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Original Research Article

ROLE OF MANNITOL IN IMPROVING THE OUTCOMES OF MODERATE TO SEVERE PERINATAL ASPHYXIA

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ABSTRACT

Background: *Birth asphyxia, defined as inadequate oxygen supply to a newborn during delivery, is a major cause of neonatal morbidity and mortality, second only to sepsis. While its incidence in developed countries ranges from 1% to 1.5% of live births, it rises significantly in developing nations, reaching up to 5%. Effective management of moderate to severe birth asphyxia remains a challenge. This study evaluates the efficacy of Mannitol infusion in improving survival outcomes in neonates diagnosed with moderate to severe perinatal asphyxia.* ***Objective:*** *To assess the effectiveness of Mannitol in managing cases of moderate to severe perinatal asphyxia in full-term neonates.* ***Study Design:*** *Case series study.* ***Setting:*** *Department of Pediatrics Medicine, Sughra Shafi Medical Complex, Narowal.* ***Duration of Study:*** *March 2, 2023, to September 1, 2023.* ***Methods:*** *A total of 141 full-term neonates diagnosed with moderate to severe perinatal asphyxia were included using consecutive non-probability sampling. Mannitol 20% was administered intravenously at a dosage of 1.5 mL/kg over 20 minutes every 8 hours. All neonates received standard supportive treatment according to established neonatal care protocols. The primary outcome measure was survival or mortality. Data were analyzed using SPSS version 25.0, and post-stratification analysis was conducted using the Chi-square test, with statistical significance set at $p \leq 0.05$.* ***Results:*** *Among the 141 neonates, 91 (64.5%) were males and 50 (35.5%) were females. The mean age was 16.35 ± 6.534 days. Mannitol therapy resulted in a survival rate of 82.3% (116 neonates), while mortality was observed in 17.7% (25 neonates).* ***Conclusion:*** *Mannitol infusion demonstrated promising effectiveness in the management of moderate to severe perinatal asphyxia, significantly improving survival rates. These findings support the potential role of Mannitol as a therapeutic option in neonatal intensive care settings, warranting further large-scale studies to validate its efficacy and safety.*

Keywords: *Perinatal Asphyxia, Mannitol, Mortality, Survival*

INTRODUCTION

Perinatal asphyxia, a condition frequently encountered in neonates, presents a significant challenge in the realm of newborn health. The impact of moderate to severe perinatal asphyxia is profound, as it stands as a leading contributor to both morbidity and mortality during the neonatal phase. Within the healthcare systems of developing nations, perinatal asphyxia remains a prominent concern, demanding attention and effective interventions. The exact prevalence of birth asphyxia leading to cerebral disturbances is not precisely determined but is estimated to range from 1.5 to 6 cases per 1000 live births (1).

This condition is widely regarded as one of the most prevalent factors contributing to perinatal brain injuries, often resulting in long-term neurological impairments that can significantly affect the affected individual's quality of life. As efforts continue to enhance understanding and management strategies for perinatal asphyxia, the need for further research and improved clinical practices becomes increasingly apparent in addressing this complex health issue (1). The management strategies for cases of moderate to severe birth asphyxia encompass a dual approach that combines supportive measures with interventions aimed at preventing or addressing cerebral edema. Supportive care involves the regulation of convulsions, the avoidance of hypotension, and the mitigation of metabolic imbalances. In instances where there is a suspicion of intracranial hypertension, therapeutic interventions such as dehydration protocols, corticosteroid administration, and the use of osmotic agents are commonly advised. These recommendations underscore the importance of a comprehensive and multi-faceted approach to the management of birth asphyxia, with a focus on both supportive care and targeted treatments to address potential complications (2). Mannitol's ability to reduce elevated intracranial pressure, as directly measured from the subarachnoid space, has been documented in various studies (3). It is crucial to note that a significant number of term newborns experience some level of perinatal asphyxia; however, only a small percentage of them develop permanent brain damage as a result. Those neonates who are at a higher risk of experiencing severe neurological impairments exhibit abnormalities in multiple organ systems, exhibit diminished cerebral function at birth that persists for a prolonged period, and often present with seizures shortly after delivery. These findings underscore the importance of early detection and intervention in newborns exhibiting these risk factors to prevent long-term neurological complications (4).

