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Original Article

Paediatrics Section

Role of Therapeutic Hypothermia in Prevention of Acute Kidney Injury in Neonates with Perinatal Asphyxia- A Prospective Observational Study

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ABSTRACT

Introduction: Perinatal Asphyxia (PA) remains a leading cause of neonatal mortality, especially in resource-limited settings like India, contributing to over 13% of neonatal deaths. Acute Kidney Injury (AKI) is a significant complication of PA, with an incidence ranging from 50-72%. Therapeutic Hypothermia (TH), the only evidence-based intervention for Hypoxic Ischaemic Encephalopathy (HIE), has demonstrated neuroprotective effects. However, its renoprotective potential in preventing AKI is inadequately explored.

Aim: To evaluate the role of TH in preventing AKI in term neonates with PA by comparing renal outcomes between neonates receiving TH and those receiving standard care.

Materials and Methods: This prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of FH Medical College in Agra, Uttar Pradesh, India, from September 2022 to May 2024. A total of 81 neonates with moderate to severe HIE were enrolled. The enrolled neonates were categorised into two groups: Group A received standard care (n=40), while Group B received TH (n=41). AKI was diagnosed according to the neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria, and outcomes were monitored over a 72-hour period. Neurological outcomes were additionally assessed using the Thompson encephalopathy score. Data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0, with a p-value <0.05 considered statistically significant.

Results: The incidence of AKI was significantly lower in the TH group (31.7%) compared to the non TH (52.5%) (p=0.047*). Neonates in group B also demonstrated better neurological outcomes, with 73% achieving mild Thompson scores at discharge compared to 51.5% in group A. Complications like hypotension and coagulopathy showed no significant differences between groups.

Conclusion: TH significantly reduces AKI incidence and improves neurological outcomes in neonates with PA, reinforcing its role in neonatal care.

Keywords: Body cooling, Encephalopathy, Hypoxic-injury, Neonatal care, Renal insufficiency

INTRODUCTION

The Perinatal Asphyxia (PA), or birth asphyxia, refers to oxygen deprivation during the birth process, leading to significant neonatal morbidity and mortality [1]. Globally, the burden of PA varies, with developed countries reporting 1-6 cases per 1000 live births and developing nations, such as India, witnessing rates as high as 20 per 1000 [2]. According to United Nations International Children's Emergency Fund (UNICEF), PA contributes to over 13% of neonatal deaths in India, underscoring its clinical significance [3]. This condition has far-reaching systemic effects, with complications affecting multiple organs, including the brain, kidneys, heart, and liver [4].

Only supportive management was indicated until last decade, after which newer modalities have come to light, most of which are still under evaluation. TH is evidence-based treatment currently being used in treatment for PA. It has been associated with improved neurological outcomes in neonates with hypoxic ischaemia encephalopathy. However, beneficial effect of TH in protecting other organs is yet to be proven.

The AKI is a frequent and severe complication of PA, impacting 50-72% of affected neonates [5]. The neonatal kidney is particularly vulnerable to hypoxic ischaemia injury, leading to a high risk of renal dysfunction. However, the variability in AKI definitions and diagnostic criteria complicates accurate assessment and comparison of outcomes. The KDIGO guidelines, combining features of Risk Injury Failure Loss End (RIFLE) and Acute Kidney Injury Network (AKIN) criteria, offer a standardised approach to defining AKI, emphasising a rise in serum creatinine (S.Cr) by >0.3 mg/dL [6,7]. Despite these advancements, data on AKI in asphyxiated neonates remain sparse, particularly in low-resource settings.

TH has revolutionised the management of HIE, significantly reducing mortality and long-term neurodevelopmental impairment [8]. By lowering cerebral metabolism, inhibiting excitotoxicity, reducing oxidative stress, and suppressing inflammation, TH provides robust neuroprotection. Emerging experimental and clinical studies have suggested a possible renoprotective effect of hypothermia by attenuating ischaemia-reperfusion injury and inflammatory pathways; however, available human data remain limited and inconsistent, with most studies being secondary analyses or involving small cohorts and heterogeneous definitions of AKI [9-11]. Moreover, the majority of existing literature has focused predominantly on neurological outcomes, with renal outcomes receiving comparatively little attention, particularly in low- and middle-income settings.

Consequently, there remains a significant knowledge gap regarding the impact of TH on the incidence and severity of AKI in term neonates with PA, especially when standardised neonatal AKI definitions such as the modified KDIGO criteria are applied. This study aimed to evaluate the role of TH in preventing AKI in term neonates with PA by comparing renal outcomes between neonates receiving TH and those receiving standard care.

