Original Research Article

Unravelling the Possibilities Of Achieving Full Enteral Feeds During Therapeutic Hypothermia Without Adverse Effects-A Retrospective Observational Study In A Tertiary Neonatal Intensive Care.

ABSTRACT:

AIMS & OBJECTIVES

The aim of our study is to evaluate the effects of perinatal asphyxia and subsequent treatment with therapeutic hypothermia especially on gastrointestinal system in newborns diagnosed with moderate-to-severe HIE.

The primary objective was to determine the time for initiation of enteral feeds, enhancing the feeds and achieving full feeds in a group of newborns with HIE undergoing therapeutic hypothermia.

The secondary objective was to determine the risk of necrotising enterocolitis, late onset sepsis and duration of hospital stay.

DESIGN

Retrospective observational study

PARTICIPANTS &METHODS:

A retrospective study at NICU, Sarji hospital, a tertiary care centre in Shivamogga was conducted. An extensive search was done by going through medical records including feeding charts of the babies who underwent TH between December 2018 and October 2021. The study was approved by the Sarji Ethics Committee. 50 newborns either in-born at(n = 3) or out-born and referred(n = 47) to the NICU of Sarji hospital, Shivamogga were included.

RESULTS:

Descriptive statistical analysis of hemodynamicallyunstable babies (n=16). Out of 16 neonates, 15 were born at full term by normal vaginal delivery (FTND) and one through lower segment caesarean section (LSCS).Descriptive statistical analysis ofhemodynamically stable babies(n=34). Out of 34 babies, 27 were born at full term by normal vaginal delivery (FTND) and 07 were lower segment caesarean section (LSCS)

CONCLUSION:

It is high time to have large scale multi-centric studies in different ethnicities, income groups and to come up with a standardized guideline for enteral feeds in babies undergoing TH which can help in achieving full feeds at the earliest hence alienating the high risk of infection, delayed initiation of feeding, over staying in the NICU and possible emotional stress, economic burden to the parents.

KEYWORDS:

Therapeutic Hypothermia,

Hypoxic Ischemic Encephalopathy (HIE),

Necrotising enterocolitis,

Lateonset sepsis

INTRODUCTION

Incidence of Hypoxic Ischemic Encephalopathy (HIE) in developing countries is estimated to be 2.3-26.5 per 1000 live birthsand in developed countries it is 1.5 per 1000 live birth[1].The hypoxaemia which can be intrapartum, peripartum and postpartum is an important etiology of neonatal mortality as well as long term morbidities like neurodevelopmental disability, cognitive impairments, neurosensory deficits in infants[2,3].Therapeutic hypothermia (TH) at present, is the only proven intervention to treat neonates with mild to moderate HIE and even may be beneficial in severe HIE[4]. It minimises the brain damage by decreasing the energy requirements & cerebral edema[5]. It attenuates the oxidative damage to DNA bases which is the most important mechanism underlying neuro-protective effect [6,7]. It is a known fact that after effects of hypoxic ischemic insult can extend beyond the brain and neurodevelopment. Perinatal asphyxia may be followed by decreased perfusion of the gastro-intestinal tract [8] and decreased motility leading to feeding intolerance [9]. It is plausible to believe that TH could have similar preventative effects on the ischemic damage to the gastrointestinal system since TH acts to prevent secondary damage to the brain from ischemia and reperfusion injury.There are studies indicating adverse effects of TH on varioussystems like hepatic and haematological systems [10,11]. Even though the therapeutic hypothermia guidelines are well defined based on high-quality randomised controlled trials, only fewstudieshave been conducted to assess the feasibility ofprovisionof enteral nutrition to infants with HIE during cooling and rewarming [12, 13].

NEED OF THE STUDY

A literature review regarding therapeutic hypothermia for HIE and enteral feeding was performed. In many trials, either enteral feeds were withheld during TH or not mentioned about. We lack a clear cut guideline for initiation of enteral feeds in babies receiving TH.

