

## Therapeutic Hypothermia in Asphyxiated Newborn: Its Applicability, Feasibility and Accessibility in Developing Country India: A Long Way to Go

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### Introduction

About four million newborn children die annually. Almost one quarter (23%) of these deaths are caused by perinatal asphyxia, most of them in developing countries [1-3]. The clinical signs following perinatal asphyxia have been called hypoxic ischemic encephalopathy (HIE). HIE occurs in 1 to 3 per 1,000 live births in high income countries, and up to 20 per 1,000 live births in low and middle-income countries [4]. In addition, perinatal asphyxia causes an even greater number of children to develop neurological sequelae. The clinical signs following perinatal asphyxia have been called hypoxic ischemic encephalopathy (HIE) [5,6]. The onset of the asphyxial event leading to HIE could start antenatally or close to/during birth and the reported incidence of asphyxia with antenatal vs. perinatal onset differs substantially between studies [7,8].

Therapeutic hypothermia has become the standard of care for asphyxiated term and near term newborn infants. American Academy of Pediatrics (AAP) committee on fetus and newborn recommends therapeutic hypothermia to be started within 6 hours of birth and continued for 72 hours followed by gradual rewarming [9]. In the developed countries therapeutic hypothermia has become standard of care and easily assessable to asphyxiated newborns but low and middle income developing countries like ours is still in primary phase with only few institute and tertiary care hospital providing therapeutic hypothermia. The cooling devices can be high tech like blanketrol, tecotherm (Figures 1 and 2), MTRE criticoool, Cool cap or low tech like natural cooling, water bottles, fans, gels packs and phase changing mattresses [10]. Hypothermia acts through multiple mechanism to decrease the brain injury and effects primary phase, latent phase and secondary phase of brain injury and reduce penumbral brain injury taking place due to free radical generation [11,12].



Figure 1: High tech cooling devices



Figure 2: High tech cooling device

There are few studies conducted in India on therapeutic hypothermia in which the researchers have used different methods for cooling like gel packs. The limitations of these studies includes very small number of neonates in all the groups and the majority of the trials lacked long term follow-up of neurodevelopmental outcome (Table 1).

The problems of effective implementation of therapeutic hypothermia in India and other low-middle income groups are many which include:

- The financial aspect is very important as the high technology machines comes in millions of Indian rupees which every hospital can't afford which leads to avoidance of buying these machines for providing therapeutic hypothermia to asphyxiated neonates
- In the developing countries like ours there are very few well established level three care NICU which can provide hypothermia as providing hypothermia requires multiple other things like multi-parametric monitors, blood gas analysis machine, ventilators, EEG machine which puts great economic burden to the health care facilities.
- There is lack/shortage of well-trained pediatricians and nursing staff for hypothermia applications and its associated complication management.
- Failure to get the relevant history of perinatal asphyxia in the newborns and the treating pediatricians may not be able to identify the hypoxic encephalopathy.
- In resource restricted countries like ours, neurological damage due to perinatal asphyxia may be an add on because of associated maternal malnutrition, intra-uterine growth restriction of fetus,

obstructed labor and poor or suboptimal obstetric / neonatal care at the time of delivery.

- As the incidence of intrauterine growth retarded newborns (IUGR) is very high in low-middle income countries and the response of these IUGR newborns or small for gestational age may be different from there counterpart appropriate for gestational age newborns.

- As in the low middle income group countries majority of the deliveries happen outside the hospital either at home or primary health care which don't have adequate resuscitation and referral facilities hence late referral of these asphyxiated newborns may reduce the usefulness of cooling once the therapeutic window has elapsed.

Sl. no	Investigations	Type of hypothermia	Device used for hypothermia	No. of newborns	Results
1	Bharadwaj et al. (13)	Whole body cooling	Frozen gel packs	62	TH group showed significant reduction in the combined rate of death or developmental delay at 6 months of age by 21% (8.1% in the TH group vs. 29% in the control, RR 0.28, 95% CI: 0.11-0.70; p = 0.003).
2	Joy et al. (14)	Whole body cooling	Frozen gel packs	58	After 72 h of TH, TAS (total antioxidant status) was significantly higher (p = <0.001) (761.69 ± 114.01 vs. 684.16 ± 88.86) and malondialdehyde (MDA) was significantly lower (p = <0.001) in TH group (1.73 ± 0.66 vs. 5.2 ± 1.06). Risk of developing deficit was lower (p < 0.001) in TH group with relative risk of 0.49 and 95 % confidence interval: 0.29-0.68.
3	Gane et al. (15)	Whole body cooling	Frozen gel packs	60	After 72 h, the hypothermia group showed lower olive tail moment (12.88 ± 2.14) than the control group (22.16 ± 5.26) (p < 0.001). 8-HDG (8 hydroxy 2-deoxyguanosine) levels were significantly increased in the control group (1252.87 ± 357.07) as compared to the hypothermia group (757.03 ± 198.49) (p < 0.001). Neurodevelopmental assessment at 12 months showed significantly higher motor and mental developmental quotient in the hypothermia group than control.
4	Thomas et al. (16)	Whole body cooling	Frozen gel packs	20	The mean rectal temperature during cooling was 32.9 ± 0.11°C. The target temperature could be maintained for 72 hours without difficulty in all babies.
5	Thomas et al. (17)	Whole body cooling	Frozen gel packs	40	Skin temperature cannot be used instead of rectal temperature when practicing TH for HIE
6	Thayyail et al. (18)	Whole body cooling	Not specified	17	TH did not reduce the brain injury apparent on MRI imaging
7	Bhat et al. (19)	Whole body cooling	Not specified	20	Neonates treated by TH less likely to have abnormal neurological examination at discharge (p<0.001).

**Table 1:** Table showing various therapeutic hypothermia studies conducted in India

- In developing countries perinatal asphyxia and neonatal sepsis may be co-existent and it may be sometimes impossible to differentiate them, and as therapeutic hypothermia decrease the resistance power and neutrophil function which may paradoxically increase the neonatal mortality [1].
- Un-controlled and accidental hypothermia is observed in many asphyxiated newborns in developing countries due to a number of factors including lack of proper transport facility, home birth, lack of basic neonatal care and overhead radiant warmers
- Therapeutic hypothermia window is very short (less than 6 hours), hence timely referral becomes difficult as there is lack of transport or adequate referral facilities in the low middle income group countries.

Therapeutic hypothermia is the call of hour as this has proved that therapeutic hypothermia results in a statistically significant and clinically important reduction in the combined outcome of mortality or major neuro developmental disability to 18 months of age. The

Cochrane database recommends institution of therapeutic hypothermia in term and late preterm infants with moderate-to-severe hypoxic ischaemic encephalopathy within six hours of age [20]. The developing countries have to go long way for the implementation of hypothermia so that every asphyxiated newborn gets therapeutic hypothermia in these low-middle income groups of countries [21]. There is also need to get cheap hypothermia devices which can be safe, affordable, maintains constant rectal temperature, less adverse effects, have adequate safety mechanism [22,23].

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