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A five year retrospective clinical outcome on necrotizing enterocolitis among neonates of University Hospital, Kelantan, Malaysia

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Abstract

Background: Necrotizing enterocolitis (NEC) is a common neonatal gastrointestinal disease with multifactorial etiology among the neonates. We aimed to provide descriptive information about the current prevalence of necrotizing enterocolitis and evaluate the total parenteral nutrition management against the treatment outcomes and clinical complications.

Methods: A descriptive cross-sectional observational study was carried out on necrotizing enterocolitis cases in Universiti Sains Malaysia Hospital (HUSM), Kelantan, Malaysia. Study frame was a five-year retrospective review from January 2003 till August 2007. Universal sampling was employed to collect the data from medical profiles. Ethical approval was made with Ministry of Health, Malaysia and data was analyzed by using SPSS 12®.

Results: By the end of the study period, 46 patients were selected. Majority of the patients were Malays 44 (95.6%) patients. This is followed by Chinese 1 (2.2%) patient and 1 (2.2%) others. Gender distribution was found equally susceptible 22 (47.8%) females and 24 (52.8%) were males. We found that majority 39 (84.8%) of neonates were under the range of ≤ 2500 g. The majority received total parenteral nutrition (TPN) 15 (32.6%) neonates received TPN for more than 14 days, followed by 11 (23.9%) between 6-8 days. Significant relationships were found between gestation age and duration of TPN (<0.001), between birth weight and complication (0.041) and between necrotizing enterocolitis cases and outcomes (0.005).

Conclusion: Providing TPN is wrought with unique potential risks and complications to these fragile infants and calls for a diligent interdisciplinary team approach.

Key Words: Neonatal disease, Necrotizing enterocolitis, Total parenteral nutrition, Nutrition, Neonatal infections, Low birth weight diseases

Introduction

Necrotizing enterocolitis (NEC) is a common neonatal gastrointestinal disease that affects approximately 11% of premature neonates weighing less than 1500 g (Berseth 1990, Uauy et. al., 1991). The average mortality is 20% to 40%, and survivors after either medical or surgical therapy can present with failure to thrive (Berseth 1990), feeding abnormalities (Uauy et. al., 1991), diarrhea, or bowel obstruction (Berseth 1990, Eibl et al., 1988). The etiology of NEC is multifactorial, and the most important risk factors are prematurity, hypoxia and/or intestinal ischemia, and enteral feeding and gastrointestinal bacteria colonization (Halac et al., 1990). The association of such risk factors might trigger a local inflammatory cascade with release of inflammatory mediators, resulting in NEC (Siu et al., 1998). Early signs of NEC are indistinguishable from sepsis neonatorum (Walsh, Kliegman, & Hack 1989). The usual presentation includes abdominal distension, gastric residuals, bilious vomiting, and bloody stools. Lethargy, apnea, and hypoperfusion also may be a prominent feature (Halac et al., 1990, Siu et al., 1998, Walsh, Kliegman, & Hack 1989, Sonntag et al., 2000).

Since prematurity is the most important risk factor associated with NEC, possible therapeutic approaches that promote maturation of the gastrointestinal mucosal barrier (Vohr et al., 2000), such as the prenatal administration of corticosteroids (Rabinowitz et al., 2001), have been explored. With the increased survival of very low birth weight (VLBW) and premature infants, the incidence of NEC has been increasing (Berseth 1990, Halac et al., 1990, Siu et al., 1998, Walsh, Kliegman, & Hack 1989, Sonntag et al., 2000, Rabinowitz et al., 2001) and at present ranges between 1-5% of all admissions in the neonatal intensive care unit. In spite of appreciable medical and surgical therapy, the mortality has ranged between 20-50 percent.

Since a combination of factors initiate and propagate the disease and the pathogenesis is incompletely understood (Eibl et al., 1988, Sonntag et al., 2000, Rabinowitz et al., 2001, Edelson 1999) .various preventive measures have been unsuccessful (Berseth 1990, Eibl et al., 1988, Walsh, Kliegman, & Hack 1989, Sonntag et al., 2000, Rabinowitz et al., 2001). Greater emphasis is placed on the early recognition of disease, so that prompt management may be initiated to lessen the severity and complication of this disease.

