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ORIGINAL ARTICLE

Comparison of Short Term Neurological Outcome in Patients of Hypoxic Ischemic Encephalopathy Treated with Erythropoietin Versus Intravenous Magnesium Sulphate

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ABSTRACT

Aim: Hypoxic-ischemic encephalopathy (HIE) in neonates remains a significant challenge in medical practice, requiring effective and reliable treatment options. Erythropoietin (EPO) and Intravenous Magnesium Sulphate (MgSO4) have been explored as potential therapies, but a direct comparison of their effectiveness has been lacking.

Method: This study compared the effects of EPO and Intravenous MgSO4 in a sample of 38 neonates, evenly distributed between the two treatment groups. Parameters including maternal age, gestational age, neonatal age, weight, and several biochemical variables were assessed. Statistical analyses were conducted to reveal any significant differences between the two groups.

Results: The evaluation across various parameters revealed no significant differences between the two treatments. All the tested variables, including primary outcomes such as HB levels, showed a similarity in the overall impact of Erythropoietin and Intravenous MgSO4, with p-values consistently above 0.05.

Conclusion: The findings suggest that both Erythropoietin and Intravenous MgSO4 exhibit comparable effects in the treatment of neonates with HIE. The lack of significant differences prompts a need for further research to understand the nuanced differences and potential applications of each treatment method. These insights will be instrumental in guiding future therapeutic strategies for HIE.

Keywords: Neonates, Hypoxic-Ischemic Encephalopathy, Erythropoietin, Intravenous Magnesium Sulphate, Treatment Comparison, Biochemical Variables.

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) significantly contributes to neonatal morbidity and mortality. This condition is characterized by the inability to start or sustain breathing after birth, leading to neurological impairment and dysfunction of multiple organs[1, 2] Hypoxic-ischemic encephalopathy (HIE) is purported to be between 1-8 instances per 1000 live births in developed nations and 26 occurrences per 1000 live births in developing countries[3]. Worldwide asphyxia is the cause of approximately 25% of the 3.6million neonatal deaths every year.. A research study carried out among the urban populace of Pakistan revealed that the mortality rate among newborns was 47 out of every 1000 live births. Additionally, a considerable proportion of deaths, amounting to 26%, were attributed solely to the conditions known as birth asphyxia or hypoxia[4].

Newborns with HIE risk experiencing long-lasting and severe neurological impairments, such as cognitive dysfunction, visual and hearing impairments, and cerebral palsy[3]. Therapeutic hypothermia has emerged as gold standard of treatment for infants with moderate to severe HIE. Therapeutic hypothermia is not widely available in Pakistan. Different methods have been researched to provide hypothermia in resource limited settings, including frozen gel packs and have been proved beneficial[5]. The most effective treatment for HIE is resuscitation, supportive care that includes maintaining a balance of fluids and electrolytes, maintaining blood glucose homeostasis, and controlling seizures. Despite this, even with the most effective treatment, around one-half of individuals with moderate to severe HIE will either pass away or develop disabilities[6].

Erythropoietin (EPO), originally identified as the primary hematopoietic growth factor, has anti-apoptotic, anti-inflammatory and anti-oxidative properties. Hypoxic ischemic injury leads to increased expression of erythropoietin and erythropoietin receptors and it acts as a neuroprotective mechanism. In the recent years erythropoietin has emerged as promising therapy to improve the neurological outcome in HIE as sole therapy and also as adjuvant to hypothermia[7] The rationale of my study is to compare the effectiveness of intravenous magnesium sulphate versus erythropoietin for management of hypoxic ischemic encephalopathy. As hypothermia is not a readily available option and needs intense staffing and monitoring and in low income countries like Pakistan, we can use alternate treatments for HIE. Safety and efficacy of erythropoietin and intravenous magnesium sulphate therapy is established but there is no previous head to head comparison study between the two. This study will be helpful in comparing between the two therapies and will pave a path to choose one better option for our patients in future while saving the cost and lives at the same time.

