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Original Article

Spectrum of Dyselectrolytemia Induced by Liposomal Amphotericin B In Neonates

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ABSTRACT

Objective: To compare the spectrum of dyselectrolytemia induced after treatment by liposomal Amphotericin B (LAmB) in neonates being treated for fungal infections

Study Design: Quasi-experimental study

Place and Duration of Study: Department of Pediatrics, Combined Military Hospital Rawalpindi, Pakistan from Aug 2023 to Jan 2024

Methodology: Pre-therapy baseline investigations including Blood complete picture, Urine RE and serum electrolytes (Na, K, Ca, Mg, PO4) were sent baseline values were recorded. LAmB therapy was initiated in all patients at a dose of 4 mg/kg/day for a total of 14 days. Primary variables studied were changes in serum sodium, potassium, calcium, magnesium, phosphate, and for glycosuria before starting and after completion of therapy.

Results: When comparing the primary variables before and after LAmB treatment, mean levels of sodium were 140.77±0.99 MEq/L before therapy versus 132.16±1.05 MEq/L after therapy (p<0.001). Mean levels of potassium were 5.48±0.09 MEq/L before the start of anti-fungal therapy versus 4.61±0.13 MEq/L after therapy (p<0.001). When comparing the levels of calcium, mean levels before therapy were 2.27±0.10 mmol/l before therapy and 2.27±0.10 after therapy (p=0.859).

Conclusion: LAmB results in derangement of nearly all electrolyte parameters but effective monitoring and replacement results in successful completion of therapy in neonates and prevents morbidity and mortality.

Keywords: Amphotericin B, Anti-fungal Agents, Electrolytes, Dyselectrolytemia, Liposomes, Neonates

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INTRODUCTION

Fungal infections and their frequency have increased in the past decade due to urbanization, poor living conditions especially in the developing countries and increased resistance to standard therapies[1]. Various drugs have been developed which are used in conjunction with steroids and antibiotics to increase effectivity[2]. Among the drug classes introduced, Amphotericin B (AmB) was first introduced clinically in the late 1950s but with its increasing use, the issue of its crippling nephrotoxicity gained widespread reports in the 1980s and 1990s[3]. With concerns about conventional Amphotericin B deoxycholate (DAmB), the concerns led to the development of the Azole and Echinocandin class of drugs which included Itraconazole, Fluconazole And Voriconazole[4]. With their administration replacing conventional Amphotericin B treatment, long term studies revealed their limitations including photosensitivity, hallucination, cutaneous malignancies, and limited antifungal spectrum. Their increasing resistance to Candida and Aspergillus also raised concerns and work started for alternative class drugs for treatment[5-6].

The extended spectrum and excellent response of Amphotericin B resulted in contemplation of improving its pharmacokinetic and pharmacodynamic profile with decreased nephrotoxicity and a more favorable therapeutic index[7]. The lipid formulation of Amphotericin B (LAmB) gained widespread acceptance due to decreased nephrotoxicity, and excellent effectivity against invasive fungal infections especially in immunocompromised, neutropenic and critical patients8. But all these merits, came demerits of the liposomal form as well. Dyselectrolytemia has been reported with treatment which has been reported to cause cessation of therapy[9]. The imbalances correct itself once the drug is stopped but in various cases, the drug is the only option for effective treatment. Adult studies are still available but study on neonates especially in Pakistan regarding electrolyte imbalance following treatment has been scanty and our study aims to provide the spectrum of electrolyte disturbances seen after treatment with the liposomal

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form and deduce conclusion as to the best treatment strategies in neonates.

METHODOLOGY

This quasi experimental study was carried out at the Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan after approval form the ethical review board (vide letter no 512 dated 31 July 2024). Minimum sample size was calculated keeping the confidence interval at 95%, power of test at 80% with anticipated population proportion of dyselectrolytemia seen in patients with fungal infections undergoing treatment with and without liposomal Amp B being 63% versus 37% respectively10. Minimum sample size for one group comparing the two population proportions came out to be 55 patients. We included a total of 140 patients in the final study protocol according to the inclusion criteria furnished.

Inclusion Criteria: Neonates diagnosed with invasive fungal infections confirmed by culture, CT scan or organism specific immune panel as candidates for liposomal Amphotericin B therapy (LAmB) were included.

Exclusion Criteria: Patients with birth defects or anomalies, pre-mature neonates (<36 weeks), neonates with severe bradycardia or respiratory distress, non-invasive fungal infection not requiring Amphotericin B therapy, neonates with kidney disease or severe sepsis and non-willingness of the parents or next of kin to be included in the study were excluded.

