IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access

Original Article

Therapeutic Hypothermia by Cold Intravenous Fluid and Short Outcome in Asphyxiated Newborn

Ashraf Mohamadzadeh[1*], Ahmadshah Farhat[1], Ezzat khodashenas[1], Mojtaba Adineh[2], Aradokht Vaezi[2], Pouya Taji[2], Mahdi Salimifar[2]

1. Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Background: Therapeutic hypothermia has reduced mortality and morbidity in asphyxiated newborns. The study aims to induce hypothermia by cold intravenous 10% dextrose and its effect on hospital stay and mortality in asphyxiated newborns..
Methods: Filthy one neonate with asphyxia was randomly assigned to either cold intravenous dextrose 10% for 72 hours started within 6 hours of birth with rectal temperature maintained33-34℃ (no 25 cases) or conventional care (no 26 controls). The primary outcome was hospital stay and death. The optimal rate of rewarming did not exceed the rate of 0.5°C/h. All of them had birth weight ≥ 2500 grams and gestational age ≥ 36 weeks. Those with congenital anomalies, sepsis, DIC, and shock were excluded.
Results: The two groups were the same regarding demographic and obstetric complications. Hospital stays and mortality rates were significantly lower in the case group p-values 0.05 and 0.01, respectively.
Conclusion: Therapeutic hypothermia by cold intravenous dextrose is possible and can reduce hospital stays and mortality with low incomes for asphyxiated newborns.

Keywords: Neonatal asphyxia, Mortality, Therapeutic hypothermia

Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is associated with high neonatal mortality and a high risk of lifelong disability. It occurs in 2/1000 live births. Therapeutic hypothermia (TH) is now well-established as a standard treatment for newborns with moderate to severe hypoxic-ischemic encephalopathy (1). Recently, it was approved that 72 hours of hypothermia started in the first 6 hours of age reduces mortality and morbidity in asphyxiated newborns.

Moderate cerebral hypothermia initiated in the latent phase, between 1 and as late as 6 hours after reperfusion, and continued for sufficient duration in relationship to the severity of the cerebral injury has been associated with potent, long-lasting neuroprotection in both adult and prenatal species. A review of animal studies revealed that brain cooling to approximately 32-34 C within 5.5 hours after hypoxic-ischemic injury and continuing for 12-72 hours reduce secondary energy failure and cell death and was associated with neuropathological and functional improvement (2). Laptook et al. showed HIE infants with hypothermia started at 6-24 hours after birth resulted in a 76% probability of any reduction in death or disability and a 64% probability of at least 2% less death or disability at 18-22 months targeted esophageal temperature at in33.5 c for 96 hours(3). Shankaran et al., by induction whole-body cooling in neonatal hypoxic-ischemic encephalopathy, found a lower death rate and decreased severe disability among survivors (4). Utilization of cooling devices for the whole body and selective head cooling needs

* *Corresponding author*: Ashraf Mohammadzadeh, Neonatal Research Center, Mashhad University of Medical Sciences. Mashad, Iran. Email: mohamadzadeha@mums.ac.ir

Please cite this paper as:
Mohamadzadeh A, Farhat A, Khodashenas E, Adineh M, Vaezi A, Taji P, Salimifar M. Therapeutic Hypothermia by Cold Intravenous Fluid and Short Outcome in Asphyxiated Newborn. Iranian Journal of Neonatology. 2025 Apr: 16(2). DOI: -10.22038/ijn.2025.85185.2634

excess cost and, therefore, may be unavailable in low-income regions, but using cold intravenous fluid is simple, low-income, and available everywhere. We hypothesized that intravenous cold fluid would be relatively safe and effective to induce hypothermia in this newborn. We used intravenous cold 10%dextrose to induce hypothermia in asphyxiated newborns.

Methods

This study was conducted for one year in the NICU of Emam Reza Hospital of Mashhad University of Medical Science in 2017.

In a clinical trial, 51 asphyxiated newborns with birth weight ≥ 2500 grams and gestational age ≥ 36 weeks were included. Babies with congenital abnormalities ،congenital heart disease, shock, sepsis, and core temperatures more than 37℃ during the study were excluded. After the parent's permission, they were randomized by purposive sampling and consecutively to either cold intravenous dextrose 10% for 72 hours started within 6 hours of birth with rectal temperature maintained at 33-34℃ (no 25 cases) or conventional care (no 26 controls). The primary outcome was death and hospital stay. Gradually rewarming was not exceeding the rate of 0.5℃ /h.