The present study aimed to compare the short term neurological outcome of neonates with hypoxic ischemic encephalopathy treated with erythropoietin to intravenous magnesium sulphate.

MATERIALS AND METHODS

The study was designed as a retrospective cross-sectional analysis conducted at the Department of Neonatology, Recep Tayyip Erdogan Hospital, Muzaffargarh. The duration of the study encompassed a record review of patients in Neonatology from October 2022 to March 2023. The sample size included all patients from the record review over the last 6 months who met the specified inclusion criteria. A purposive sampling technique was employed.

Inclusion criteria were comprised of all inborn and outborn neonates with gestational age greater than 36 weeks diagnosed with moderate or severe Hypoxic Ischemic Encephalopathy (HIE) and who were less than 24 hours of age. Exclusion criteria included lack of consent, congenital anomalies, and a weight of less than 1800g at birth.

The operational definition of HIE was characterized by an APGAR score of less than 5 at 5 minutes, metabolic acidosis with pH less than 7.0 or a base deficit greater than or equal to 12mmol/L, neonatal neurological abnormalities, and multiple organ system involvement. Additionally, for outborn patients, a history of failure to initiate or sustain breathing at birth with three out of six signs of encephalopathy according to modified Thompson scoring was used. Severity of HIE was defined according to modified Thompson scoring. The primary outcome was considered to be an improved neurological outcome, defined as fewer than three signs

of encephalopathy according to the modified Thompson scoring system at the time of discharge. Secondary outcomes included the duration of hospital stay, frequency of clinical seizures, age at commencement of full oral feed, need for anticonvulsant drugs at discharge, and mortality.

The study commenced after receiving approval from the Institutional Review Board (IRB). Record review was conducted at the Recep Tayyip Erdogan Hospital in Muzaffargarh over the past 6 months. Patients who met the inclusion criteria were selected from the record, and the required information was entered into a specially designed proforma attached to the synopsis.

Data analysis was carried out using SPSS 20. The quantitative data that were analyzed included factors such as age, weight, gestational age, maternal age, Modified Thompson scoring, the age at which oral feeding began for the infant, and duration of hospital stay. These factors were described by their mean or median, depending on whether they followed a normal distribution curve. Qualitative variables like gender, mode of delivery, presence or absence of seizures, need for inotrope support, respiratory support, hepatic or renal dysfunction, and improved Modified Thompson scoring were described in terms of frequency and percentage. The frequency of patients with improved Modified Thompson scoring between the two groups was assessed by chi-square test, with a P-value of less than 0.05 being considered significant. Effect modifiers were controlled by stratification of data, and post-stratification t-tests were applied. Overall, the comprehensive analysis allowed for a detailed exploration of the characteristics and trends within the study population, contributing valuable insights for future research in the field.

RESULTS

The baseline characteristics of neonates treated with Erythropoietin and Intravenous MgSO4 were compared and presented in Table 1 across several variables, including maternal age, gestational age, neonatal age, weight, Apgar score, pH of arterial blood gas, LDL, CPK, HB level, ALT, AST, creatinine, and age at the first drug dose. The means and standard deviations for each group were provided, with P-values assessing the significance of differences between the two treatment groups.

Table 1: Baseline Characteristics of Neonates

Study Variables	Erythropoietin (n=19)	Intravenous $MgSO_4$ (n=19)	P-Value
	Mean ± SD	Mean ± SD	
Maternal Age (years)[#]	29.0±5.58	26.0±3.81	0.061
Gestational Age (weeks)	36.89±1.96	36.37±1.70	0.384
Neonatal Age (hours)	4.74±13.41	12.21±22.82	0.226
Weight (grams)	2889.95±626.6	2373.68±496.47	0.144
Apgar at 5 minutes	5.58±1.12	5.53±1.21	0.891
PH of Arterial Blood Gas	7.18±0.22	7.15±0.11	0.630
LDL (unit/L)	1641.68±412.1	1520.74±270.37	0.292
CPK (units/L)	658.32±133.86	579.79±198.27	0.161
HB Level (mg/dL)	15.28±2.15	15.44±2.45	0.840
ALT (U/L)	35.63±26.58	44.47±20.81	0.261
AST (units/L)	39.79±25.26	42.26±22.04	0.750
Creatinine (mg/dL)	1.02±0.42	0.85±0.35	0.196
Age at 1st drug dose (hours)	17.16±15.44	15.79±21.41	0.823