MATERIALS AND METHODS

This was a prospective observational study conducted in NICU, Department of Paediatrics, a tertiary care hospital, FH Medical College, Agra, Uttar Pradesh, India from September 2022 to May 2024 after due approval from the Institute Ethical Committee. (IEC no. FHMC/IEC/R.Cell/2022/19). Written informed consent was secured from the parents after explaining the study details. Participation was voluntary, and confidentiality was maintained throughout.

Sample size: The sample size was determined for comparing the incidence of AKI between neonates receiving TH and those receiving standard care. Based on previously published studies [12,13], the expected incidence of AKI was assumed to be approximately 50% in the standard care group and 25% in the TH group [12,13]. With a two-sided alpha error of 5% and a statistical power of 80%, the minimum required sample size was calculated to be 38 neonates in each group. To account for potential attrition and incomplete data, a total of 81 neonates were ultimately enrolled in the study.

Inclusion criteria: Neonates admitted within six hours of life with gestational age >36 weeks and evidence of PA as shown by any one of following: a) pH <7 or base excess >16 in cord blood gas or arterial blood gas within one hour of life; b) Apgar <5 at 10 minutes of age; c) Positive Pressure Ventilation (PPV) for at least 10 minutes; d) History of acute peripartum event like cord collapse, uterine rupture etc., and having evidence of moderate to severe encephalopathy according to Sarnat and Sarnat classification [14-16].

Exclusion criteria: Neonates with: a) major congenital kidney and urinary tract abnormalities; b) severe Intrauterine Growth Restriction (IUGR); c) Severe coagulopathy or intracranial bleed; d) Maternal use of medications affecting neonatal renal function (e.g., ACE inhibitors) were excluded from the study [11].

Study Procedure

All enrolled neonates fulfilled the study inclusion criteria. Neonates who met standard eligibility criteria for TH and whose parents provided informed consent received TH (group B). Neonates who were otherwise eligible for TH but did not receive cooling due to parental refusal or operational constraints-such as unavailability of cooling equipment at the time of admission, delayed referral beyond the optimal therapeutic window, or resource limitations-received standard supportive care and constituted the comparison group (group A). All neonates received standard evidence-based neonatal intensive care irrespective of group allocation.

Protocol for Therapeutic Hypothermia (TH) [8,16,17]: Group B neonates underwent TH (Whole body) using MiraCraddle-Neonate cooler. A target temperature of 33-34°C was maintained by continuously monitoring rectal and skin temperatures every 15 minutes for the first four hours, and then every two hours for the subsequent 68 hours (Total 72 hours).

Cooling was done in two phases:

- Passive cooling: Passive cooling was implemented promptly upon identifying a potentially eligible neonate by turning off the radiant warmer.
- Active cooling: using MiraCraddle- Neonate cooler. Neonates in the standard treatment group (group A) adhered to the institutional NICU protocol for PA, including maintaining their rectal temperature at 36.5°C using a warmer in servo-controlled mode.

Monitoring and supportive care: Both groups received similar supportive care, including anticonvulsants, inotropic agents, and respiratory support {Oxygen, Continuous Positive Airway Pressure (CPAP), mechanical ventilation} as required. Vital signs, renal function tests (serum creatinine, blood urea, serum electrolytes), and urine output were monitored at baseline, 24, 48, and 72 hours. Urine output was monitored every six hours for 72 hours. Neonates with rising creatinine values/decreasing urine output were classified into three stages of AKI based on the modified KDIGO criteria [7].

The primary outcome was the incidence of AKI in both groups. Additionally, overall clinical outcomes including mortality, discharge status, and neurological status were evaluated. Overall outcomes were also evaluated in terms of mortality and discharge rates.

Among the discharged patients, neurological outcomes were assessed using the Thompson score [16], and classified into mild, moderate, and severe neurological deficits. Other complications also reported as secondary outcome.

The parameters analysed included demographic variables, incidence and staging of AKI [17], associated systemic complications (necrotising enterocolitis, sepsis, coagulopathy, hypotension, hypoglycaemia, leukopenia, thrombocytopenia), neurological outcomes assessed using the Thompson encephalopathy score [18], and final outcomes including mortality and discharge status.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and analysed using SPSS version 21.0. Continuous variables were tested for normality using the Shapiro-Wilk test, and parametric tests (e.g., independent t-tests) were applied for intergroup comparisons. The Chi-square test was used for categorical data. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline demographic and perinatal characteristics were comparable between group A and group B. Males constituted 67.5% of group A and 75.6% of group B, while females accounted for 32.5% and 24.4%, respectively. Vaginal delivery was the most common mode of delivery in both groups (60.0% in group A vs 65.9% in group B), with no statistically significant difference observed [Table/Fig-1].