Cold 10 %dextrose water was put in the 8℃refrigerator before use. Core temperature was checked every 2 hours to catch up 33-34℃ by rectal prob YSI 700 compatible rectal temperature sensors, cable length 3 cm, and monitored continuously. Intravenous infusion was done using an umbilical venous catheter. Case groups were treated at ambient environmental temperature by turning off the radiant warmer and then applying refrigerated 10 % dextrose to maintain rectal temperature at 33-34℃. Intravenous fluid started 60 ml per kilogram daily, adding 10 ml per kilogram daily till 80 in day 3. Vital signs, including blood pressure, heart rate, respiratory rate, and O2 saturation, were monitored continuously. Demographic criteria, metabolic outcomes, hospital stay, obstetric complications, and mortality rate were recorded. Asphyxia was diagnosed by one of these items: Ten mins Apgar score ≤ 5; need for ventilator support after resuscitation; cord PH <7.20; base deficits ≥16 mmol/L .

Statistical Analysis

Continuous variables were expressed as mean ± SD and categorical variables were reported as percentages. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. The independent sample t-test and Mann—Whitney U test were used to compare two groups in normal and non-normal continuous variables, respectively. The chi-square or Fisher's Exact test was used to compare categorical variables between groups. A p-value less than 0.05 was considered to be statistically significant.

Ethical Approval

The study was approved by the ethical committee of Mashhad University of Medical Sciences, with reference number IR.MUMS. MEDICAL.REC.1397.537. Signed informed parental consent was obtained. This study was a registered clinical trial gov (NO: IRCT20190204042609N1).

Results

Fifty-one newborns were included. The two groups were the same in birth weight, gestational age, sex, delivery mode, and obstetric complications (Table 1). Also, there were no significant differences between the two groups in hypoglycemia, hypoglycemia, and Thrombo-cytopenia. We found no mortality in case groups but 3.8% in the control group. There were significant differences between the two groups in hospital stay and mortality rates, P <0.05 and P< 0.01, respectively (Table 2).

Table 1. Demographic characteristic of two groups

	Case=25 n	Control=26 n	p-value
Birth weight (gram) Mean ± SD	3352±825	3462±433	.54
Gestational age (week) Mean ± SD	39.12±1.35	38.65±1.09	.18
Gender % Male/ female	13/12	15/11	.68
Delivery mode CS (NO)%	15 (60%)	16 (60%)	.56

Table 2. Perinatal complications

Group	Case=25 n	Control=26 n	p-value
Umbilical cord PH Mean ± SD	6.9±0.12	6.9±0.08	0.99
Umbilical Cord Base deficit Mean ± SD	-16.84±1.76	-16.62±1.92	0.66
obstetric complication Yes (n)	9	16	.12
Mechonial Amniotic Fluid Yes (n)	16	11	1

Table 3. Primary outcomes:

	Case	Control	P-Value
Intubation Period Hour Mean ± SD	24±11	43±28	0.003
Time of first feeding toleration (Day) Mean ± SD	2.5±0.5	3.1±0.8	0.005
Time of full breastfeeding by mother (Day) Mean ± SD	5±1	6±2	0.016
Hospital Stay (Day) Mean ± SD	8.±1	13±11	0.05
Mortality Rate	0	1(3.8%)	.01

Discussion

Recently, large clinical trials demonstrated the benefits of therapeutic hypothermia in intrapartum asphyxia. The National Institute of Child Health and Human Development (NICHD) held a workshop on hypothermia as a potential treatment modality for perinatal HIE in May 2005. There is only a supportive measure to treat perinatal HIE, a condition with high mortality and morbidity (5). Although hypothermia was used for asphyxia neonatorum in in 1995, many studies were carried out on the safety and efficacy of hypothermia in HIE.

We found that cold intravenous fluid represents a tool to promptly induce hypothermia in neonates in a way that is simple,low-income, available, and safe, on the other hand. In our study, the mortality and hospital stays were reduced. Bonifacio et al. found that hypothermia may reduce brain metabolism and preserve its microstructure by minimizing cytotoxic edema and cell death (6). A Meta-analysis and systematic studies showed that low-technology therapeutic hypothermia, the same as our finding, reduces mortality and neurological morbidity in survivors at discharge (7).

The initial insult in HIE produces immediate cell loss of varying degrees and, more significantly, leads to delayed impairment in energy metabolism and apoptotic cell death. This pathophysiological. The mechanism provides the basis of hypothermia therapy (8). Jacobe et al. determined the effectiveness and safety of moderate whole _body hypothermia by applying refrigerated gel packs to maintain the rectal temperature at 33_34 in newborns with HIE born in hospitals with or without newborn intensive care facilities or complicated hypothermia equipment. Our results also found this simple method is effective and safe in nontertiary neonatal settings while awaiting retrieval and transport to the regional NICU. They found it safe and effective in a nontertiary neonatal setting while awaiting retrieval and transport to a regional NICU (9). In a study in Japan, Takenouchi et al. recommend that TH should be conducted in NICUs capable of multidisciplinary care and under the standard protocol (10). Gluckman et al. induced head cooling in 234 term infants. In this multicenter randomized controlled trial, the researchers found that induced head cooling is not protective in a mixed population of babies with neonatal encephalopathy, but it could safely improve survival without severe neurodevelo-pmental disability in babies with