Part of Material and methods

MATERIALS & METHODS

STUDY POPULATION:

A retrospective study at NICU, Sarji hospital, a tertiary care centre in Shivamogga was conducted. An extensive search was done by going through medical records including feeding charts of the babies who underwent TH between December 2018 and October 2021. Thestudy

was approved by the Sarji Ethics Committee. 50 newborns either in-born at(n = 3) or out-born and referred(n = 47) to the NICU of Sarji hospital, Shivamogga were included.

STUDY DESIGN:

A retrospective observational study was done to answer the research question 'what is the optimum nutrition strategy for newborns during and aftertherapeutic hypothermia?' In addition we aimed to compare the outcomesbetween subgroups of hemodynamically stable and unstable neonates. Standard definitions for Sepsis, DIC, and Hypotension were considered. An informed consent in vernacular language about therapeutic hypothermia and feeding practises are routinely taken as a part of our NICU Standard operating procedure. Data collected included the following parameters, the initiation of feeds, and achievement of full feeds and duration of hospital stay. By definition,enteralfed is receiving milk feedsof following types (expressed maternal breast milk,expressed donor breast milk and artificial formula). This can be administered either by nasogastrictube or pallada. In all the babies feeds were initiated at 10-15ml/kg/day. Feeds were escalated at 20-30ml/kg/day and target full feeds were between 60-100ml/kg/day between days of life (DOL) 3-5 days respectively. In the index study, full feeds were achieved with median 5 days.

STATISTICAL METHODS

The data was entered in Microsoft excel and analysed using SPSS software (version 21). The Data is expressed as mean ± standard deviation (SD) for continuous outcome variables and percentage for categorical outcome variables. New-bornsthat did not reach full oral feeds due to death or discharged on gavage feeds were also treated as censored data.

RESULTS

Descriptive statistical analysis of hemodynamicallyunstable babies (n=16). Out of 16 neonates, 15 were born at full term by normal vaginal delivery (FTND) and one through lower segment caesarean section (LSCS) as shown in table 1.Descriptive statistical analysis ofhemodynamically stable babies(n=34). Out of 34 babies, 27 were born at full term by normal vaginal delivery (FTND) and 07 were lower segment caesarean section (LSCS) as shown in table 2.

DISCUSSION

As per standard textbooks/guidelines [3,5] during TH, enteral feed is withheld until baby is rewarmed (at about 84 hours of life). However, few tertiary care centres are providing low volume "trophic" or "gut priming" feeds (10mL/Kg/Day) if there are no direct contraindication such as hypotension. In the index trials [14-17] of therapeutic hypothermia (Cool cap trial,NICHD Trial,Eicher, TOBY) the issues related to enteral feeding is not described. Nutrition plays an important role during TH, as there is a hypo-metabolic state during TH. Hence most of the centres do provide parenteral nutrition to these babies, which may put babies at high risk of infection, delayed initiation of enteral feeds and a possible longerNICU stay. Therefore, it is noteworthy that there are no clear guidelines regarding enteral nutritional practises in cooled asphyxiated newborns. In a small retrospective case control study of 34 neonates in the United Kingdom, minimal enteral feeds were given without any adverse events[18]. A large multi- centric retrospective UK population based cohort study[18] involving 6030 babies who underwent TH, concluded that enteral feeding is safe and even associated with benefits to baby as well as parents. In another study by Hazeldine B et al,[19] similar outcomes were seen, but was found to have lot of heterogeneity in nutritional practices and hence advocated for further studies. Similar

observations were made by Mona Markus et al[20] in a multi centric study involving four NICUs in Germany.Most of these studies have been done recently, but there are no studies from the Indian subcontinent.

