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Outcome of Neonates Given Therapeutic Hypothermia For Severe Birth Asphyxia

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ABSTRACT

Objective: To evaluate outcomes in neonates afflicted with severe birth asphyxia provided with therapeutic hypothermia.
Study Design: Comparative prospective study.
Place and Duration of Study: Military Hospital Rawalpindi from Jan 2018 to Dec 2018.
Methodology: 124 birth asphyxiated neonates were enrolled with further segregation in Group A (Cases) and Group B (Controls). Group A neonates were instituted therapeutic hypothermia with specialized equipment (Techotherm Machine). Complications (such as hemorrhage, infections, hepatic injury, and mortality) were noted and subsequently neurological examinations at six, and twelve months were done to look for hypoxic-ischemic encephalopathic symptoms in both groups.
Results: 124 birth asphyxiated neonates were admitted, and procedure was initiated at 3.45 hour approx. Rectal temperature was recorded to be 33.41 ± 0.5°C. It was found that neonates in Group A have lesser hypoxic-ischemic encephalopathic and other complications than neonates in Group B i-e thrombocytopenia (A: 16(26.3%), B:23(36.8%), hepatic injury (A: 23(36.8%), B: 35(57%) and acidosis (A: 13(21%), B: 23(36.8%). Pulmonary hypertension 19(31%) which was more prevalent in Group B and bradycardia 56(90%) was incessant in Group A due to hypothermia. A follow up neurological exam at six and twelve was observed to be normal in 35(56%)of patients in group A whereas only 25(41%) showed a normal response in group B.
Conclusion: Therapeutic hypothermia can succor as a paradigmatic treatment modality for asphyxiated neonates, if instituted well in time and appropriately. Based on available resources and protocols, guidelines can be established regarding active or passive cooling.

Keywords: Encephalopathy, Hypothermia, Neonate.

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INTRODUCTION

Birth asphyxia and related complications are significant contributors to neonatal mortality especially in developing countries with an estimated rate of 24% compared to 1% in developed countries. Recent research signifies the importance of therapeutic hypothermia for treatment of hypoxic-ischemic encephalopathy. This study aims at the effect of hypothermia on Hypoxic-ischemic encephalopathy which is a fatal outcome of birth asphyxia adding to neonatal mortality and morbidity. Neonatal asphyxia is a global healthcare problem usually seen in the neonatal units with a high rate of multisystem complications and mortality throughout the globe. Approximately 24% of the deaths in newborns are reported in neonates born with neonatal asphyxia.[1,2] Despite advancements in treatment strategies and availability of advanced equipment in modernized and developed countries mental and physical retardation owing to moderate and severe hypoxic-ischemic encephalopathy is inevitable adding to the agony of parents and the victims. Lack of ineffective neuroprotective treatment protocols is primarily associated with this adverse outcome.[3,4]

Phosphocreatinine and adenosine triphosphate exhaustion in acute hypoxic-ischemic encephalopathy defined as primary energy failure, are mainly responsible for brain injury and neuronal damage. Latent phase, approximately six hours after ischemic injury is characterized by reperfusion with resuscitative measures,leads to either complete convalescence or in critical damage, proceed to secondary energy failure evident after approximately six to fifteen hours of the primary event. Apoptotic cell death ensues after three to ten days of acute asphyxia.This therapeutic aperture can be utilized to prevent or reduce this ancillary brain neuronal damage by deliberate hypothermia.[5,6]

It has been implied in various research works that therapeutic hypothermia provided in the early six hours of life in late preterm and term infants withechoing a notable turn down in mortality and

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neuronal morbidity when followed at the age of eighteen months in survivors.[7,8]

Developed countries are using Therapeutic hypothermia as a standardized protocol and treatmentstrategy for example in theUnited States, 50% of the neonatal intensive care units are equipped for provision of therapeutic hypothermia whereas the centers deficient in the facility opt for referral of appropriate patients tothe centers where treatment can be offered.[9,10]

The rationale of this study is to determine the impact of therapeutic hypothermia in neonates afflicted with birth asphyxia at our setup.Studies and research in Pakistan are still scarce therefore it was essential to establish guidelines for this treatment modality and strategy to rehabilitate the neonatal population and reduction in mortality of this age group.

METHODOLOGY

This Comparative Prospective Study was conducted at MH (Military Hospital) Rawalpindi after approval of ethical review board (ERC # A/28/EC/387) over a period of 1 year from Jan2018 to Dec 2018. The minimum sample size calculated for the study was (124)with anticipated mortality of 15% in cases whereas 37% in controls in birth asphyxiated newborns with associated moderate and severe hypoxic-ischemic encephalopathy managed with therapeutic hypothermia with a power of the study 80%, confidence level of 95%,5% level of significance, the sample size ratio between groups of as reported by previous literature presented by Maoulainine *et al*.[11] With non-probability consecutive sampling, a total of (124)birth asphyxiated neonates suffering from neonatal asphyxia were enrolled with further uniform segregation in Group – A (Cases) n = 62 and Group – B (Controls) n = 62.

