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ORIGINAL ARTICLE

The Short Term Outcome of Therapeutic Hypothermia Compared with Standard Treatment among Asphyxiated Newborns Presenting after 6 hours of Life

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ABSTRACT

Objectives: To compare the short term outcome of therapeutic hypothermia in asphyxiated newborn with standard treatment presenting after 6 hours of life.

Methodology: It was Randomized controlled trial conducted in the department of Pediatric Medicine, Bahawal Victoria Hospital, Bahawalpur from December 2018 to June 2019 after taking ethical approval from institutional ethical review committee and informed written consent from parents of patients. Confidentiality of the data was maintained and it was assured that no harm to study participants is done. A total of 108 term neonates with moderate to severe HIE presenting >6 hours of life were included. Preterm infants, major congenital anomaly and overt bleeding were excluded. Then selected patients were placed randomly into Group A (hypothermia group) & Group B (conservative group), by using lottery method. Outcome variable like mortality within 1st week was noted. There was no conflict of interest in the study and funding was done by the authors.

Results: The mean age of patients in group A was 17.69 ± 6.68 hours and in group B was 17.60 ± 6.65 hours. Out of 108 patients, 62 (57.41%) were males and 46 (42.59%) were females with male to female ration of 1.3:1. There was mortality within one week (short term outcome) in 07 (12.96%) patients in Group A (hypothermia group) while in Group B (conservative group), it was seen in 16 (29.63%) patients.

Conclusion: This study concluded that there is benefit of therapeutic hypothermia in asphyxiated newborns after 6 hours of life and short term outcome is better after therapeutic hypothermia in asphyxiated newborns.

Keywords: Asphyxia, Encephalopathy, Mortality, Cooling.

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE), another name for perinatal asphyxia, is characterised by biochemical and clinical signs of acute or subacute brain injury brought on by smothering, hypoxia, acidosis, and hypoperfusion. The key factor contributing to morbidity and mortality is neonatal birth asphyxia. Birth asphyxia incidence in wealthy countries is approximately 0.5-1/1000 live births, compared to the range of 100-250/1000 live births in underdeveloped countries, due to superior perinatal and prenatal care.[1]. Each year, 1.1 million stillbirths and around a million newborn deaths are attributed to birth asphyxia[2]. Birth asphyxia is to blame for 23% of all newborn fatalities worldwide[3].

In Pakistan, birth asphyxia is the secondary cause of 64% of neonatal deaths. How many newborns experience birth asphyxia and go on to have severe neurophysical developmental issues, such as cerebral palsy, is still not known with accuracy[5]. The majority of deliveries in underdeveloped nations, including Pakistan, take place at home, and there are no accurate data available to calculate the disease burden in these nations. Neonatal fatalities and birth asphyxia may have a far greater impact than previously thought. Pakistan is one of the 10 developing nations that account for two thirds of all newborn fatalities worldwide[2]. Hypoxic ischemic encephalopathy causes 20–30% of neonatal fatalities, and it also causes lasting neurological problems in 33–50% of survivors (cerebral palsy and mental retardation)[6]. An estimated 14.5% of cerebral palsy cases are linked to intrapartum hypoxic-ischemia.[7]

Neonatals respond by shifting and maintaining perfusion to the body's important organs once compensatory mechanisms are triggered in response to the birth asphyxia. When the brain's auto-regulatory mechanisms break down, blood flow to the cerebral regions depends on the systemic blood pressure, which has already been compromised by the asphyxia insult. This leads to cerebral ischemia, which ultimately results in primary energy failure, a drop in brain temperature, and the release of inhibitory neurotransmitters like GABA as a body's defence mechanism to reduce the impact of hypoxia. The initial energy failure and early cell death period can last up to twenty-four hours, giving doctors a window of opportunity. It typically lasts for roughly six hours. Secondary energy failure and reperfusion injury cause neuronal death through apoptosis, which has long-term neurodevelopmental repercussions in the event that the clinician does not step in and help.

After severe neonatal hypoxic ischemia, hypothermia is a therapeutic technique that lessens secondary neuronal impairment. Although there have been reports on the diversity of prenatal hypoxia and different cooling techniques, consistent data show that hypothermia lessens brain damage and increases survival without handicap. Hypothermia after HIE is found to have a therapeutic benefit with a relative risk of 0.76 (95% C.I., 0.65-0.89) for neurodevelopmental impairment and death[8].