The etiology of brain injury in hypoxic-ischemic encephalopathy continues to be a topic of debate among experts in the field, with no definitive treatment showing clear efficacy (4). Immediate management of a newborn suffering from asphyxia at birth necessitates addressing the dysfunctions in various bodily systems and considering the administration of anticonvulsants if deemed necessary (5, 6). The delay that may be incurred in securing informed parental consent for clinical trials could potentially mask a significant therapeutic impact that is crucial for the effectiveness of the treatments being evaluated, thus impacting the overall interpretation of the study results (7, 8).

Mannitol induces a decrease in intracranial pressure alongside a concomitant decrease in systemic blood pressure. The impact of Mannitol on blood pressure appears to be temporary, followed by a gradual restoration and enhancement in cerebral perfusion pressure. This phenomenon suggests a complex interplay between Mannitol administration, hemodynamic parameters, and cerebral blood flow regulation, warranting further investigation into the underlying mechanisms and clinical implications (2).

The intravenous administration of Mannitol at a concentration of 20.0% has been shown to significantly decrease both morbidity and

mortality rates in cases of moderate to severe perinatal asphyxia, contributing to improved outcomes and prognosis for affected infants. The use of this treatment approach has demonstrated efficacy in reducing the negative consequences associated with perinatal asphyxia, highlighting its potential as a valuable intervention strategy in clinical practice (3, 9).

We performed a comprehensive analysis involving a series of cases focusing on newborn infants who experienced moderate to severe asphyxia at full term to evaluate the effectiveness of Mannitol in the treatment of perinatal asphyxia of varying severity levels. The purpose of our study was to investigate the potential benefits of Mannitol in improving outcomes for infants affected by perinatal asphyxia, particularly in cases characterized by moderate to severe levels of hypoxia at birth.

METHODOLOGY

The investigation was carried out at the Department of Pediatrics Medicine, located within the premises of Sughra Shafi Medical Complex in Narowal, spanning from March 2, 2023, to September 1, 2023. Following the necessary steps of obtaining approval from the hospital's Ethical Committee and securing informed consent from the attendant/parents, a total of 141 children who were afflicted with moderate to severe perinatal asphyxia, specifically term neonates with a gestational age of 37 weeks or more and a birth weight exceeding 2500 grams, were enrolled in the research study. This stringent selection criterion aimed to ensure that the study cohort consisted of infants who met the specified criteria for accurate and meaningful data analysis, thus enhancing the reliability and validity of the research findings.

Neonates who presented with congenital anomalies such as polycystic kidney disease, ectopic kidneys, or horseshoe kidneys, as well as those who were undergoing treatment with medications like acyclovir or vancomycin, or had experienced hypotension defined as a mean arterial pressure of 40mmHg or lower, were deemed ineligible for inclusion in the research investigation. The sample size of 141 was estimated at an 8% margin of error, 95% confidence level, and the expected percentage of mortality as 37.5%.

Severe birth asphyxia was defined as four conditions fulfilled out of five, i.e.

1. History of prenatal fetal distress (late deceleration, loss of beat-to-beat variability) fetal bradycardia (heart rate < 100 beats per min) on CTG, meconium-stained amniotic fluid,

2. Neonates present with initial low APGAR < 5 and need immediate neonatal ventilation with a bag and mask or through endotracheal tube intubation for > 2 min after delivery,

3. 5 min APGAR score of < 6,

4. pH of < 7 measured by ABGs in hospital ICU and

5. Neurological manifestations like seizure (one or more episodes of generalized fits), hypotonia, and coma (unresponsive to pain or auditory or visual stimulation).

