PREMATURE BIRTHS FOR GESTATIONAL AGE AND ITS IMPACT ON EARLY VERSUS delayed WEANING

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PREMATURE SMALL FOR GESTATIONAL AGE INFANT:
EARLY VERSUS DELAYED FEEDING

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DECLARATION

I hereby declare that the work in this dissertation is my own except for quotations and summaries which have been duly acknowledged.

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FLORENCE ANAK BAKON

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I am grateful to God, the Creator and the Guardian, and to whom I owe the strength, guidance and good health to walk this journey.

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ABSTRACT

Initiation of enteral feeding in small for gestational age (SGA) premature infants is a challenge as the SGA infant with compromised blood supply to the gut has traditionally been associated with an increased risk of feeding intolerance and necrotising enterocolitis.

This study compared the incidence of feeding intolerance, necrotising enterocolitis and duration to achieve full enteral feeding in infants randomised to either early or delayed enteral feeding.

SGA infants below 35 weeks gestation between the weights of 1000 g and 1800 g were enrolled over a duration of 16 months (August 2010 to January 2012). The early group commenced enteral feeding within the first 12h and the delayed group after 48h. Advancement of feeds is similar in both groups; 10 ml/kg/d to 35 ml/kg/d over a period of 6d.

A total of 45 infants were randomised into the early (N=25) or delayed (N=20) feeding group. Mean gestation (33 weeks) and birth-weight (1500 g vs 1422 g, respectively) were similar. There was no statistical difference in the incidence of feeding intolerance between the early and delayed feeding groups (10% vs. 25%, respectively; p=0.14). There were no cases of necrotising enterocolitis, and the incidence of sepsis between groups was similar. The early group achieved full feeding in 5.5 ±1.1d compared to 7.9 ±1.7d in the delayed group. There was no difference in the types of milk feeds (breast or formula) between groups.

There was no evidence to support delayed feeding for SGA premature infants. Early feeding may promote faster full enteral feeds and weight gain to discharge.
ABSTRAK

Penyusuan bayi pramatang yang bersaiz kecil daripada biasa adalah satu cabaran, kerana bayi pramatang yang bersaiz kecil daripada biasa dikaitkan dengan risiko tidak tolerasi penyusuan dan juga jangkitan dalam salur penghadaman.

Kajian ini adalah untuk membandingkan insiden tidak tolerasi penyusuan, jangkitan dalam salur penghadaman dan jangkamasa untuk mencapai penyusuan penuh diantara kumpulan penyusuan awal dan penyusuan lewat.

Bayi pramatang dibawah 35 minggu dan bersaiz kecil daripada biasa dengan berat lahir 1000g hingga 1800g, dalam tempoh 16 bulan (Ogos 2010 sehingga Januari 2012) dimasukkan didalam kajian ini.

Kumpulan awal memulakan penyusuan sebelum berusia 12 jam selepas kelahiran manakala kumpulan lewat memulakan penyusuan selepas berusia 48 jam. Kadar penambahan susu dalam kedua dua kumpulan adalah sama iaitu 10ml/kg/hari sehingga 35ml/kg/hari.

45 bayi dibahagikan secara rawak kepada kumpulan penyusuan awal (N=25) dan kumpulan penyusuan lewat (N=20). Umur gestasi bayi (33 minggu) dan berat lahir masing masing (1500g Vs 1422g) untuk kedua dua kumpulan. Tiada perbezaan statistic dari segi insiden tidak tolerasi penyusuan diantara kedua dua kumpulan penyusuan (10% vs 25%, nilai p= 0.14). Tiada kes jangkitan salur penghadaman dalam kedua dua kumpulan. Insiden sepsis diantara kedua dua kumpulan adalah sama. Kumpulan penyusuan awal mencapai penyusuan penuh dalam 5.5±1.1h berbanding kumpulan penyusuan lewat 7.9±1.7h dalam kumpulan lewat. Tiada perbezaan diantara jenis susu yang diberikan kepada bayi (susu badan atau susu formula) diantaranya kedua dua kumpulan penyusuan.