Inclusion Criteria: Neonates with gestational age ≥ 36weeks with birth weight of 1800g having acute perinatal hypoxia (moderate asphyxia) were included in the study.

Exclusion Criteria: Neonates with gestational age < 36weeks having history of fetal growth restriction with a birth weight of <1800g presenting with head trauma, major intracranial bleed, or with any congenital anomalies were excluded from the study.

Demographic characteristics (such as gestational age, birth, and gender), perinatal-neonatal profile (e.g. origin, delivery mode, acute intrapartum episodes, Apgar score at 1, 5, 10 minutes, neonatal resuscitation history) were noted before cooling.[12] Complications during hospital stay (such as hemorrhage, infections, hepatic dysfunction and mortality) were also noted. Due to lack of availability, an amplitude-integrated electroencephalogram (aEEG) evaluation based on grades suggested by Al Naqeeb *et al*.[13] was not done. Subsequent general neurological examination and developmental assessment at six and twelve was done to evaluate for any sensory motor or cognitive deficits. For infants in the protocol group, we have registered the time of cooling initiation after birth, the rectal temperature monitoring, the adverse effects, and interventions during cooling.Participants were enrolled after written informed consent provided by the parents and subjected to treatment as guidelines advocated by the French Society of Neonatology which primarily endorse initiation of treatment (active cooling up to 33.5-34°C) before six hours elapsed after birth.[14]

At admission, an automated infant warmer was used which would work only if the temperature will be < 34°C.Therapeutic hypothermia was instituted with specialized equipment (Techotherm Machine) to achieve a rectal temperature of 34-35°C checked after every.[15] minutes and later two-hourly with the constant placement of skin probe up to seventy-two hours after initiation of protocol.After seventy-two hours gradual rewarming at the rate of 0.2 to 0.4°C per hour for six to twelve hours was continued. Meticulous cardiopulmonary, glucose (six to eight hourly),blood pressure (two hourly or hourly during the warming)and urine output monitoring was ensured. The battery of investigations including chemistry profile, complete blood count, and coagulation parameters was carried out on daily basis.The Control group was not subjected to therapeutic hypothermia and was treated at normal temperature due to presentation after six hours of life,non-availability of equipment, and intensive care inpatient facility or contraindication to hypothermia (cephalhematoma and pulmonary arterial hypertension).

Data was entered and analyzed by data management software IBM Statistical Package for the social sciences (SPSS) version 23.00 (SPSS). The descriptive statistics for the categorical variable were presented as frequency and percentage while the mean and standard deviation was reported for continuous variables. The categorical groups were

compared by using the Chi-square test or Fisher Exact test whichever applicable. A significance value of ≤0.05 was considered significant.

RESULTS

A total of (124) birth asphyxiated neonates, out of which 41(34.21%) were females whereas 79(65.79%) were males,were enrolled with average maternal age of 26±31 in cases (Group -A) and 27±51 in controls (Group – B). Characteristics of the pregnant mothers were recorded as mentioned in table -I while neonatal characteristics are shown in table II. The most common complication seen during the process was bradycardia in group A and renal injury in group B as shown in Table -III. It was found that neonates in Group A have lesser hypoxic-ischemic encephalopathic and other complications than neonates in Group B i-e thrombocytopenia (A: 16(26.3%), B:23(36.8%), hepatic injury (A: 23(36.8%), B: 35(57%) and acidosis (A: 13(21%), B: 23(36.8%). Pulmonary hypertension 19(31%) which was more prevalent in Group B and bradycardia 56(90%) was incessant in Group A due to hypothermia as shown in table - III. A follow up neurological exam at six, twelve and 18months was observed to be normal in 35(56%) of patients in group A whereas only 25(41%) showed a normal response in group B as shown in Table-IV.

Table-I: Maternal Characteristics of the Study Participnats

	Group – A (n = 62)	Group – B (n = 62)
Gestational Diabetes	-	3(5.0%)
Gestational Hypertension	3(5.0%)	-
Meconium or stained amniotic fluid	42(68.4%)	35(57%)
Prolapsed cord	6(10.0%)	6(10.0%)
Head Retention	6(10.0%)	-
Shoulder dystocia	3(5.0%)	3(5.0%)

Table-II: Neonatal Characteristics

	Group – A (n = 62)	Group – B (n = 62)
Apgar score ≤ 5 at 5 min	55(89.5%)	62(100.0%)
Apgar score ≤ 5 at 10 min	39(63.1%)	52(84.0%)
CPR in the delivery room	16(26.1%)	20(31.5%)
HIE 2 with seizure	29(47.3%)	20(31.5%)
HIE 2 without seizure	3(5%)	6(10.0%)

DISCUSSION

This study results inferred a statistically significant impact of therapeutic hypothermia on the reduction of mortality and morbidity in birth asphyxiated neonates.