The study method included all patients as per the inclusion criteria furnished. Before the start of therapy, the parents were counselled regarding the need for anti-fungal therapy, it's possible complications and study protocol. Pre-therapy baseline investigations including Blood complete picture, Urine RE and serum electrolytes (Na, K, Ca, Mg, PO4) were sent baseline values were recorded. LAmB therapy was initiated in all patients at a dose of 4 mg/kg/day for a total of 14 days. The same baseline panel was repeated every 48 hours and values were recorded by the resident on duty in the NICU unaware of the study or its protocol under barrier nursing under strict aseptic measures. Serum electrolytes reaching the lower threshold according to neonatal age were replaced through IV infusions daily and according to standard protocols. Consistent fall in levels were recorded before commencement of replacement therapy. Mean values for electrolytes and presence of glycosuria in the urine was tabulated on an excel sheets for all patients at the end of 14 days or prior if completion of therapy was indicated according to the metabolic panel, changes in CT or regression of immune panel for the fungal species isolated.

Primary variables studied were changes in serum sodium, potassium, calcium, magnesium, phosphate, and for glycosuria before starting and after completion of therapy. Duration of therapy was also noted after starting treatment for fungal infections confirmed by culture report.

Mean and demographic variables were studied along with the clinical variables using the paired samples t test. Frequency variables were compared using the Chi-square test. A p value of ≤0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

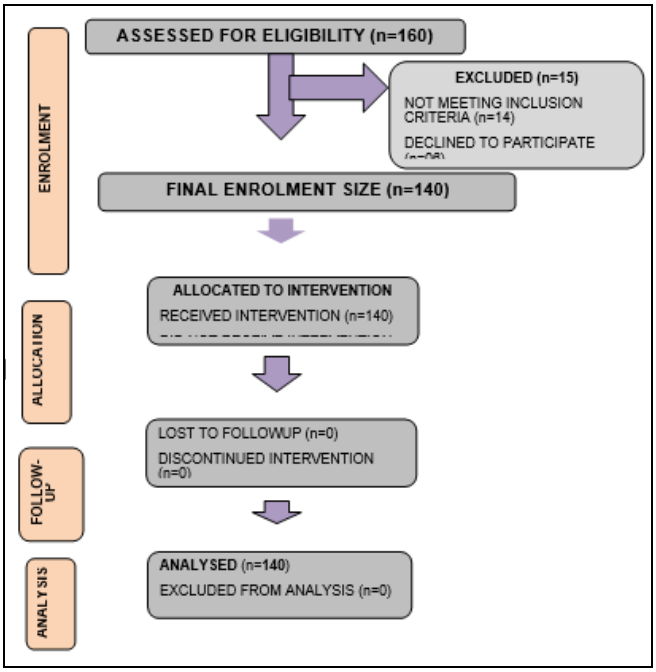

Figure: Phases of study

RESULTS

A total of 140 patients were analyzed in the final study protocol. Mean age of patients was 22.49±1.81 days. Mean weight at time of admission was 3312.14±242.43 grams. Gender distribution revealed 99(70.7%) males and 41(29.3%) females. Mean duration of therapy was 13.21±0.82 days. The type of organism identified and confirmed through culture and immune serology revealed 68(48.6%) cases of Candida, 30(21.4%) cases of Aspergillus, 28(20.0%) cases of

Malassezia and 14(10.0%) cases were diagnosed with other fungal species (Table-I).

Table-I: Demographic Variables (n=140)

Variable(s)	Liposomal Amphotericin B Treatment Group
Mean Age at Admission (Days)	22.49±1.81
Mean Weight (Grams)	3312.14±242.43
Gender	
Male	99(70.7%)
Female	41(29.3%)
Mean Duration of Therapy (Days)	13.21±0.82
Fungal Species Diagnosed	
Candida	68(48.6%)
Aspergillus	30(21.4%)
Malassezia	28(20.0%)
Others	14(10.0%)

When comparing the primary variables before and after LAmB treatment, mean levels of sodium were 140.77±0.99 MEq/L before therapy versus 132.16±1.05 MEq/L after therapy (p<0.001). Mean levels of potassium were 5.48±0.09 MEq/L before the start of anti-fungal therapy versus 4.61±0.13 MEq/L after therapy (p<0.001). When comparing the levels of calcium, mean levels before therapy were 2.27±0.10 mmol/l before therapy and 2.27±0.10 after therapy (p=0.859). Mean levels of magnesium were 0.90±0.09 mmol/l versus 0.60±0.07 mmol/l before and after completion of therapy respectively (p<0.001). Mean levels of phosphate were 1.83±0.07 mmol/l before the start versus 0.91±0.09 mmol/l after the end of anti-fungal therapy (p<0.001). The presence of glycosuria in the urine was positive in 86 (61.4%) patients during the duration and at the end of therapy (Table-II).