Variables		Group A (n=40)	Group B (n=41)	Total (n=81)	p-values
Gender	Females	13 (32.5%)	10 (24.4%)	23 (28.4%)	0.287
	Males	27 (67.5%)	31 (75.6%)	58 (71.6%)	
MOD[1]	LSCS	16 (40.0%)	14 (34.1%)	30 (37.0%)	0.376
	VD	24 (60.0%)	27 (65.9%)	51 (63.0%)	

[Table/Fig-1]: Demographic profile.
Chi-square test; MOD: Mode of delivery; LSCS: Lower segment caesarean section; VD: Vaginal delivery; values are expressed in n (%)

Intergroup comparison of AKI staging (as per modified KDIGO criteria) [7] are shown in [Table/Fig-2]. The AKI was observed in 31.7% of neonates in the TH group compared to 52.5% in the NTH group, with the difference being statistically significant (p=0.047*). Among neonates who developed AKI, the majority had stage 1 disease. Severe AKI (stage 3) was less frequent in the NTH group compared to the TH group (5% vs 7.3%).

Parameters	No AKI	AKI			
		AKI stage 1	AKI stage 2	AKI stage 3	Total
Non Therapeutic Hypothermia group (NTH)	19 (47.5%)	11 (27.5%)	8 (20%)	2 (5%)	21 (52.5%)
Therapeutic Hypothermia group (TH)	28 (68.3%)	5 (12.2%)	5 (12.2%)	3 (7.3%)	13 (31.7%)
Total	47 (58%)	16 (19.7%)	13 (16%)	5 (6.1%)	34 (42%)
p-value					0.047*

[Table/Fig-2]: Intergroup comparison of AKI staging (as per modified KDIGO criteria) [7].
Chi-square test

Mortality was lower in the TH group (9.8%) compared to the NTH group (17.5%), but the difference was not statistically significant (p=0.309). Among the survivors, 51.5% of neonates in group A had mild neurological deficits at discharge, 27.3% had moderate deficits, and 21.2% had severe deficits. In comparison, group B had 73.0% with mild deficits, 10.8% with moderate deficits, and 16.2% with severe deficits at discharge, while neonates receiving TH exhibited a higher proportion of mild neurological deficits, the difference was not statistically significant (p=0.132). Intergroup comparison of outcome of babies are shown in [Table/Fig-3].

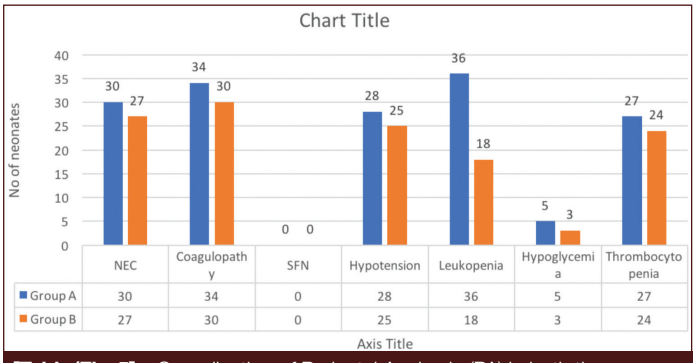
Outcomes	Group A n (%)	Group B n (%)	p-value
Death	7 (17.5%)	4 (9.8%)	0.309
Discharge Thompson score [18] • Mild • Moderate • Severe	33 (82.5%) 17 (51.5%) 9 (27.3%) 7 (21.2%)	37 (90.2%) 27 (73%) 4 (10.8%) 6 (16.2%)	0.132
Total	40	41	

[Table/Fig-3]: Intergroup comparison of outcome of babies.
Chi-square test

No statistical significance found in both the group on comparing complications due to PA except for leukopenia, which was statistically significant [Table/Fig-4,5].

Complications	Group A n (%)	Group B n (%)	p-value*
NEC1	30 (75%)	27 (65.9%)	0.646
Coagulopathy	34 (85%)	30 (73.2%)	0.327
SFN	0	0	-
Hypotension	28 (70%)	25 (61%)	0.288
Leukopenia	36 (90%)	18 (43.9%)	<0.001**
Hypoglycaemia	5 (12.5%)	3 (7.3%)	0.462
Thrombocytopenia	27 (67.5%)	24 (58.5%)	0.478

[Table/Fig-4]: Intergroup comparison of complications.
NEC: Necrotising enterocolitis; SFN: Subcutaneous fat necrosis



[Table/Fig-5]: Complication of Perinatal Asphyxia (PA) in both the groups.

DISCUSSION

The PA is a critical condition where impaired gas exchange leads to hypoxemia (low oxygen), hypercapnia (high carbon dioxide), and metabolic acidosis. While the brain is particularly vulnerable-resulting in HIE- the impact extends to multiple organ systems, often resulting in Multiorgan Dysfunction Syndrome (MODS) [19].