Applied Independent t-test

#: Age is presented as mean ± sd, Potential of Hydrogen (pH), Low-Density Lipoprotein (LDL), Process Capability Index (CPK), Hemoglobin (HB), Alanine Transaminase (ALT), Aspartate Aminotransferase (AST)

*Significant at p<0.05, **Significant at p<0.01

Demographic and clinical parameters of enrolled participants are presented in table 2. The given data does not indicate any statistically significant differences between the Erythropoietin and Intravenous MgSO4 groups across the listed study variables.

Table 2: Demographics of participants Characteristics Between Group

Study Variables	Erythropoietin (n=19)	Intravenous $MgSO_4$ (n=19)	P-Value
Gender of Baby			
Male, n(%)	7(18.4%)	10(26.3%)	0.328
Female, n(%)	12(31.6%)	9(23.7%)	
Maternal Education			
Primary, n(%)	11(28.9%)	10(26.3%)	0.994
Matric, n(%)	7(18.4%)	8(21.1%)	
Matric, n(%)	1(2.6%)	1(2.6%)	
Prolonged Labor			
Yes, n(%)	3(7.9%)	6(15.8%)	0.224
No, n(%)	16(42.1%)	13(34.2%)	
Rupture of Membrane >12 hours			
Yes, n(%)	2(5.3%)	4(10.5%)	0.330
No, n(%)	17(44.7%)	39.5(39.5%)	
Liquor			
Yes, n(%)	11(28.9%)	16(42.1%)	0.076
No, n(%)	8(21.1%)	3(7.9%)	
Mode of Delivery			
SVD, n(%)	3(7.9%)	9(23.7%)	0.051
Instrumental, n(%)	0(0.0%)	1(2.6%)	
C-Section, n(%)	16(42.1%)	9(23.7%)	
Birth at Hospital			
Yes, n(%)	18(47.4%)	15(39.5%)	0.170
No, n(%)	1(2.6%)	4(10.5%)	
Birth attended by trained person			
Yes, n(%)	1(2.6%)	2(5.3%)	0.500
No, n(%)	18(47.4%)	17(44.7%)	
Encephalopathy			
Moderate, n(%)	17(44.7%)	16(42.1%)	0.500
Severe, n(%)	2(5.3%)	3(7.9%)	
Seizures before treatment			
Yes, n(%)	10(26.3%)	6(15.8%)	0.189
No, n(%)	9(23.7%)	13(34.2%)	
Hepatic Dysfunction			
Yes, n(%)	3(7.9%)	3(7.9%)	0.670
No, n(%)	16(42.1%)	16(42.1%)	
Need for Ionotropic Support			
Yes, n(%)	5(13.2%)	3(7.9%)	0.346
No, n(%)	14(36.8%)	16(42.1%)	
Renal Dysfunction			
Yes, n(%)	11(28.9%)	6(15.8%)	0.103
No, n(%)	8(21.1%)	13(34.2%)	
Mechanical Ventilation			
Yes, n(%)	6(15.8%)	7(18.4%)	0.500
No, n(%)	13(34.2%)	12(31.6%)	

Applied Fisher's Exact & Chi-Square test

The comparison of Hemoglobin (HB) levels at the end of treatment between the Erythropoietin (mean = 14.47, SD = 2.03) and Intravenous MgSO4 (mean = 13.24, SD = 2.54) groups revealed a slightly higher mean HB level in the Erythropoietin group. However, the difference was not statistically significant, with a P-value of 0.108 (Table 3).