Because we are located in a third-world country with limited health care facilities, an ineffective referral system, and inadequate and incorrect perinatal care services, the majority of babies delivered outside of our area arrive at our hospital after six hours, and there are no studies that demonstrate the effectiveness of therapeutic hypothermia at that point in time. Given that the problem of primary and secondary energy failure is connected to the delay in presentation, we were interested in determining whether there is any benefit for newborns brought to units after 6 hours and comparing the results. The two therapy modalities would be contrasted, and the one that produced the best outcomes would be used extensively.

MATERIAL AND METHOD

It was a randomized controlled trial conducted in Pediatric Medicine Department of Bahawal Victoria Hospital, Bahawalpur from December 2018 to June 2019 after taking ethical approval from institutional ethical review committee. Sample size calculated for the study anticipating the therapeutic benefit of hypothermia after HIE on neurodevelopmental disability and death with a relative risk of 0.76 (95% C.I, 0.65-0.89)[8], power of the study 80% and ratio of case to control 1:1 was 108 (54 in each group). Total 108 term newborns (37-42 weeks of gestation), with moderate to severe HIE presented after six hours of life were included in the study through non probability consecutive sampling technique. The

patient was labelled as case of moderate HIE if history of delayed cry (more than 5 minutes after birth) and lethargy (decreased active movements), hypotonia (muscle tone), flexion posture, and weak moro's reflex (head of newborn is allowed to fall for 15 degrees, and response of baby is noted) and tendon reflexes present. Similarly severe hypoxic ischemic encephalopathy was labelled if history of delayed cry (more than 5 minutes after birth) and stuporous, coma (unresponsive to stimulation and pain), flaccid (muscle tone), decerebrate posture and moro's reflex and tendon reflexes absent. The exclusion criteria was preterm newborn, major congenital anomaly, overt bleeding and requirement of ventilator support.

"After taking informed consent from parents, we divided the babies into two groups A & B by lottery method, group A (the hypothermia group) treated at ambient environmental temperature by turning off radiant warmer and then applying two refrigerated gel packs (medicare hot and cool packs) across the chest and/or under the head and shoulder to maintain rectal temperature at 33.5C (range 33 -34'C) followed by slow rewarming over 8-12 hours at a rate of 0.5 C every 2 hours. While the group B was given conservative treatment with the regular monitoring of the temperature, pulse, respiration, capillary refill time and oxygen saturation of the patient. Conservative treatment included resuscitation and stabilization of the neonate, adequate ventilation, perfusion and blood pressure management, careful fluid management, avoidance of hypoglycemia and hyperglycemia, hyperthermia and treatment of seizures."

The data obtained was analyzed by using SPSS version 22.0. The results obtained from the group A & B were compared for the mortality and discharge from the hospital. The final outcome was measured at the end of 1 week. Mean and standard deviation were calculated for age (hours of life). Frequency and percentages were calculated for gender and mortality. Effect modifier were controlled through stratification of age, gender and severity of illness to see the effect of these on outcome followed by Chi-square test taken, P≤0.05 as significant.

RESULTS

Mean age of neonates included in the study was 17.64 ± 6.65 hours. The mean age of patients in group A was 17.69 ± 6.68 hours and in group B was 17.60 ± 6.65 hours. Majority of the patients 85 (78.70%) were between 6-24 hours of age . Out of 108 patients, 62 (57.41%) were males and 46 (42.59%) were females with male to female ration of 1.3:1.

There was mortality within one week (short term outcome) in 07 (12.96%) patients in Group A (hypothermia group) while in Group B (conservative group), it was seen in 16 (29.63%) patients with p-value of 0.034.

Stratification of short term outcome was done with respect to age, gender and severity of disease in both groups.

Table-I: Age and gender distribution

	Group A (n=54)		Group B (n=54)		Total (n=108)	
Age (hours)	N	%	N	%	N	%
6-24	43	79.63	42	77.78	85	78.70
>24	11	20.37	12	22.22	23	21.30
Mean ± SD	17.69 ± 6.68		17.60 ± 6.65		17.64 ± 6.65	
	Group A (n=54)		Group B (n=54)		Total (n=108)	
Gender	N	%	N	%	N	%
Male	32	59.26	30	55.56	62	57.41
Female	22	40.74	24	44.44	46	42.59

Table II: Distribution according to severity of disease

	Group A (n=54)		Group B (n=54)		Total (n=108)	
Severity	N	%	N	%	N	%
Moderate	37	68.52	35	64.81	72	66.67
Severe	17	31.48	19	35.19	36	33.33

Table III: Comparison of Short term outcome (mortality) between both Groups (n=108).