One of the key outcomes assessed was the effect of TH on renal function. The study findings demonstrated that neonates managed with TH had a lower risk of developing deranged renal function compared to those receiving standard care. Although the overall severity of AKI, as defined by the neonatal modified KDIGO criteria, remained relatively low in both groups. The majority of affected neonates presented with Stage 1 AKI, which is consistent with findings reported in previous studies [9-11]. No significant difference was observed in the distribution of higher stages of AKI between the two groups.

A total 81 neonates with PA were enrolled. Majority of neonates in both groups were male (58 male and 23 female), consistent with previous studies by Gupta BD et al., (66.3%) and Kamath N et al., (76%), suggesting a possible bias in healthcare-seeking behavior favoring male infants in these regions [5,12]. Mode of delivery is important risk factor for PA. Most of the babies (63%) were delivered vaginally, which is comparable to findings by Tanigasalam V et al., (60.8%) and Aggarwal A et al., (60%), emphasising its association with PA [13,20].

The PA causes multiple organ dysfunction after birth. Due to shunting of blood to vital organs renal injury may occur following PA. Incidence of AKI in present study is 42%. And on comparing between groups (TH and NTH) TH demonstrated a significant reduction in AKI incidence. In the present study, the non therapeutic group showed a 52.5% incidence of AKI, while the therapeutic group had 31.7%, which is statistically significant (p=0.047*). These findings are consistent with previous studies. Tanigasalam V et al., reported AKI in 60% of neonates receiving standard care compared to 32% in those receiving TH [13], while Kamath N et al., [12] observed a similar reduction (50% vs 18%, respectively) [12]. A meta-analysis by Van Wincoop M et al., also supported these results, reporting AKI incidences of 42.3% in the non therapeutic group and 33.3% in the therapeutic group [21].

While incidences vary based on study settings and diagnostic criteria, the consistent reduction in AKI with TH underscores its renoprotective potential. Studies like those by Simbruner G et al., and Mok TY et al., highlight the role of TH in reducing AKI incidence and severity, emphasising the need for standardised diagnostic criteria such as the neonatal modified KDIGO [22,23].

Complications like hypotension and coagulopathy were common but showed no statistically significant differences between the groups. Hypotension occurred in 61% of the TH group compared to 70% in the non therapeutic group (p=0.288). This finding is comparable to the study by Eicher DJ et al., who reported hypotension in 67% of cooled neonates and 43% of non cooled neonates [24]. Coagulopathy was observed in 73.2% of the TH group and 85% of the non therapeutic group (p=0.327). Eicher DJ et al., also reported similar rates of coagulopathy between cooled and non cooled neonates (61% vs 58%) [24].

The improved neurological outcomes as well. Moderate to severe neurological disabilities were observed in 27% of neonates in the therapeutic group compared to 48.5% in the non therapeutic

group. Gluckman PD et al., reported similar findings, with severe neurological outcomes in 19% of neonates in the therapeutic group versus 31% in the non therapeutic group [25]. Another study by Lin Z et al., highlighted improved neuroimaging outcomes, with moderate-to-severe HIE changes in 13% of the therapeutic group versus 64% in the non therapeutic group [26].

In the present study, the mortality rate was lower in the TH group (10%) compared to the non therapeutic group (18%), although the difference was not statistically significant (p=0.309). Discharge rates were higher in the therapeutic group (90.2% vs. 82.5%), reflecting better recovery. These findings align with results from Catherine RC et al., who reported lower mortality in the therapeutic group (28.2% vs. 34.5%), and the meta-analysis by Pauliah SS et al., which showed that TH did not significantly reduce mortality but had a positive trend in improving outcomes [27,28].

Further research is needed to explore the long-term effects of TH on renal function and neurological outcomes in neonates with PA. Incorporating advanced biomarkers for early detection of AKI could enhance diagnosis and intervention strategies. Expanding access to TH in resource-limited settings should be prioritised to improve neonatal outcomes.

Limitation(s)

The study was conducted at a single centre, which may limit the generalisability of the findings. AKI was diagnosed and staged based on changes in serum creatinine and urine output according to the neonatal modified KDIGO criteria; however, reliance on serum creatinine may have delayed early detection due to its inherent limitations as a biomarker. Additionally, the absence of long-term follow-up precluded assessment of sustained renal and neurodevelopmental outcomes following TH.

CONCLUSION(S)

The significantly reduced the incidence of AKI among term neonates with PA without increasing the frequency of associated systemic complications. Although the severity of AKI and short-term neurological outcomes did not differ significantly between groups, TH was associated with a lower overall burden of renal injury. These findings support the role of TH as an important intervention in the management of PA, particularly in resource-limited settings.

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