In the comparison of short-term neurological outcomes in patients with Hypoxic Ischemic Encephalopathy treated with Erythropoietin versus Intravenous MgSO4, the study revealed no statistically significant differences in death rates across the various time points. At day 5, there were more deaths and fewer cases of moderate encephalopathy in the Erythropoietin group compared to the Intravenous MgSO4 group, but the differences were not statistically significant (P=0.199). At the same time, the Erythropoietin group had no severe encephalopathy cases, whereas the Intravenous MgSO4 group had a 5.3% occurrence. The outcomes at the 1st and 2nd weeks showed slight variations

between the groups in terms of moderate encephalopathy and no encephalopathy but remained consistent with day 5 findings (Table 4).

Table 3: Comparison Of Primary & Secondary Neonatal Outcome Between Groups

Comparison	Erythropoietin (n=19)	Intravenous $MgSO_4$ (n=19)	P-Value
Primary Outcome			
HB at End of Treatment (mg/dL)			
Mean	14.47	13.24	0.108
±SD	2.03	2.54	
Secondary Outcome			
Occurrence of Seizures During First 7 days of Life			
Yes, n(%)	10(26.3%)	8(21.1%)	0.516
No, n(%)	9(23.7%)	11(28.9%)	
Anticonvulsant at Discharge			
Yes, n(%)	1(2.6%)	4(10.5%)	0.170
No, n(%)	18(47.4%)	15(39.5%)	
Age at Full Oral Feeding (days)			
Mean	7.95	11.11	0.211
±SD	5.22	9.45	
Duration of Hospital Stays (days)			
Mean	6.79	5.14	0.328
±SD	9.42	10.35	

Applied Independent t-test, Chi-Square & Fisher's Exact test

Table 4: Comparison Of Outcome At 5th Day, 1st Week & 2nd Week Between Group

Outcome Variables	Erythropoietin (n=19)	Intravenous $MgSO_4$ (n=19)	P-Value
Outcome at day 5			
Death, n(%)	2(5.3%)	0(0.0%)	0.199
Moderate, n(%)	3(7.9%)	5(13.2%)	
Severe Encephalopathy, n(%)	0(0.0%)	2(5.3%)	
No Encephalopathy, n(%)	14(36.8%)	12(31.6%)	
Outcome at 1st week			
Death, n(%)	2(5.4%)	0(0.0%)	0.367
Moderate, n(%)	2(5.4%)	2(5.4%)	
No Encephalopathy, n(%)	15(40.5%)	16(43.2%)	
Outcome at 2nd week			
Death, n(%)	2(5.3%)	1(2.6%)	0.272
Moderate, n(%)	2(5.3%)	0(0.0%)	
No Encephalopathy, n(%)	15(39.5%)	18(47.4%)	

Applied Chi-Square test

DISCUSSION

The purpose of this study was to compare the efficacy of two treatment methods, Erythropoietin and Intravenous MgSO4, in a specific clinical context, likely related to neonatal care or a particular disease condition (such as Hypoxic Ischemic Encephalopathy). The primary outcome, measured in terms of HB levels at the end of treatment, was meticulously analyzed to discern the comparative advantages of each treatment method. While both treatments were evaluated across various parameters including maternal age, gestational age, neonatal age, weight, and several biochemical variables, the statistical analysis revealed no significant differences between the two groups. The results suggest a similarity in the overall impact of Erythropoietin and Intravenous MgSO4 on the primary outcome, thereby prompting a need for further investigation to understand the nuanced differences and potential applications of each treatment method.

Both Erythropoietin (EPO) and Intravenous MgSO4 were examined across parameters like maternal age, gestational age, neonatal age, weight, and several biochemical variables in the present study. Similarly, the cited studies by NEATO[8], RR Malla et al.[9], and MA Siddiqui et al.[10] examined various treatments and their impact on similar parameters, though the interventions varied.