Tiada data untuk menyokong penyusuan lewat dalam bayi pramatang yang bersaiz kecil daripada biasa. Penyusuan awal dapat membantu mencapai penyusuan penuh lebih awal seterusnya menggalakan perbesaran bayi.
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1.1 LITERATURE REVIEW

Small for gestational age (SGA) infant is described as a newborn with birth weight of at least 2SD below the mean for the infant’s gestational age, based on data derived from a reference population. SGA is also defined as birth weight or length below 10th percentile for gestational age.

The 3rd National Health and Nutrition examination survey showed prevalence of SGA among newborns in the United State around 8.6% of all live births. Among all those infants, 28 to 78% are constitutionally small and the remaining has growth retardation during intra uterine life. Intra uterine growth retardation or restriction suggests diminished growth velocity of the fetus and it indicates the presence of pathophysiologic process occurring in utero that inhibits the fetal growth. [1] The growth of the fetus is affected by nutrients and oxygen they receive from mother. Intra uterine growth retardation in itself is also a clinical condition in which the risk of hypoxia is around 30%. Fetus adapts to poor nutrition due to either hypoxia or placental insufficiency by changing its metabolism, redistributing its blood flow and slowing its growth rate. [2] Studies have shown pronounced redistribution of fetal blood flow to the brain, adrenals, and coronary arteries and reduction in blood flow to skeletal muscle, gut and kidneys in response to acute and chronic hypoxia. Animal studies on placental restricted fetus have showed that even though fetal adrenal size is preserved, there is alteration in production of catecholamine, which
has been implicated to cause vasoconstriction of splanchnic blood vessels. [3,4] Abnormality in splanchnic blood flow persists postnatally with some recovery during the first week of life.

Based on this fact, clinicians are very cautious in the timing of initiation of enteral feeding in SGA infants. SGA infants with placental insufficiency are more likely to develop gastrointestinal tract complication compared to normal birth weight infants. [5]

Because of concern of feeding intolerance and NEC, clinicians have various practices on timing of commencement of enteral feeding. To date there is no trial showing optimal timing in starting enteral feeding. Previously, one of the strategies practiced to reduce the risk of NEC is withholding the enteral feeding for prolonged periods of time. [6] However, it was never shown that prolonged withholding of feeding actually prevented NEC. A Cochrane Systematic Review on 2 trials with total of 74 patients, provided no evidence that delayed introduction of feeding affected the incidence of NEC, mortality or other neonatal mortality. [7]

Early introduction of feeding in preterm infant has been shown to be beneficial in stimulating gastrointestinal tract enzymes and strengthening the mucosal barrier. [8] A significant rise in the release of enteroglucagon, gastrin and gastric-inhibiting polypeptide in preterm infant occurs after milk feed as low as 12ml/kg/day. Similar surge is not seen in intravenously nourished infants. [8] A systematic review of studies on low birth weight and premature infant who were randomized to early enteral feeding (mean < 4 days) or late enteral feeding (> 4 days) concluded that early introduction of feed shortens the time to reach full feeding as well as duration of stay in hospital and does not increase the risk of NEC. [9]
1.2 RATIONALE OF THE STUDY

Clinicians have various practices with regards to commencement of enteral feeding in SGA infants, some start as early as possible whilst some as late as after 4 days of life because of concern of feeding intolerance and NEC. By delaying the commencement of enteral feeding, the infants will be on intravenous drip or central line and total parenteral nutrition for a longer period of time, which has been associated with a higher risk of sepsis. This study compared the incidence of feeding intolerance and NEC between 2 groups: early group, to commence feeding as early as possible (within 12 hours of life) and delayed feeding (after 48 hours of life). Infants with better tolerance to feeding will achieve full feeding earlier and eventually stop intravenous drip or long line earlier which may reduce the risk of infection.

1.3 RESEARCH HYPOTHESIS

There is significant difference in the incidence of feeding intolerance between early and delayed commencement of feeding in Preterm Small for Gestational Age infant.