Preterm infants are at increased risk of adverse neonatal outcomes (Edelson 1999, Dimmitt et al., 2003). However they frequently demonstrate intolerance of milk feeds and have been shown to have an increased incidence of necrotizing enterocolitis (NEC) (Maalouf et al., 2000).

Since NEC is an infant disease it is necessary to identify disease burden in hospital setting. The purposes of our study were: 1) to provide epidemiological statistics of necrotizing enterocolitis in university hospital, and 2) to determine the clinical outcome of TPN in necrotizing enterocolitis treatment. Lastly, but not least, we seek to identify the likelihood associated with necrotizing enterocolitis among pediatric patients.

Study significance lies under the potential evaluation of current and past clinical practices for the management of NEC. Given the increase of mortality and morbidity per annum with increased risk among preterm infants, our emphasis is to review the teaching university

practice regarding the therapeutic effectiveness of care and clinical outcomes. The majority of cases in NICU require TPN because of either gastrointestinal (GI) malformations or necrotizing enterocolitis. TPN is the main source of nutrients during the transition period and should be started in the first 48 hours of life when possible.

Methodology

Study description and location: Study was done in University Hospital (HUSM), Kuban Kerian, Kelantan, Malaysia. A descriptive cross-sectional observational study was designed on cases of necrotizing enterocolitis. Study was conducted as five-year retrospective review from January 2003 till August 2007. Patient medical records were reviewed and data extracted by using a standardized data collection form. Study scope was based on the patients diagnosed with NEC between the duration of January 2003 to December 2007.

Sampling Technique: Universal sampling technique was employed as to include all the cases being identified in the five years of retrospective study frame. Vehicle of the study was records of medication profile of patients available in record office of the Hospital. The patient records were sorted out according to the inclusion and exclusion criteria employed in this study allowing us to include all the registered cases for NEC in the NICU (all term, preterm and post-term neonates) from January 2003 till December 2007.

Ethical approval: Study protocol was approved from the Ministry of Health Malaysia and also with the local Clinical Research Committee.

Data Analysis: Collected data were then analyzed by using statistics software name Statistical Package for Social Science, (SPSS®12.0). Descriptive statistic was used as appropriate against the prelimary identification of the problem. For categorical data, the correlation chi squire test was used to test levels of significance ($p < 0.05$). For the secondary evaluation of risk (likely to develop), relative risk interval (with 95% confidence interval (CI)) was calculated against risk ratio. Confidence interval 95 % was taken for level of significance with 5% margin of error.

Results & Discussions

Demographic Data

By the end of the study period, 46 patients were identified. Majority of the patients were Malays 44 (95.6%) patients. This is followed by Chinese 1 (2.2%) patient and 1 (2.2%) others. Gender distribution was equivalent with 22 (47.8%) females and 24 (52.8%) males. Birthweight is recognized as one of the high predictor for NEC among neonates (Siu et al., 1998, Sonntag 2000, Vohr et al., 2000, Rabinowitz et al., 1990, Brown & Sweet 1978, Rayyis et al., 1999). We found that the majority, 39 (84.8%) of neonates, were under the range of ≤ 2500 g. While the distribution pattern showed that among these 39 birthweight cases about 24 (61.5%) of them were in between 2000gms – 2500 g (Maalouf et al., 2000, Brown & Sweet 1978, Kamitsuka, Horton & Williams. 2000). By using modified Bell's (Bell & Acarregui 2001) classification of NEC, we found that 26 (56.5%) had stage I of suspected disease, 14 (30.4%) had on definitive stage II and 3 (13.1%) were on advanced stage III.

We compared the per annum incidence of necrotizing enterocolitis among NICU neonates. We reviewed the number of admissions on a yearly basis to the NICU and second set of information reflects the number of NEC cases among these NICU admission. We found that admission to the NICU does not predict the NEC susceptibility as 1.34% (Rayyis et al., 1999) incidence was found in 2005 among 1119 neonates, while only 0.42% (Siu et al., 1998) among 1187 in 2006. Similarly 1.16% (Maalouf et al., 2000) among 1031 were identified in year 2003.