Kinoshita Aet al. conducted a trial to evaluate the efficiency of therapeutic hypothermia achieved with low-cost devices (ice packs) in newborns with birth asphyxia instead ofservo-controlled cooling devices due to cost and constraints of availability in developing countries. In this study, complications were evaluated and as per their results pulmonary hypertension, arrhythmia, and coagulopathy were seen in 11.3%,4.2%, and 26.7% patients respectively, findings well versed with our research project. They concluded low-cost devices to be of comparable efficacy.[15]

Table-III:Complications of the Study Participnats

	Group – A (n = 62)	Group – B (n = 62)
Bradycardia <90/min	56 (90.0%)	6(10.0%)
Thrombocytopenia	16(26.3%)	23(36.8%)
Hepatic Injury	23(36.8%)	35(57.0%)
Acidosis	13(21.0%)	23(36.8%)
Renal Injury	23(36.8%)	42(68.0%)
Pulmonary Hypertension	-	19(31.0%)
Head Edema	3(5.0%)	-
Nosocomial Infection	16(26.0%)	13(21.0%)

Table-IV:Follow Up of the Study Participnats

	Group – A (n = 62)	Group – B (n = 62)	*p*-value
Mortality	9(15.0%)	23(36.8%)	0.007*
Normal neurological exam at discharge	26(42.0%)	16(26.0%)	<0.001 *
Follow up at 12 months age			
Normal neurological exam	35(56.0%)	25(41.0%)	0.011*
Psychomotor delay	9(15.0%)	6(10.0%)	
Seizure Disorder/Epilepsy	3(5.0%)	3(5.0%)	
Neurosensory disorders	3(5.0%)	15(25.0%)	

Xu *et al*. conducted the impact of hypothermia treatment for hypoxic-ischemic encephalopathy in the neonatal population of Canada in a descriptive study and evaluated possible causes of death concluding thatlowAPGARscores,vigorousresuscitation,andsevere encephalopathyare contributory factors that are to be addressed appropriately in addition to deliberate hypothermia.[16] Sarafidis *et al* examined twelveasphyxiated neonates,treatedthem with whole-body passive cooling and confirmed results with magnetic resonance imaging available.Twelve participants survived through treatment and out of those one had normal neurodevelopment whereas three,one, and two had mild, moderate, and severe manifestations, respectively.Although findings are

consistent with our study we could not achieve a level of accuracy with magnetic resonance imaging attributableto constrained medical resources and limited financial capacity of the general population, this parameter could not be assessed in our study.[17]

Literature reported 28 randomized control trials with a sample size of 3592 asphyxiated neonates suffering from hypoxic-ischemic encephalopathy out of which 1832 were subjected to hypothermia whereas 1760 patients were not provided hypothermia and follow up was done.The study revealed a significant decrease in the mortality of newborns when therapeutic hypothermia was employed in asphyxiated newborns.[18]

Shankaran S *et al*. estimatedconsequences ofdepth and duration of cooling on mortality and morbidity at 18 months in neonates havinghypoxic-ischemic encephalopathy. Among term neonates with moderate birth asphyxia cooling for longer than 72 hours, cooling to lower than 33.5°C, or both did not reduce death or moderate to severe disability at 18 months of age.Hence warrants the need for standardization of protocols.[19]

Gulczynska *et al*. made a comparison of head versus whole-body cooling in asphyxiated newborns.78 neonates with perinatal asphyxia were involved in this study. The selective headcooling was provided to 51 newborns whereas the whole body cooling group consisted of 27 patients. Both study groups had similar baseline characteristics and conditions at birth. There were no significant differences in hospital course, neurological status, and adverse effects associated with cooling procedure between groups. We failed to employ this comparison in our study, hence could be regarded as a limitation.[20]

Despite its limitations small sample size, limited resources, lack of correlation regarding variable duration and depth of hypothermia, the study certainly adds to our understanding of therapeutic hypothermia as a useful treatment modality for birth asphyxiated neonates. Numerous literature quoted above are indicative of fact that even low-cost equipment and whichever intervention used for therapeutic hypothermia proved to be beneficial, a fact of much potential for the developing countries to reduce neonatal mortality attributable to birth asphyxia.

CONCLUSION

Therapeutic hypothermia can succor as a paradigmatic treatment modality for asphyxiated neonates with associated hypoxic-ischemic encephalopathy if instituted well in time and appropriately. Based on available resources and protocols,guidelines can be established regarding active or passive cooling.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HA & AR: Data acquisition, data analysis, critical review, approval of the final version to be published.

UA & MF: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RK & SJ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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