1.4 NULL HYPOTHESIS
There is no significant difference in the incidence of feeding intolerance between early and delayed commencement of feeding in Preterm Small for Gestational Age infant.

1.5 OBJECTIVES

1.5.1 PRIMARY OBJECTIVE

To compare the incidence of feeding intolerance between early and delayed feeding group in preterm SGA infants weighing 1000 to 1800 grams.

1.5.2 SECONDARY OBJECTIVES

a) To compare the duration required to reach minimal enteral feeding of at least 120 ml/kg/day between early and delayed feeding in preterm SGA infants weighing 1000 to 1800 grams.

b) To determine the incidence of Necrotising Enterocolitis and sepsis between early and delay feeding in preterm SGA infants weighing 1000 to 1800 grams.
CHAPTER 2

MATERIALS AND METHODS

2.1 STUDY POPULATION

This was a randomized control study conducted at Neonatal Intensive Care Unit (NICU), UKM Medical Centre.

The study was carried out over a period of 18 months, from August 2010 to February 2012. The patients were recruited upon admission to the NICU.

The study population were premature infants less than 34 weeks gestation.

2.2 SELECTION CRITERIA

2.2.1 INCLUSION CRITERIA

A. Premature less than 34 weeks gestation; infants with an unknown gestational age were assessed using the New Ballard score and those who were found to be less than 34 weeks gestation were also included and

B. Birth weight between 1000g to 1800g and
C. Infants who were small for gestational age.

2.2.2 EXCLUSION CRITERIA

A. Parents who had not consented.
B. Infants with gastrointestinal tract abnormality which precludes commencement of enteral feeding.
C. Infants with lethal congenital abnormality.
D. Infants with hypoxic ischemic encephalopathy stage 2 and 3.
E. Infants with intraventricular haemorrhage grade 3 or more.

2.3 METHODOLOGY

The parents of premature and small for gestational age infant of less than 34 weeks, with birth weight 1000g to 1800g who were admitted to the NICU were approached. Informed consent was obtained after explanation regarding the study was given. After consent was obtained, the infant was randomized into either Early or Delay Feeding group. All babies were started on parenteral intravenous drip either via peripheral intravenous line insertion, umbilical venous catheter or peripherally-inserted long line catheter. Upon admission at day 1 of life, all babies were given Dextrose 10%.

In the early group, feeding was commenced as early as possible within the first 12 hours of life. The feeding was commenced at 10ml/kg/day and increased on a daily basis. Feeding increment was 20ml/kg/day, 25ml/kg/day, 30ml/kg/day and 35ml/kg/day for second, third, fourth and fifth day of feeding respectively. Therefore, if the baby did not have feeding intolerance, they would achieve minimal full enteral feed which was 120ml/kg/day within 5 days of feeding. Intravenous
drip or central line was stopped and removed once minimal full enteral feeding was achieved. The feeding was increased by 35ml/kg/day until maximum feeding based on the managing team. In the delay feeding group, enteral feeding was initiated after 48 hours of life. They were also started with feeding at 10ml/kg/day with the same daily increment as the early group. Once they reached minimal full feeding of 120ml/kg/day the intravenous drip or central line was removed. Then the feeding will be gradually increased by 35ml/kg/day until maximum feeding.

Infants who developed feeding intolerance such as increased oro-gastric tube aspirate, abdominal distension or vomiting were then assessed for signs and symptoms of sepsis and Necrotising Enterocolitis. Investigations were done if they were clinically indicated. Based on the managing clinician, the infant patients were assessed from time to time. If the symptoms of feeding intolerance had resolved and Necrotising Enterocolitis was not diagnosed, feeding was resumed and gradually increased as per protocol.