We identified that NICU admission load is not matter of concern against the susceptibility of NEC among neonates (Table 2). Overall indicators of nutritional support and feeding practices such as: total parenteral volume, number of days to regain birth weight (Dimmitt et al., 2003, Caplan et al., 1997, Juul, Joyce, Zhao & Ledbetter 1999, Ledbetter & Juul 2000), days to reach full enteral feeds, duration of parenteral nutrition and days to reach 1800-2000g weight among others, serve to underscore the variation in clinical practices that may directly or indirectly affect NEC prevalence (Kliegman 1990).

Duration of TPN used among the gender distribution showed no significant difference between male and female neonates as majority of both (58.3% vs 72.7%) remained on TPN more than 9 days. But it was found that male neonates were more prone to develop renal and liver complications as compared to females. On other hand female neonates showed increased recovery with complications as with male neonates with low mortality ratio, Robert et al., (1997) found that the necrotizing enterocolitis infant mortality rate was higher for males than females. But birth weight showed no significant association with duration of TPN and outcomes but we observed a significant increase in complication (bacterial sepsis, thrombocytopenia and renal complications) among VLBW neonates (1000g to 2000g). Secondly we found an inverse relationship between gestational age and duration of TPN. For the clinical outcomes of NEC, we observed a high rate of recovery with complication in suspected disease, but high rate of deaths with definitive disease (Table 3).

A significant relationship was found between gestational age and duration of TPN with p-value <0.001, Birth weight and complication was significant with p-value = 0.041 and NEC cases and outcomes were significant with p-value = 0.005 (Table 3).

Our study identified that infants born at less than 32 weeks gestational age and who survived for at least five days have a higher incidence of NEC as compared to patients born at more than 32 weeks of gestation (Kovacs & Papageorgiou 2007). While doing the comparison between the birthweight and gestational age we found that a gestational age of more than 32 weeks were found in all domains of birthweights but with highest value in between 2000g – 2500g, followed by 1500 g-1999g (fig 01). Very low birth weight infants growing poorly tend to have higher prevalence of impaired immune system (Rayyis et al., 1999, Berseth, Bisquera & Paje 2003, Schanler et al., 1999, Lopez, Taeusch, Findlay & Walther 1995). We sought to identify potential medical complications found among neonates with NEC, and we used descriptive statistics and found abdominal distention 43 (93.5%), jaundice 36 (78.3%), gastric aspiration 34 (73.9%), failure to tolerate feeding 30 (65.2%), and dilated bowel 27 (58.7%). We also identified that pneumotosis intestinalis was present in all 46 NEC cases. Most premature infants that require nutritional support need TPN because of the immaturity of the gastrointestinal tract. Parenteral nutrition was however not free of complications;

infections, mucosal atrophy, hepatic damage and cholestasis. In addition osteopenia of prematurity have been associated with prolonged use of TPN (Arant, Friis-Hansen, Hay 1993).

Majority (58.7%) of the neonates received solution A, followed by 23.9% with AB1, then 13.1% with AB2 and 4.3% with Sol. C (Solution A: glucose + calcium, Solution B: amino acid + electrolytes, Solution C: lipid, AB1= 85% of A + 15% of B and AB2= 75% of A + 25% of B). Duration of therapy ranged from a minimum of 5 days to more than 14 days (Figure 2). Recommendations on nutrient intake from enteral and parenteral sources (Caplan, Hedlund, Adler & Hsueh 1994) in preterm infant are usually established based on needs for growth and optimal development (Walker 1997, Caplan, Hedlund, Adler & Hsueh 1994); in addition we should consider the need to prevent the health risks associated with nutritional deficiency or excess (Juul, Joyce, Zhao, Ledbetter 1994, Ledbetter & Juul 2000, Lawrence et al., 1997). The information base to scientifically support (Ledbetter & Juul 2000, Lucas, Bloom & Aynsley-Green 1986) the definition of nutritional needs of neonates, especially for extremely low birth weight (ELBW) (< 1000 gram) neonate is quite limited for most specific nutrients (Gross et al., 1993).