The statistical analysis in the main study revealed no significant differences between the EPO and Intravenous MgSO4 groups in the primary outcomes. This contrasts with the findings in the cited studies [8-10], where differences were observed in various outcomes between the treatment and control groups.

In the context of EPO, both NEATO's[8] and RR Malla et al.'s[9] studies reported positive effects, though varying in specifics. However, the present study did not identify significant differences between EPO and Intravenous MgSO4, suggesting the potential similarity in their overall impact on HIE. With regard to Intravenous MgSO4, MA Siddiqui et al.'s[10] study found improved outcomes, whereas the main study found no difference in comparison to EPO. This divergence may prompt further investigation into the nuanced differences and potential applications of both treatment methods.

The effectiveness of the treatments varied across the studies. In NEATO's trial, EPO treatment resulted in lower global brain injury scores and better recovery from moderate/severe encephalopathy in the early stages, though mortality rates were not significantly different. RR Malla et al. found that EPO treatment reduced the incidence of death or impairment and the need for anticonvulsants, without affecting mortality. MA Siddiqui et al. revealed that magnesium sulphate treatment led to improved seizure control, feeding, and survival rates, although 25% of patients in the treatment group still expired.

Nonomura et al.[11] focused on the safety and short-term outcomes of a specific intervention in nine patients with HIE, highlighting the absence of adverse effects and mixed neurodevelopmental outcomes. Sajjad et al.[12] conducted a broader study of 60 patients, examining the combined use of therapeutic hypothermia and MgSO4, and concluded that this combination was safe, with similar short-term outcomes between the two groups. Oorscot et al.[13] provided a review of the literature, considering erythropoietin (EPO) as a neuroprotectant to augment hypothermia, highlighting promising results in animal studies and the need for further research on combination therapies. While all three studies contribute to the understanding of HIE treatment, they vary in their focus, methodology, and conclusions, ranging from safety assessments to combined therapeutic strategies and literature reviews on the potential of EPO in enhancing existing treatments.

Current literature collectively broadens the perspective on HIE treatment by exploring safety, combined treatment strategies, and long-term outcomes.[14-18] While differing in their focus and methodologies, they contribute valuable insights that can guide further research and clinical practice. They emphasize the complexity of HIE treatment and the potential of various approaches to enhance outcomes, reflecting the main study's call for more nuanced understanding and investigation of these treatments.

The insights from these studies along with the present results have profound implications for the treatment of HIE. They underline the potential of EPO as a therapeutic option, albeit with variations in effectiveness depending on the regimen. The promising results of magnesium sulphate offer a potential alternative or complementary approach. Clinicians may consider these findings in tailoring treatment strategies for neonates with HIE, keeping in mind the individual characteristics of the patients and the specific contexts of their practice. Collaboration with future research and continuous monitoring of outcomes will be crucial to refine these interventions and enhance the quality of life for infants suffering from this debilitating condition.

CONCLUSION

In conclusion, this study provides a comprehensive analysis of the effects of Erythropoietin and Intravenous MgSO4 in the treatment of neonates with hypoxic-ischemic encephalopathy (HIE). Through

the evaluation of various parameters, including maternal and gestational age, neonatal age, weight, and several biochemical variables, the study revealed no significant differences between the two treatment methods. The findings underscore the need for further investigation to elucidate the nuanced differences and specific applications of both treatments. The outcomes align with existing literature, demonstrating the safety and potential effectiveness of these therapies, yet also emphasize the importance of exploring combination strategies with other modalities, such as therapeutic hypothermia. The results of this study contribute valuable insights to the existing body of knowledge on HIE and support ongoing research efforts aimed at optimizing treatment approaches for this complex and life-threatening condition. Future research should consider long-term neurodevelopmental outcomes, gender effects, and the optimization of dosing and timing to refine the therapeutic strategies for neonates affected by HIE.

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