Children were administered a solution of 20% Mannitol intravenously at a dosage of 1.5ml per kilogram of body weight over 20 minutes, repeated every 8 hours. During this treatment, electrolytes and urea creatinine levels were closely monitored at 8-hour intervals. The target range for serum sodium concentration was set to be maintained between 145-155 milliequivalents per deciliter. The treatment regimen was limited to a maximum duration of 72 hours. Monitoring of electrolytes, urea, and creatinine levels continued every 8 hours throughout the treatment period. In cases where children experienced complications such as shock or renal failure, which necessitated the discontinuation of therapy, treatment was promptly stopped. The outcomes were evaluated based on the survival or death of the patients. It was observed that all the children enrolled in the study were effectively managed following a standardized treatment protocol.

The collected data were input into the Statistical Package for the Social Sciences (SPSS) version 25.0 for analysis. Quantitative parameters such as age, birth weight, and gestational age were expressed as Mean ± Standard Deviation. On the other hand, qualitative variables like gender and mortality rates were presented in terms of frequency and percentages. To account for potential effect modifiers, the data were further stratified based on gender, age, gestational age, and birth weight. Following the stratification process, a Chi-square test was conducted to assess the significance of any observed differences. A p-value equal to or less than 0.05 was considered statistically significant, indicating a meaningful relationship between the variables under consideration.

RESULTS

Inclusion criteria encompassed a total of 141 infants diagnosed with perinatal asphyxia. Within this cohort, it was observed that 91 newborns, constituting 64.5% of the sample, were male, whereas 50 infants, representing 35.5%, were female. The average age of the neonates was calculated to be 16.35±6.534 days. Upon categorizing the subjects based on age, it was revealed that 57 individuals, equivalent to 40.4%, belonged to the age group of ≤14 days, with the remaining 84 neonates, amounting to 59.6%, falling into the >14 days age category. The mean gestational age at birth was determined to be 38.41±1.341 weeks. Distribution analysis based on gestational age exhibited that 74 neonates (52.5%) were born in the 37-38 weeks group, while 67 infants (47.5%) were in the 39-40 weeks category.

Furthermore, the average birth weight of the neonates was recorded at 2835.41±18.413 grams. Delving into the distribution based on birth weight, it was found that 63 newborns (44.4%) fell within the ≤ 3000-gram weight range, while 78 infants (55.5%) were classified under the > 3000-gram weight category. Evaluation of the survival rate following Mannitol therapy indicated positive outcomes in 116 neonates (82.3%), while 25 infants (17.7%) faced mortality. Subsequent analysis involved stratifying the treatment outcomes concerning various factors, revealing no significant variances (p>0.05) among the different variables considered.

Table 1: Frequency distribution of demographic variables

Gender	Frequency	Percent
Male	91	64.5
Female	50	35.5
Total	141	100.0
Age groups		
≤14 days	57	40.4
>14 days	84	59.6
Total	141	100.0
Gestational age		
37-38 weeks	74	52.5
39-40 weeks	67	47.5
Total	141	100.0
Birth weight		
≤3000 gram	63	44.7
>3000 gram	78	55.3
Total	141	100.0
Treatment outcome		
Mortality	25	17.7
Survival	116	82.3
Total	141	100.0

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Table 2: Stratification of treatment outcome concerning different variables

Variables		Treatment outcome		p-value
		Mortality	Survival	
Gender	Male	15(16.5%)	76(83.5%)	0.601
	Female	10(20.0%)	40(80.0%)	
Age groups	≤14 days	7(12.3%)	50(87.7%)	0.163
	>14 days	18(21.4%)	66(78.6%)	
Gestational age	37-38 weeks	14(18.9%)	60(81.1%)	0.698
	39-40 weeks	11(16.4%)	56(83.6%)	
Birth weight	≤3000 gram	13(20.6%)	50(79.4%)	0.417
	>3000 gram	12(15.4%)	66(84.6%)	