Reasons for discontinuation of TPN in our study were ability to tolerate oral feeding among 29 (63.04%) infants, disease recovery among 4 (8.7%) and others reasons for 13 (28.26%) including death, cyanosis, shock, liver and renal complications (Sonntag et al., 2000, Edelson et al., 1999, Heird 1999, Arant, Friis-Hansen & Hay 1993, Eyal, Sagi, Arad & Avital 1982). The clinical outcomes following the use of TPN were that 15 (32.6%) infants recovered without complications, 18 (39.1%) were recovery with complications and 13 (28.3%) died. The medical complications included bacterial sepsis 20 (60.6%), thrombocytopenia 10 (30.3%), liver complications 2 (6%) and renal complications 1 (3%).

Unfortunately, the achievement of appropriate therapeutic goal was not an easy task considering the special needs of the premature infants resulting from the immaturity of the gastrointestinal tract (Caplan et al., 1999), difficulties in metabolic adaptations and the concomitant neonatal medical disease conditions (Kliegman 1990, Walker 1997).

The rate of death was quite high (28.3%) in our study similar to finding identified by Wiswell et al in 1988. The death rate of 61.5% among male infants was significantly higher as compared to female infants (Brown & Sweet 1978, Heird 1999, Eyal, Sagi, Arad & Avital 1982). Majority of deaths (76.2%) were found with birth weight less than 2000g, among them 60.0% deaths were between the range of <1000g to 1499g and 40.0% in the range of 1500g to 1999g (Eyal, Sagi, Arad & Avital 1982, Kovacs & Papageorgiou 2007).

It was prevailed that 84.6% of infant deaths after 14 days of TPN use may be associated with the significant use of either solution A and AB1 alone or in combinations. Hence, all VLBW infants should be closely monitored for early signs of NEC independent of feeding strategy used (Sonntag et al., 2000, Edelson et al., 1999). As we managed to find out that birth weight had no influence on NEC class, but gestational age <30 weeks was associated with a higher number of deaths than > 30 weeks gestational age babies. Males with pre-term delivery were more prone to definitive class of disease, than females with more advanced status. Mode of delivery either simple vaginal labor or emergency lower segment caesarian section had no

clinical impact on the number of deaths/ NEC class. Major causes of deaths were septicaemia (38.5%), thromboembolic events (30.7%), cyanosis (15.4%), and others (15.4%) (40). All death cases showed no breast feeding or intolerance of enteral feeding similar with the findings of Pickard et al (2009).

Conclusion

We concluded that use of TPN for more than 14 days with low birth weight / gestational age less than 30 weeks highlighted a risk of developing clinical manifestation as well as death. Majority patient was treated with Sol.A and duration of TPN > 14 days. Providing TPN was wrought with unique potential risks and complications to these fragile infants and calls for a diligent interdisciplinary team approach. The implementation of standardized feeding protocols by birth weight categories (e.g., <750 g; 750-1000; 1000-1250; 1250-1500) decreases the variability in feeding practice and lowers the risk of NEC, limiting the use of riskier feeding methods.

Recommendation

Current knowledge on nutritional needs of premature infants underscores the importance of providing appropriate nutrients to premature infants for immediate survival, growth and neurodevelopment, and for long-term health. Gastrointestinal priming has emerged as a safe and effective practice with demonstrable beneficial effects for the VLBW by allowing earlier establishment of enteral nutrition, decreasing time of exclusive total parenteral nutrition and improving weight gain. Although TPN has not demonstrated to enhance the risk of NEC, we should be concerned with avoiding gut atrophy and thus should start early trophic feeds even in the smallest and sickest infants.

