huang *et al.* (2004) in Taiwan, birth asphyxia was a protective factor to develop severe hyperbilirubinemia underwent exchange blood transfusion (OR:0.34, 95% CI: 0.04, 3.09; p=0.034).

2.8.8 Infection

In Africa, infection caused more than 14% cases of severe neonatal jaundice underwent exchange transfusion. In the Middle East, half of total cases of kernicterus was discovered caused by infection, while in North America and Europe, infection was compromised in 2% of neonates who underwent exchange blood transfusion and 14% cases of kernicterus. Septicaemia or any infections in neonates were risk factors for hyperbilirubinemia needing exchange blood transfusion (Begum *et al.*, 2012; Olusanya and Slusher, 2015; Pius *et al.*, 2017)

2.8.9 G6PD deficiency

G-6PD deficiency is the commonest inherited red cell enzymopathy worldwide, affecting about 400 million people globally and affecting as many as 4,500,000 newborns worldwide each year. The G-6PD gene is located on the X chromosome and hemizygous males have the full enzyme deficiency. G6PD deficiency is an enzyme defect that commonly classified as significant risk factor for the severe neonatal jaundice and exchange blood transfusion (Badiee, 2007; Behjati *et al.*, 2009; Owa and Ogunlesi, 2009). In Africa, G6PD deficiency accounted for over 35% of cases of significant hyperbilirubinemia and kernicterus. In North America and Europe, G6PD deficiency was found in 5% of neonates who received exchange blood transfusion, and one fifth of the cases of kernicterus (Begum *et al.,* 2012).

2.8.10 Excessive weight loss

Behjati *et al.* (2009) and Bjerre *et al.* (2008) stated that excessive weight loss above ten percent of birth weight is indicator for severe jaundiced neonates underwent exchange blood transfusion procedure, similar findings was observed in 22 neonates (31.9%) in the north province of Iran (Esfandiarpour *et al.*, 2012). Based on study in Mashhad, Iran, they highlighted that weight loss above ten percent after 1 week of birth was an associated factor to exchange transfusion, contributed 16.1% with p value <0.001 (Heydarian and Majdi, 2010).

2.8.11 Inadequate breastfeeding

Behjati *et al.* (2009) found in their study that almost half of neonates who received the exchange transfusion had a specific gravity of urine more or equal to 1012 specific gravity, highest possibility because of insufficient fluid intake in these infants. A study

in Turkey found that second leading cause of hospital admissions for exchange blood transfusion among jaundice babies was dehydration related to improper feeding which contributes of 1,551 babies (27.6%) out of 5,620 babies (Erdeve *et al.*, 2018).

2.8.12 History of previous siblings had severe neonatal jaundice

History of previous siblings had similar severe neonatal jaundice influence exchange blood transfusion among severe jaundiced neonates by 10% (Behjati *et al.*, 2009; Listernick, 2015). According to a study in Fars Province, South of Iran, history of previous siblings had severe hyperbilirubinemia was statistically significant by 5.3% (p=0.006) (Najib *et al.*, 2013). In contrast with a study in North India, they found that history of severe jaundice in sibling during neonatal period was insignificant risk factor for jaundice babies underwent exchange blood transfusion (OR:1.3; 95% CI: 0.42,4; p=0.65) (Kumar *et al.*, 2016).

2.10   Conceptual framework

Conceptual framework of identified factors that influence exchange blood transfusion among severe neonatal jaundice shown in Figure 2.2. There are many factors associated with exchange blood transfused neonatal jaundice based on literature review. Since our study based on secondary data, so only twelve variables were available which were maternal age, number of parity, place of delivery, rhesus negative disease, mother's blood group O, ABO incompatibility, infections in neonates, preterm birth, low birth weight, birth trauma, inadequate breastfeeding and G6PD deficiency in neonates.