DISCUSSION

Perinatal asphyxia was historically defined as a critical insufficiency of oxygen supply to the fetus during the processes of labor and delivery. This condition, known as ischemic encephalopathy, describes the clinical manifestation of disrupted brain functions that can occur as a consequence of hypoxic ischemia following instances of moderate to severe perinatal asphyxia. In addressing cerebral edema, which is a common outcome of such conditions, one of the most rapid and efficient strategies is osmotherapy. The primary objective of osmotic therapy is to facilitate the removal of excess water from the brain by leveraging an osmotic gradient. Among the various osmotic agents available for this purpose, Mannitol stands out as the most widely utilized choice due to its efficacy and safety profile. First introduced in the year 1960, Mannitol is a compound derived from alcohol and the simple sugar mannose. Over the decades, it has maintained its status as the predominant osmotic agent employed in the treatment of cerebral edema. Studies and clinical experience have consistently demonstrated that the administration of Mannitol does not lead to any adverse disruptions in the body's electrolyte balance, particularly when utilized in the context of managing cerebral edema. This favorable safety profile further enhances its appeal as a therapeutic option for addressing cerebral edema resulting from conditions such as ischemic encephalopathy linked to perinatal asphyxia. As such, Mannitol continues to play a central role in the arsenal of treatments aimed at mitigating the impact of cerebral edema and related complications in clinical practice (11).

In the early 1980s, it was demonstrated that isotonic saline had beneficial impacts on individuals suffering from hemorrhagic shock, which was a significant finding in the medical field at that time (12). Further research conducted subsequently highlighted the efficacy of hypertonic saline as a form of osmotherapy particularly in the treatment of cerebral edema, showcasing its potential for managing such conditions in a clinical setting (13, 14).

In a prospective, randomized comparison conducted to evaluate the effects of administering either 2.5 ml/kg of 20% mannitol or 7.5% hypertonic saline on patients undergoing elective supratentorial procedures, the intracranial pressure (ICP) measurements and intraoperative clinical evaluation of brain swelling demonstrated no significant differences between the two treatment cohorts (15). Most of the research viewpoints considered in these studies focused on the adult demographic, with a limited number of studies dedicated to the pediatric population, indicating a disparity in the amount of research available for different age groups (16, 17).

Our investigation constitutes a case series that focuses on the neonatal population. The comparison made in our study is with the research conducted by Yildizdas et al., which adds a valuable dimension to our findings. Furthermore, the study carried out by Upadhyay et al. has a particular emphasis on the adolescent demographic, providing a comprehensive overview of age-related differences in the outcomes observed (16, 17).

In the research conducted, it was observed that male children were prevalent, which aligns with the findings of Upadhyay and colleagues as reported in their previous study. In contrast, the study conducted by Yildizdas and team revealed a predominance of the female population. These gender disparities in the distribution of children within the study populations highlight the importance of considering gender as a factor in future research and interventions aimed at addressing pediatric health issues.

Mortality comparisons across different age groups and genders did not yield statistically significant results, a finding consistent with the research conducted by Upadhyay and colleagues. In contrast, the study carried out by Yildizdas and the team reported a statistically significant decrease in mortality rates. These contrasting outcomes suggest the need for further investigation to understand the factors contributing to variations in mortality among different populations.

CONCLUSION

The utilization of Mannitol infusion in cases of moderate to severe perinatal asphyxia appears to yield positive and advantageous results regarding treatment efficacy, particularly in terms of enhancing survival rates. This intervention has shown promising outcomes in improving the overall prognosis and clinical outcomes for neonates experiencing perinatal asphyxia.

DECLARATIONS

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned.

Consent for publication

Approved

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Not applicable

CONFLICT OF INTEREST

The authors declared the absence of a conflict of interest.

AUTHOR CONTRIBUTION

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Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript.

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Study Design, Review of Literature.

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