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Table 1: Demographic presentation

NO	Descriptive issues	Sub-title of the issues	Cases (%)
1	**Race**	Malay Chinese Indians Others	44 (96.7) 1 (2.2) 0 (0.0) 1 (2.1)
2	**Gender**	Male Female	24 (52.2) 22 (47.8)
3	**Birth weight**	<1000 grams 1000 – 1499 g 1500 – 1999 g 2000 – 2499 g 2500 – 2999 g >3000 g	8 (17.4) 7 (15.2) 12 (26.1) 12 (26.1) 4 (8.7) 3 (6.5)
4	**Gestation age**	<24 weeks 24 – 26 weeks 27-29 weeks 30-32 weeks >32 weeks	1 (2.2) 6 (13.0) 2 (4.3) 11 (23.9) 26 (56.6)
5	**Class of NEC**	Suspected disease - I Definitive - II Advanced - III	26 (56.6) 14 (30.4) 6 (13.0)

Table 2: Percentage increase in per annum continuum of NEC

Unit	*2003*	*2004*	*2005*	*2006*	*Aug 2007*	*Total*
NEC	12	8	15	5	6	46
NICU	1031	929	1119	1187	787	5053
NEC/NICU	1.16%	0.86%	1.34%	0.42%	0.76%	0.91%

Table 3: Association of dependant variable with clinical practice by using Chi-square

Variables	**Duration of TPN**		**Complications**		**Outcomes**	
Gender Male / Female	NS	0.692	NS	0.494	NS	0.639
Birth weight <1000g 1000-1499g 1500-1999g 2000-2499g 2500-2999g >3000g	NS	0.100	**S**	**0.041**	NS	0.273
Gestation age < 24 weeks 24-26 weeks 27-29 weeks 30-32 weeks >32 weeks	**S**	**<0.001**	NS	0.210	NS	0.616
NEC classes **Suspected** **Definitive** **Advanced**	NS	0.553	NS	0.132	**S**	**0.005**

Table 4: Clinical modalities associated with the Necrotizing enterocolitis

Clinical features associated with the study (N = 46)			
		Cases observed per 46 sample	
No.	**Clinical conditions**	**Number**	**Percentage**
1	Gastric aspirated	34	73.9%
2	Not tolerated feeding	30	65.2%
3	Dilated bowel	27	58.7%
4	Lethargy	11	23.9%
5	Hematochezia	6	13%
6	Brady cardia	10	21.7%
7	Apnea	12	26.1%
8	Pallor	9	19.6%
9	Jaundice	36	78.3%
10	Bleeding manifestation	10	21.7%
11	Shock	2	4.3%
12	Oedema	8	17.4%
13	Distention	43	93.5%
14	Tenderness rigidity	8	17.4%
15	Absent bowel sound	7	15.2%
16	Ascites	5	10.9%
17	Pneumotosis intestinalis	46	100%

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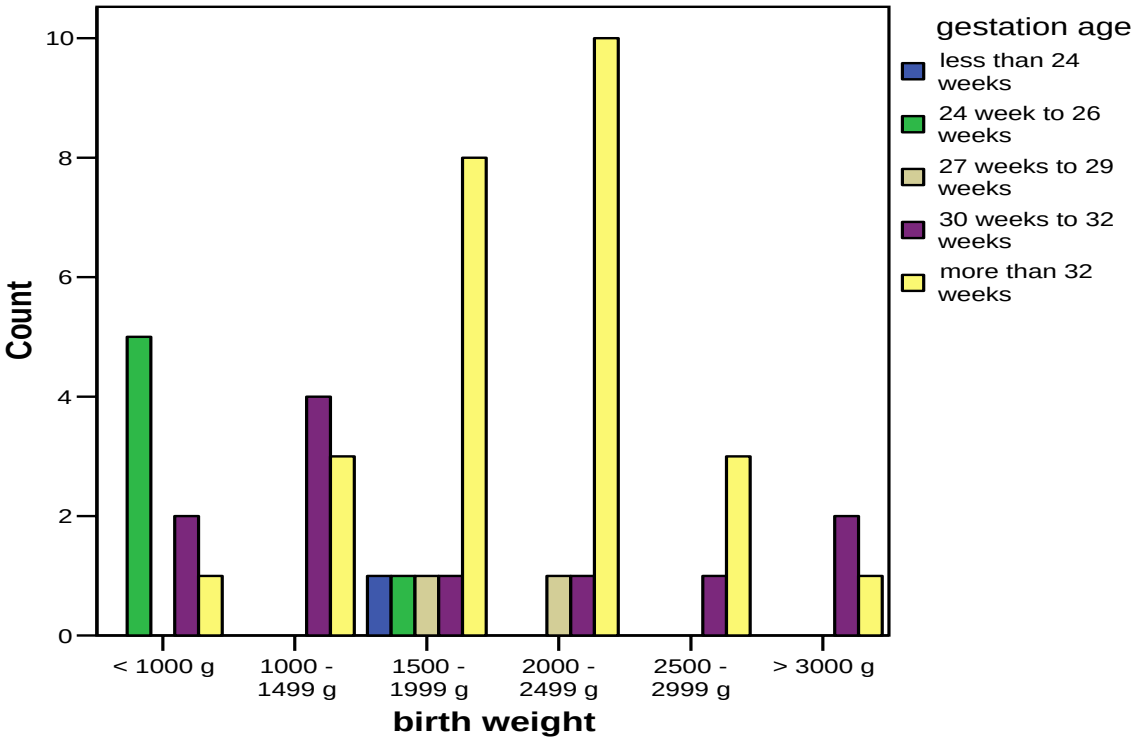