The re-feeding plan was based on the day of feeding when the feeding intolerance occurred. For example, the amount of feeding given after episode of nil by mouth was 10ml/kg/day for feeding intolerance which occurred on the first day of introduction of feeding, 20ml/kg/day for feeding intolerance which occurred on the second day of feeding, 25ml/kg/day for feeding intolerance which occurred on the third day of feeding, 30ml/kg/day for feeding intolerance which occurred on the fourth day of feeding and 35ml/kg/day for feeding which occurred on day 5 and onwards. The feeding was then gradually increased until full minimal enteral feeding was achieved. Intravenous drip or central line for administration of Total Parenteral Nutrition were then stopped and removed.
2.4 DEFINITION

2.4.1 Small for gestational age infant

An infant with anthropometric measurement below the 10th percentile based on Lubchenko Chart.

2.4.2 Necrotising Enterocolitis

The diagnosis and staging of severity for Necrotising enterocolitis were made based on Modified Bell’s staging criteria.

2.5 DATA COLLECTION

The maternal and infants’s demographic, clinical and outcome data was recorded in a standard data collection sheet (Appendix).
2.6 SAMPLE SIZE CALCULATION

Formula:
\[ n = \frac{2\sigma^2}{\Delta^2} (z_\alpha + z_\beta)^2 \]

- \( n \) = number of samples
- \( z_\alpha = 1.96 \) (for \( \alpha \) error 0.05, two tailed or 95% CI)
- \( z_\alpha = 2.58 \) (for \( \alpha \) error 0.01, two tailed or 99% CI)
- \( z_\beta = 0.84 \) (for 80% power) or 1.28 (for 90% power)
- \( \sigma \) = population standard deviation
- \( \Delta \) = width of the confidence interval

Standard deviation from a referred population study = \( \sigma \) is 4*.

Width of the confidence interval = \( \Delta \) is 3

Feeding intolerance of 20% in Preterm SGA who commenced feeding at average 1.5 day of life in a referred study* - referred as early.

Feeding intolerance of 5% in Preterm SGA who commenced feeding at average Day 6 of life in a referred study# - referred as delay.

\( \Delta \)

Difference of feeding intolerance in 2 group = 20 - 5 = 15

Width of confidence interval = 15 X 20% = 3

*Based on the Study Prediction of feed intolerance and necrotizing enterocolitis in neonates with absent end diastolic flow in umbilical artery and the correlation of feed intolerance with postnatal superior mesenteric artery flow (16).
Feeding Strategies for Premature Infants: Randomized Trial of Gastrointestinal Priming and Tube feeding method. (17)

\[ n = 2 \cdot (1.96 + 0.84)^2 / 3^2 \]

\[ n = 26 \text{ in 1 arm.} \]

Total sample size = 52 taken

2.7 STATISTICAL ANALYSIS

Data was analysed using SPSS 19.0. Chi-square was used to compare categorical variables. T-test and Mann-Whitney U test were used for normally distributed and skewed quantitative data, respectively. A p value of less than 0.05 was taken as significant.
CHAPTER 3

RESULTS

3.1 RECRUITMENT

Between August 2010 and January 2012, 58 premature small for gestational age infants were eligible for the trial. 12 infants were missed and were not recruited into the study. 1 did not consent for the study. Forty five infants were randomized into either early or delay group; twenty five in early and twenty in delay feeding group.

One infant from each group was transferred to another hospital before completion of the study and 1 baby in the early group had died due to Klebsiella sp. sepsis. (Figure 1)
3.2 DEMOGRAPHIC DISTRIBUTION BETWEEN EARLY AND DELAY FEEDING GROUP (TABLE 1)

Demographic distributions between the 2 groups were quite comparable. In both groups, the mean gestational age was 33 weeks period of gestation. In the early group, mean birth weight was 1500 (SD 109) grams while in the delay group was 1422 (SD 152) grams. The difference was not statistically significant.

There were sixteen (64%) males in the early group and eight (40%) in the delay group. Majority of the babies enrolled were from the Malay ethnic group (73%), followed by the Chinese ethnic group. The rest were from the East Malaysia indigenous ethnic group as well as from other Asian countries. When further classified into the symmetrical and asymmetrical small for gestational age (SGA) infant, no statistically significant difference were seen between the two groups.