In our study, we initiated the enteral feeding on second day of life and increased as per tolerance to full feeds without the anticipated risk of adverse events including late onset sepsis/NEC. Among the neonates who were hemodynamically stable, the feeds were initiated at a median of DOL (Day of life) 2 and achieved full feeds by DOL 4. None of the babies developed feed intolerance/ NEC in this cohort. The neonates with complications like shock, sepsis, DIC etc were started on minimal enteral feeds at a median of DOL 2 and we could reach full volume feeds by DOL 5.5 days.Among the 5 babies who were hypotensiveand on inotropes, feeds were initiated very cautiously on the 2nd day for 4 babies and 3rd day for 1 baby. The feeds were predominantly minimal enteral feeds at 10-15 ml/kg/day. In these babies feeds were enhanced as per tolerance and all of them achieved full feeds between 2-8 DOL. For babies with thrombocytopenia, feeds were started on DOL 2 except one for whom feeds started on DOL 3. The 2 babies with thrombocytopenia relatively took more time for achieving full feeds that is between 8-11 days. Among those two babies one baby had feed intolerance and achieved full feeds by DOL 9 and none had NEC. For all babies with DIC with or without sepsis, feeds were started on 2nd DOL and achieved full feeds between 2-8 days.

Therefore, our study not only supports recent studies, but also highlights the safety of achieving complete enteral nutrition without the risk of late-onset sepsis or NEC.

CONCLUSIONS

The after effects of perinatal asphyxia on various systems are many and well documented. Contrary to the popular belief we observed in our study that feeds can be initiated and enhanced tofull feeds without increased risk of NEC/ Feed intolerance during TH treatment. It is high time to have large scale multi-centric studiesin different ethnicities, income groupsand to come up with a standardized guideline for enteral feeds in babiesundergoing TH which canhelp in achieving full feeds at the earliest hence alienating the high risk of infection, delayed initiation of feeding, over staying in the NICU and possible emotional stress, economic burden to the parents.

REFERENCES

1. Cameron WT, Stephanie LM. Hypoxic Ischemic Encephalopathy. In: Kliegman RM, Blum NJ, Shah SH, St Geme JW, Tasker RC, Wilson KM, editors. *Nelson's Text Book of Pediatrics*. 21st ed. Philadelphia: Elsevier; 2020. p. 918-22.

2. Horn AR, Swingler GH, Myer L, Linley LL, Raban MS, Joolay Y, et al. Early clinical signs in neonates with hypoxic ischaemic encephalopathy predict an abnormal amplitude-integrated electroencephalogram at age 6 hours.*BMC paediatrics*. 2013;13:52.

3. Hansen AR, Soul JS. Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy. In: Eichenwald EC, Hansen AR, Martin CR, Stark AR, editors. *Cloherty and Stark's Manual of Neonatal Care*. 9th ed. Philadelphia: Wolters Kluwer; 2017. p. 790-811.

4. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study. Whole Body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy: A Randomised Controlled Trial.*BMC Pediatrics*. 2008;8:17.

5. Agarwal R, Deorari A, Paul V, Sankar MJ, Sachdeva A. *AIIMS Protocols in Neonatology*. 2nd ed. Delhi: Noble; 2019, p. 55-72.

6. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of Therapeutic Hypothermia on Oxidative Stress and Outcome in Term Neonates with Perinatal Asphyxia: A Randomized Controlled Trial.*Journal of Tropical Pediatrics*. 2013;59:17-22.

7. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar KT, Adhisivam B. Effect of Therapeutic Hypothermia on DNA Damage and Neurodevelopmental Outcome among Term Neonates with PerinatalAsphyxia: A Randomized Controlled Trial.*Journal of Tropical Pediatrics*. 2014;60:134-40.

8. Akinbi H, Abbasi S, Hilpert PL, Bhutani VK. Gastrointestinal and renal blood flow velocity profile in neonates with birth asphyxia. *J Pediatr*. 1994;125:625-7.

9. Berseth CL, McCoy HH. Birth asphyxia alters neonatal intestinal motility in term neonates.*Pediatrics*, 1992;90:669–73.