Figure 1: Association between Birth Weight and Gestation Age

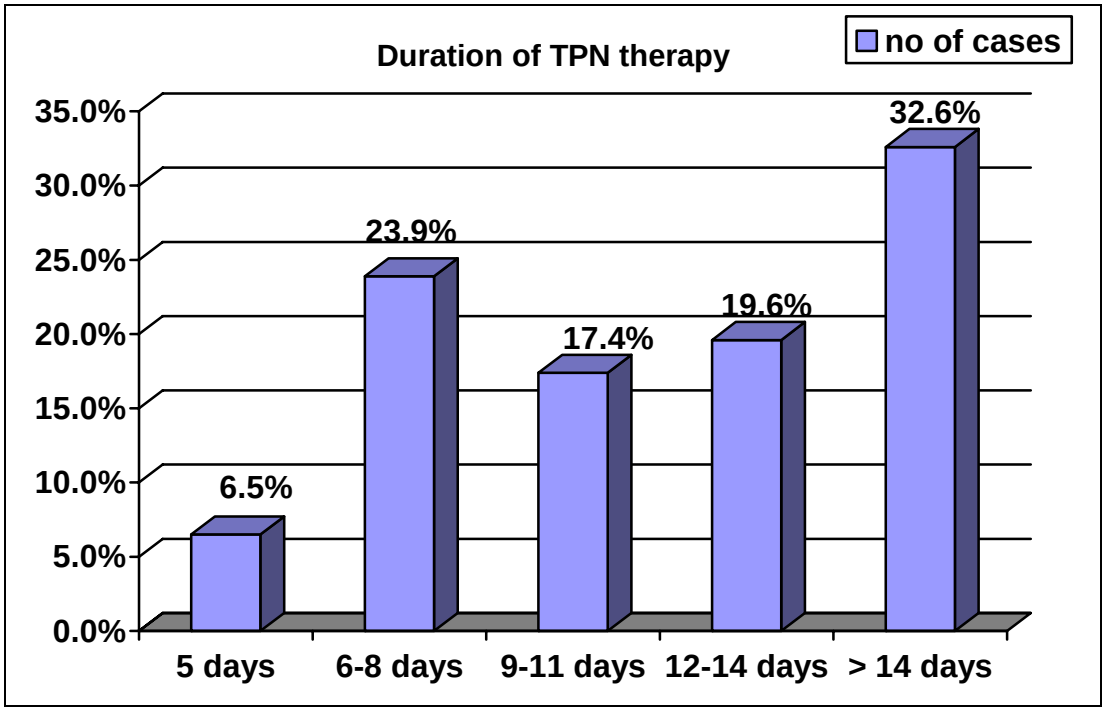

Figure 2: Duration Of total parenteral nutrition in NEC