

# Can Full Enteral Feeds during Therapeutic Hypothermia be Achieved without Adverse Effects? An Observational Study

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## Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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## ABSTRACT

**Objectives:** The aim of our study is to evaluate the effects of perinatal asphyxia and subsequent treatment with therapeutic hypothermia (TH) especially on gastrointestinal system in newborns diagnosed with moderate-to-severe Hypoxic-Ischemic Encephalopathy (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 TH with secondary objectives to determine the risk of necrotising enterocolitis (NEC), late onset sepsis and duration of hospital stay.

**Methods:** This is a retrospective study done at Neonatal Intensive Care Unit (NICU), Sarji hospital, a tertiary care centre in Shivamogga, India. A review of the medical records for feeding charts of the babies who underwent TH between December 2018 and October 2021 was carried out. A total of 50 newborns either in-born (n = 3) or out-born and referred (n = 47) to our NICU were included.

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**Results:** Among the 50 babies (both hemodynamically stable and unstable) undergoing TH, feeds were initiated at Day 2 of life. All hemodynamically stable babies were on full feeds by 5<sup>th</sup> day of life, while 14 out of 16 unstable babies were on full feeds by 8<sup>th</sup> day of life. For the remaining 2 babies, we could achieve full feeds by 11<sup>th</sup> day of life.

**Conclusion:** This study not only supports the recent studies, but also highlights the safety of achieving complete enteral nutrition in neonates (both hemodynamically stable and unstable) undergoing TH without the risk of late-onset sepsis or NEC.

*Keywords: Therapeutic Hypothermia (TH); Hypoxic Ischemic Encephalopathy (HIE); Necrotising Enterocolitis (NEC); late onset sepsis.*

## 1. INTRODUCTION

Incidence of Hypoxic Ischemic Encephalopathy (HIE) in developing countries is estimated to be 2.3-26.5 per 1000 live births and 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 gastrointestinal 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 various systems like hepatic and haematological systems [10,11]. Even though the therapeutic hypothermia guidelines are well defined based on high-quality randomised controlled trials, only few studies have been conducted to assess the feasibility of provision of enteral nutrition to infants with HIE during cooling and rewarming [12,13].

### 1.1 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.

## 2. MATERIALS AND METHODS

### 2.1 Study Population

A retrospective study at NICU, Sarji hospital, a tertiary care centre in Shivamogga, India 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, India were included.

### 2.2 Study Design

A retrospective observational study was done to answer the research question 'what is the optimum nutrition strategy for newborns during and after therapeutic hypothermia?'. In addition we aimed to compare the outcomes between subgroups of hemodynamically stable and unstable neonates. Standard definitions for Sepsis, Disseminated Intravascular Coagulation (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, enteral fed is receiving milk feeds of following types (expressed maternal breast milk, expressed donor breast milk and artificial formula). This can be administered either by nasogastric tube or pallada. In all the babies feeds were initiated at 10-15 ml/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.

**2.3 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-borns that did not reach full oral feeds due to death or discharged on gavage feeds were also treated as censored data.

**3. RESULTS**

In our cohort a total of 50 babies receiving TH were included. Among them 16 neonates were hemodynamically unstable. 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. The remaining 34 babies were hemodynamically stable. 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.

In our study as shown in Tables 1 and 2, 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 days of life (DOL) 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, Disseminated Intravascular Coagulation (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.

**Table 1. Descriptive statistical analysis of hemodynamically unstable babies (n=16)**

| Variables   | Groups              | Total | Hypotension | Thrombocytopenia | 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                    | 2 <sup>nd</sup> day | 14    | 4           | 5                | 4  | 1            |
|   | 3 <sup>rd</sup> day | 2     | 1           | 1                | 0  | 0            |
| Full feed achieved at day of life                 | 2–5 days            | 8     | 2           | 2                | 3  | 1            |
|   | 5-8 days            | 6     | 3           | 2                | 1  | 0            |
|   | 8-11 days           | 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 days           | 13    | 3           | 5                | 4  | 1            |
|   | >10 days            | 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 <sup>nd</sup> day  | 30 (88.2)       |
|                                   | 3 <sup>rd</sup> 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 | 0               |
| Duration of stay                  | 5- 10 days           | 100             |
|                                   | >10 days             | 0               |

\*Full term normal delivery

#Lower segment caesarean section

Among the 5 babies who were hypotensive and 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.

#### 4. 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, 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 longer NICU 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.

#### 5. 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 to full feeds without increased risk of NEC/ Feed intolerance during TH treatment. 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 and economic burden to the parents.

## CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

The study was approved by the Sarji Ethics Committee, Sarji Hospital, Shivamogga, India.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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