10. Kimberly M. Thornton, Hongying Dai, Seth Septer, Joshua E. Petrikin. Effects of Whole Body Therapeutic Hypothermia on Gastrointestinal Morbidity and Feeding Tolerance in Infants with Hypoxic Ischemic Encephalopathy.*International Journal of Pediatrics*,Volume 2014, Article ID 643689, 7 pages http://dx.doi.org/10.1155/2014/643689

11. Pierro A, Eaton S, Intestinal ischemia reperfusion injury and multisystem organ failure. *Seminars in Pediatric Surgery*. 2004;13:11–7.

12. NICE guidelines. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury [IPG347. Manchester:National Institute for Health and Clinical Excellence, 2010.

13. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy.*N Engl J Med*.2009;361:1349–58.

14. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar KT, Adhisivam B. Effect of Therapeutic Hypothermia on DNA Damage and Neurodevelopmental Outcome among Term Neonates with Perinatal Asphyxia: A Randomized Controlled Trial. *Journal of Tropical Pediatrics*. 2014;60:134-40.

15. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective Head Cooling with Mild Systemic Hypothermia after Neonatal Encephalopathy: Multicentre Randomised Trial. *Lancet*. 2005;365:663-70.

16. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole Body Hypothermia for Neonates with Hypoxic Ischemic Encephalopathy. *N Engl J Med*. 2005;353:1574–584.

17. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole Body Hypothermia for Term and Near Term New-borns with Hypoxic Ischaemic Encephalopathy. *Arch PediatrAdolesc Med*. 2011;165:692-700

18. Gale C, Longford NT, Jeyakumaran D, Ougham K, Battersby C, Ojha S, Dorling J. Feeding during neonatal therapeutic hypothermia, assessed using routinely collected National Neonatal Research Database data: a retrospective, UK population-based cohort study. *Lancet Child Adolesc Health*. 2021;5:408-16

19. HazeldineB,Thyagarajan B, Grant M,etal.Survey of nutritional practices during therapeutichypothermia for hypoxic-ischaemic encephalopathy.*BMJ Paediatrics Open*. 2017.

20. Markus M, Giannakis S, Ruhfus M, et al. Fluid Supply and Feeding Practices in Cooled Asphyxiated Newborns. *Children (Basel).* 2021;8(10):899. Published 2021 Oct 9. doi:10.3390/children8100899

Table 1: Descriptive Statistical Analysis of Hemodynamically Unstable Babies (n=16)

Variables	**Groups**	**Total**	**Hypotension**	**Thrombo-cytopenia**	**Disseminated intravascular coagulation (DIC)**	**Sepsis +DIC**
Gender	Male	13	4	5	3	1
	Female	3	1	1	1	0
Mode of delivery	FTND	15	4	6	4	1
	LSCS	1	1	0	0	0
Birth weight (kg)	2 – 2.5	3	0	2	1	0
	2.5 – 3	5	2	1	2	0
	3 – 3.5	6	2	2	1	1
	>3.5	2	1	1	0	0
Feeds initiated at day of life (DOL)	2nd day	14	4	5	4	1
	3rd day	2	1	1	0	0
Full feed achieved at (day of life)	2–5	8	2	2	3	1
	5-8 days	6	3	2	1	0
	8-11	2	0	2	0	0
Feed intolerance/ necrotising enterocolitis (NEC)	Male	0	1	0	0	0
	Female	0	0	0	0	0
Duration of stay	5-10	13	3	5	4	1
	>10	3	2	1	0	0

Table 2: Descriptive Statistical Analysis of hemodynamically Stable Babies (N=34)

Variables	**Groups**	**Frequencies (%)**
Gender	Male	28 (82.4)
	Female	6 (17.6)
Mode of delivery	FTND	27 (79.4)
	LSCS	7 (20.6)
Feeds initiated at (day of life)	2^{nd} day	30 (88.2)
	3^{rd} day	4 (11.8)
Full feed achieved at (day of life)	2 –5 days	30
	5- 8 days	4
	8-11 days	0
Feed intolerance/NEC	Male	0
	Female	0
Duration of stay	5- 10 days	100
	>10 days	0