Those mark with * were factors not included in this study. The aim and goal of this study to identify factors associated with exchange blood transfusion among severe jaundice neonates in Kelantan.
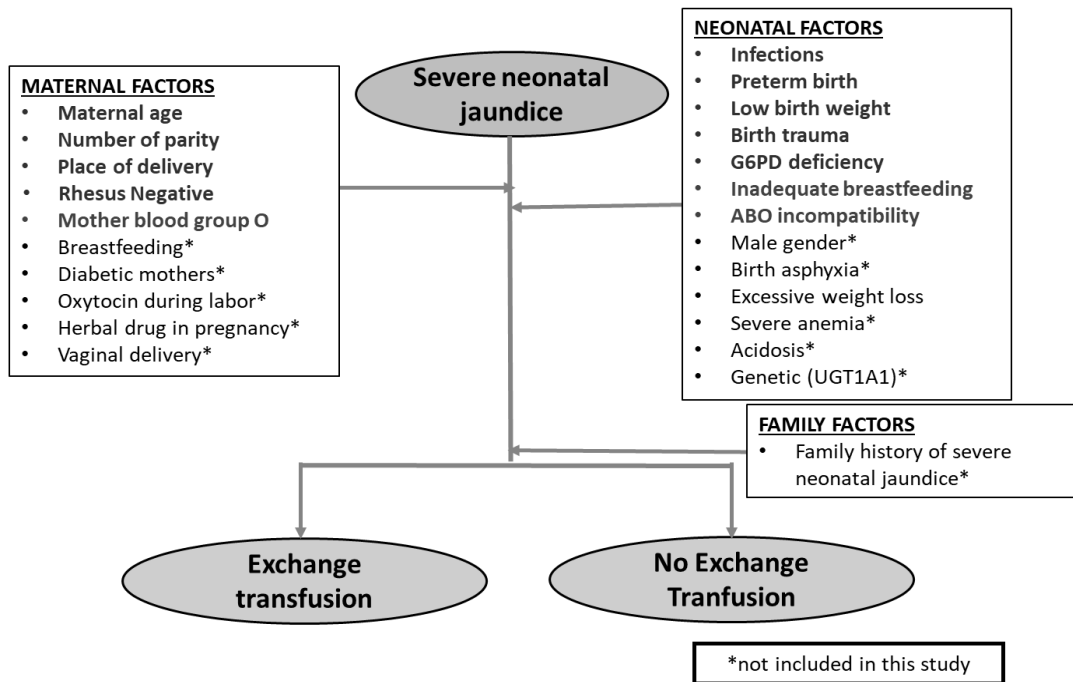
MATERNAL FACTORS
- Maternal age
- Number of parity
- Place of delivery
- Rhesus Negative
- Mother blood group O
- Breastfeeding*
- Diabetic mothers*
- Oxytocin during labor*
- Herbal drug in pregnancy*
- Vaginal delivery*

Severe neonatal jaundice

NEONATAL FACTORS
- Infections
- Preterm birth
- Low birth weight
- Birth trauma
- G6PD deficiency
- Inadequate breastfeeding
- ABO incompatibility
- Male gender*
- Birth asphyxia*
- Excessive weight loss
- Severe anemia*
- Acidosis*
- Genetic (UGT1A1)*

FAMILY FACTORS
- Family history of severe neonatal jaundice*

Exchange transfusion

No Exchange Tranfusion

*not included in this study

Figure 2.2: Conceptual framework of study

CHAPTER THREE

METHODOLOGY

3.1   Study design

This study applied a cross-sectional study design based on secondary data retrospective record review.

3.2   Study duration

This study was conducted within four months period starting from January till April 2018.

3.3   Study area

This study involved all the districts in Kelantan. Kelantan is located in east coast region of peninsular Malaysia. It is the sixth largest state of Malaysia and covers almost 5% of Malaysia (15,101 km2) with total population of 1.83 million and average annual population growth rate 2.0% (DOSM, 2018).

The majority of population in Kelantan are Malays comprising of 96.21% of the total population, followed by Chinese, Indians and others (3.19%, 0.27% and 0.63%, respectively). Total livebirth in Kelantan in 2015, 2016 and 2017 was 24253, 23994 and 23737 babies respectively.