		Group A		Group B	
		No. of Patients	%age	No. of Patients	%age
Mortality	Yes	07	12.96	16	29.63
	No	47	87.04	38	70.37

- P value is 0.034 which is statistically significant.

Table IV: Stratification of outcome with respect to age and gender.

Age of patients (hours)	Group A (n=54)		Group B (n=54)		p-value
	Outcome		Outcome		
	Yes	No	Yes	No	
6-24	05 (11.63%)	38 (88.37%)	11 (26.19%)	31 (73.81%)	0.086
>24	02 (18.18%)	09 (81.82%)	05 (41.67%)	07 (58.33%)	0.221
Gender	Group A (n=54)		Group B (n=54)		p-value
	Outcome		Outcome		
	Yes	No	Yes	No	
Male	04 (12.50%)	28 (87.50%)	09 (30.0%)	21 (70.0%)	0.091
Female	03 (13.64%)	19 (86.36%)	07 (29.17%)	17 (70.83%)	0.202
Severity	Group A (n=54)		Group B (n=54)		p-value
	Outcome		Outcome		
	Yes	No	Yes	No	
Moderate	05 (13.51%)	32 (86.49%)	10 (28.57%)	25 (71.43%)	0.116
Severe	02 (11.76%)	15 (88.24%)	06 (31.58%)	13 (68.42%)	0.153

DISCUSSION

Hypoxic-ischemic encephalopathy is one of the severe effects of prenatal hypoxia (HIE). Perinatal asphyxia is fairly common in wealthy nations like Pakistan.[9,10] One-fourth of neonatal deaths worldwide are caused by perinatal asphyxia, which occurs more frequently in developing countries.[11] Management of neonatal hypoxia in poor nations consists primarily of supportive measures. Countries with modern health care systems, the neonates with hypoxia in whom there is moderate or severe HIE are at greater risk of handicap with socioeconomic repercussions in survival or death. Lack of appropriate neuroprotective measures following prenatal hypoxia is blamed for the worst results.[12, 13]

Nowadays, therapeutic hypothermia is the gold standard of care for neonates who have asphyxiated. Nearly half of the neonatal intensive care units (NICU) in the United States reported that they were using therapeutic hypothermia.[14, 15] Therapeutic hypothermia is a therapy strategy used to alleviate hypoxia and avoid complications in European nations.[16, 17] The use of

hypothermia for management is expanding quickly in Germany and other European nations.[18, 19]

This study compared the short term outcome of therapeutic hypothermia in newborns having asphyxia with standard treatment presenting after 6 hours of life. Mean age of neonates in the study was 17.64 ± 6.65 hours. The mean age of patients in group A was 17.69 ± 6.68 hours and in group B was 17.60 ± 6.65 hours. Majority of the patients 85 (78.70%) were between 6-24 hours of age. Out of 108 patients, majority (57.41%) were males. Mortality within one week was higher in patients who were managed conservatively (29.63%) as compared to patients treated with hypothermia (12.96%). These findings are consistent with Bharadwaj and Bhat study in which 02 neonates with hypothermia treatment as compared to 12 with standard care had developmental delay (Baroda developmental screening test).[20] "The study conducted in China randomly assigned full term neonates with HIE to selective head cooling or control group. The cooling was started within 6 hours after birth for a nasopharyngeal temperature of 34±0.2°C and rectal temperature of 34.5-35.0°C in the intervention group. Neurodevelopmental outcome were evaluated at eighteen months of age. The primary outcome was a combined end point of death and severe disability. The data of 194 infants was analyzed (100 infants in the selective head cooling group and 94 infants in the control group). The severe disability and death was noted in 31% of neonates with selective head cooling group, and 49% in control group."[21]

CONCLUSION

This study concluded that there is benefit of therapeutic hypothermia in asphyxiated newborns presenting after 6 hours of life and short term outcome is better after therapeutic hypothermia in asphyxiated newborns presenting after 6 hours of life. So, we recommend that therapeutic hypothermia should be used as a primary management option in asphyxiated newborns after 6 hours of life.

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