Table-II: Primary Variables Before and After Treatment (n=140)

Variable(s)	Before therapy (n=140)	After therapy (n=140)	*p* value
Mean Levels of Sodium (Meq/L)	140.77±0.99	132.16±1.05	<0.001
Mean Levels of Potassium (Meq/L)	5.48±0.09	4.61±0.13	<0.001
Mean Levels of Calcium (Mmol/L)	2.27±0.105	2.27±0.108	0.859
Mean Levels of Magnesium (Mmol/L)	0.90±0.09	0.60±0.07	<0.001
Mean Levels of Phosphate (Mmol/L)	1.83±0.07	0.91±0.09	<0.001
Glycosuria Positive in Urine	0 (0.0%)	86 (61.4%)	-

DISCUSSION

The results of our study revealed that LAmB results in derangement of nearly all electrolyte parameters but effective monitoring and replacement results in successful completion of therapy in neonates and prevents morbidity and mortality. This study was carried out in our center of excellence to establish two main concerns for which studies were limited in our demographic setup. First is the use of LAmB in neonates which has never been studied in detail at our setup. Second was the associated derangement in the electrolyte profile and whether the changes warrant cessation of therapy in these patients or not.

Liposomal Amphotericin B is an irreversible binder to ergosterol in the fungal cell membrane11. Through molecular mechanism and disruption of cell wall integrity, it results in the formation of pores, followed by cellular ion leakage and ultimately cell death of the fungus[12]. Its effectivity is considered to be more than that of the non-liposomal formulations and proven by various studies[13]. One of the most significant advantages offered by the formulation is the incidence of least nephrotoxicity when compared to all formulations of Amphotericin B available[14]. The proposed mechanism is the preferential uptake in the liver and spleen more than the kidneys. The liposomal form also has low binding in the kidney due to less HDL receptors in the nephron and renal tubules resulting in minimal renal interaction[15]. Nevertheless, it causes renal damage and not completely devoid of renal effects as per international studies and also findings seen in our study as well. Around 60% of patients did develop glycosuria at the end of therapy but neither was significantly associated with severity of kidney injury requiring cessation of therapy unlike results of Amphotericin deoxycholate.

The mean age of starting therapy in our study group was in the third week of life which is line with diagnosis of fungal infection in neonates as evidenced by literature. We found that majority of the affected cases were male and causal relationship between gender requires further studies in our demographic. All of the patients in our study group underwent therapy for around 12-14 days but therapy was not stopped in any case owing to complications.

Candida was the most common isolated organism in our study group followed by invasive aspergillus species16. Both the forms were invasive requiring NICU care in the neonates. No mortality was reported in our study group during the duration of therapy. When talking about the primary variables, there was a complete derangement in the electrolyte profile with sodium, potassium, magnesium, and

phosphate being significantly decreased both statistically and clinically in line with reported reports,[10,17] The levels of calcium remained stable in the study group and no replacement was needed. All the other electrolytes were replaced for 48 hours, and sampling taken before starting replacement showed that the levels continued to fall as the treatment progressed. But rigorous replacement was effective in preventing electrolyte associated complications and no patient required cessation of therapy. This forms an important treatment strategy where susceptible strains requiring anti-fungal therapy can be effectively managed if electrolytes are monitored and managed.

RECOMMEDATION

The less nephrotoxicity and effectivity of LAmB can be effectively used to treat fungal infections in neonates if electrolytes are effectively monitored and managed for the duration of therapy. Future research should study long term effects in populations other than neonates for more diverse results.

CONCLUSION

We conclude that LAmB results in derangement of nearly all electrolyte parameters but effective monitoring and replacement results in successful completion of therapy in neonates and prevents morbidity and mortality.

LIMITATION OF STUDY

There were a few limitations. We did not follow up the time for the electrolyte panel to return to normal after completion of therapy to see if there were any long term issues or complications. We did not exclusively study immune compromised or low birth weight neonates in our study protocol.

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Authors' Contribution

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

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

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

JUR & BM: 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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