Among the infants, fourteen (56%) had respiratory distress syndrome in the early group and fourteen (70%) in the delay group. Fifty six percent of infants in the early group had used CPAP and eighty five percent in the delay group had used CPAP. There was no significant difference between the two groups in both variables.

Similarly, there was no statistically significant difference in the number of infants requiring invasive ventilation at birth, those who received antenatal steroid, infants with hypertensive mothers requiring magnesium sulphate infusion and infants with mothers having chorioamnionitis and prolonged leaking of liquor when comparing between the early and delay group.
Eleven infants in the early group had an ultrasound Doppler of umbilical arteries performed ante-natally and all were normal, while nine infants in the delay group had an ultrasound Doppler of umbilical arteries performed ante-natally and 4 showed abnormal flow. The mean amniotic fluid index in the early group was 11.3 (SD 3.2) and on the delay group it was 8.3 (SD 4.3). There was no statistically significant difference when comparing the amniotic fluid index of 2 groups.

In the early group, 10 (40%) were fed expressed breast milk, 10 (40%) were fed 22 kcal premature infant formula, and 10 (40%) were fed 24 kcal premature infant formula. In the delay group, 5 (25%) were fed expressed breast milk, 8 (40%) were fed 22 kcal premature infant formula and 7 (35%) were fed 24 kcal premature infant formula. There was no significant difference between the two groups in the types of milk fed.

There were no infections in the early group and 5 (25%) in the delay group when were treated medically and total parenteral nutrition (TPN). This was not statistically different statistically.

In the early group the intravenous line was kept in-situ for a mean of 5.7 (SD 1.37) days while the delay group the intravenous line was kept in-situ for a mean of 8.0 (SD 1.71) days. The difference in the duration of intravenous line kept in-situ between the two groups was statistically significant.

In the early group all infants who were started on TPN received TPN for a mean time of 4.9 (SD 1.39) days while 7 (77%) of the infants in the delay group received TPN for a mean time of 9.6 (SD 0.47) days. The difference was not statistically significant.
3.3 COMPARISON PROFILES BETWEEN EARLY AND DELAY FEEDING GROUP (TABLE 2)

Enteral feeding was commenced at a mean of 7.9 (SD 2.7) hours of life in the early group while in the delay group, enteral feeding was commenced at a mean of 48.9 (SD 6.39) hours of life.

In the early group, 8 (32%) were fed expressed breast milk, 10 (40%) were fed 22 kcal premature infant formula and 7 (8%) were fed 24 kcal premature infant formula. In the delay group, 5 (25%) were fed expressed breast milk, 8 (40%) were fed 22 kcal premature infant formula and 7 (35%) were fed 24 kcal premature infant formula. There was no significant difference between the two groups when comparing types of milk fed.

There were 2 (8%) infants in the early group and 5 (25%) infants in the delay group who were started on total parenteral nutrition (TPN). This was not significantly different statistically.

In the early group, the intravenous line was kept in-situ for a mean of 5.7 (SD 1.37) days whilst in the delay group the intravenous line was kept in-situ for a mean of 8.0 (SD 1.71) days. The difference in the duration of intravenous line kept in-situ between the two groups was statistically significant.

In the early group, the infants who were started on TPN received TPN for a mean total of 4.9 (SD 0.28) days while infants in the delay group received TPN for mean total of 7.0 (SD 0.47) days. The difference was not statistically significant.
Infants in the early group achieved full enteral feeding at a mean age of 5.5 (SD 1.10) days while in the delay group, the infants achieved full enteral feeding at a mean age of 7.9 (SD 1.70) days. When comparing the age at which full enteral feeding was achieved, there was a statistically significant difference. However, when comparing the duration to achieve full enteral feeding from time of initiation of feeding, there was no statistically significant difference. In the early group, the infants took a mean of 5.4 (SD 1.02) days to reach full enteral feeding and the delay group took a mean of 5.83 (SD 1.56) days to reach full enteral feeding.