less severe EEG changes (11). Ericha et al. used cold saline in children with acute brain injury to treat fever as an effective method to reduce temperature. They found it is effective in reducing fever in these children (12). A systematic review (in 2008) of the English language literature on the association between intrapartum hypoxia-ischemia and neonatal encephalopathy revealed the incidence of HIE 2/5 of 1000 live births with 14.5 %cerebral palsy (13). Due to the high frequency of asphyxia in newborns and the high mortality and morbidity caused by it, various diagnostic and therapeutic methods, such as the use of melatonin, cell therapy, cardiac treponin assay, etc., have been proposed to control this disease (14-18).

Conclusion

This simple method of hypothermia could be used to decrease mortality and hospital stay. It is safe and available without price for patients.

Acknowledgments

We are so appreciative of the vice Chancellor of Mashhad University for financial support and for all of them accompanied us. We appreciate dr Habibollah Esmaily to help us in data analysis.

Conflict of interests

The authors declare that they have no competing interests.

References

1. Davidson JO, Wassink G, Van den Heuij LG, Bennet L, Gunn AJ. Therapeutic hypothermia for neonatal hypoxic–ischemic encephalopathy–where to from here? Frontiers in neurology. 2015;6:198.
2. Gunn AJ, Gunn TR. The 'pharmacology' of neuronal rescue with cerebral hypothermia. Early Hum Dev. 1998;53(1):19-35.
3. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al; Eunice Kennedy shriver national institute of child health and human development neonatal research network. effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: A randomized clinical trial. JAMA. 2017 Oct 24;318(16):1550-1560.
4. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al; Eunice Kennedy Shriver NICHD Neonatal Research Network. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med. 2012;366(22): 2085-92. Erratum in: N Engl J Med. 2012; 367(11):1073.
5. Higgins RD, Raju TN, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, et al. Hypothermia and perinatal asphyxia: executive summary of the National Institute of child health and Human Development workshop. J Pediatr. 2006; 148(2): 170-175.
6. Bonifacio SL, Saporta A, Glass HC, Lee P, Glidden DV, Ferriero DM, et al. Therapeutic hypothermia for neonatal encephalopathy results in improved microstructure and metabolism in the deep gray nuclei. AJNR Am J Neuroradiol. 2012;33(11):2050-2055.
7. Rossouw G, Irlam J, Horn AR. Therapeutic hypothermia for hypoxic ischaemic encephalopathy using low-technology methods: a systematic review and meta-analysis. Acta Paediatr. 2015;104(12): 1217-1228.
8. Higgins RD, Raju T, Edwards AD, Azzopardi DV, Bose CL, Clark RH, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Hypothermia Workshop Speakers and Moderators. Hypothermia and other treatment options for neonatal encephalopathy: an executive summary of the Eunice Kennedy Shriver NICHD workshop. J Pediatr. 2011;159(5):851-858.e1.
9. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al; Infant Cooling Evaluation Collaboration. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: A randomized controlled trial. Arch Pediatr Adolesc Med. 2011;165(8):692-700.
10. Takenouchi T, Iwata O, Nabetani M, Tamura M. Therapeutic hypothermia for neonatal encephalopathy: JSPNM & MHLW Japan Working Group Practice Guidelines consensus statement from the working group on therapeutic hypothermia for neonatal encephalopathy, Ministry of Health, Labor and Welfare (MHLW), Japan, and Japan Society for Perinatal and Neonatal Medicine (JSPNM). Brain Dev. 2012;34(2):165-170.
11. 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(9460):663-670.
12. Fink EL Kochanek PM, Clark RB, Bell MJ. Fever control and application of hypothermia using intravenous cold saline. Pdiatr Crit Vare Med. 2012;13(1):80-84
13. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systemic review of the role of intrapartum hypoxic ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008; 199(6):587-595.
14. Saeidi, R. Beneficial effects of melatonin for the newborn. Iran J Neonatol. 2024;15(4):1-1.
15. Saeidi R. Cell therapy in neonates. Iran J Neonatol. 2025; 16(1): 1-2.
16. Saeidi R. Is neonatal euthanasia and end-of-life morally acceptable? Iran J Neonatol. 2024;15(3):1-2.

17. Marzban, A., Jafari, N., Zareakbari, M. Serum cardiac troponin i levels in neonates with perinatal asphyxia: A cross-sectional study. Iran J Neonatol. 2025;16(1):19-26.

18. Kamrani K, Khazraee MS, Zarkesh MR, Moeini R, Shariat M. Can a single value of cardiac troponin i predict short-term adverse outcomes in premature newborns? Iran J Neonatol. 2023;14(1):40-45.