RESEARCH PAPER

Impact of Meropenem EDTA vs Meropenem on serum and ionized electrolytes in a Medical Intensive Care Unit

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ABSTRACT

Aim and Objectives:

This study aimed to compare the effects of meropenem–EDTA combination therapy with meropenem alone on serum and ionized electrolyte levels in patients with septicemia admitted to a MICU. The primary objective was to evaluate alterations in serum and ionised electrolytes and total leukocyte count (TLC). A secondary objective was to compare the duration of hospital stay between the two treatment groups.

Methods:

A prospective observational study was conducted in a tertiary care MICU over six months. Thirty adult patients (18–70 years) with presumed or confirmed septicemia were enrolled and allocated into two groups based on prescribed therapy: meropenem (Group 1) or meropenem–EDTA (Group 2). Baseline and follow-up laboratory parameters, including serum and ionized electrolytes and TLC, were analyzed and recorded. Statistical comparisons between groups were performed.

Results:

Analysis revealed no statistically significant differences in serum or ionized levels of calcium, magnesium, phosphorus, or potassium between the groups. Although the meropenem–EDTA group showed a greater reduction in Total Leukocyte Count (TLC) and a mild decline in calcium and phosphorus, these variations were not statistically significant. Notably, patients on combination therapy had a shorter mean hospital stay of 7.93 days versus 10.73 days for meropenem alone.

Conclusion:

Meropenem–EDTA therapy did not produce significant electrolyte disturbances compared to meropenem alone. The combination regimen was associated with a trend toward improved clinical recovery and reduced hospitalization duration, indicating its potential as a safe and effective therapeutic alternative in the management of septicemia

Keywords: Meropenem, EDTA, Septicemia, Electrolyte, infection, ICU..

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INTRODUCTION

Infections were the main cause of death throughout the eighteenth century. Although the primary purpose of antibiotics was to treat infections, they also significantly reduced the rates of morbidity and mortality. [1] Antibiotics are drugs that either kill or severely hinder the growth and reproduction of bacteria in order to treat bacterial infections in both people and animals. [2] Viral infections are

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unaffected by antibiotics. Included are sore throats, coughs, colds, and the flu. Minor bacterial infections are rarely treated with antibiotics. This is due to the fact that the immune system can typically get rid of them on its own. Antibiotics' pharmacology entails eliminating bacterial cells by either blocking cell renewal or disrupting critical cellular processes or activities. [3] Among the various ways that antibiotics work are by inhibiting the development of cell walls, increasing the permeability of cell membranes, and impairing protein synthesis, nucleic acid metabolism, and other metabolic processes (such as folate synthesis).[4] Fungi, viruses, and parasites can also develop resistance against the antimicrobial drug. With 700,000 people dying due to antimicrobial resistance (AMR) per year and every other 10 million people projected to die from it by 2050, AMR alone is killing more people than cancer and other diseases.[5] Excess use or misuse of antimicrobial drugs shows the antimicrobial resistance contributed by antimicrobial use in humans: India is positioned highest amongst all nations of the world in the overall intake of antibiotics for human use.[6] The availability of less priced antibiotics without a prescription, rising incomes, and poor public health indicators are coming together to provide the right conditions for the selection and spread of resistance genes on a wide scale in India. India is not fighting this struggle alone; the most current State of the World's Antibiotics Report (2015) defines the reports of other countries coping with antimicrobial resistance as well.[7] The emergence of resistant microbial pathogens threatens the efficacy of some antibiotics.[8] This is one of the most important worldwide health crises of the twenty-first century, along with many other significant problems. There is a growing discrepancy between the production of contemporary antibiotics and the clinical need for novel antibiotics. The challenge of discovering and introducing novel antibiotics to the market is growing.[9] Antibiotic resistance develops when antibiotics fail to kill or stop the growth of bacteria. As a result, bacterial infections become more difficult to treat.[10] Antibiotic-resistant infections cost a lot of money for the nation's already overburdened healthcare system. When first- and subsequently, second-line antibiotic therapy choices are scarce or unavailable, healthcare professionals may be obliged to utilize antibiotics that are more expensive and damaging to the patient. Research shows that individuals with resistant infections typically require longer hospital stays, more doctor visits, lengthier recoveries, and are more likely to experience long-term impairment even in the presence of successful therapies.[11] Antibiotic resistance is a challenging, if not unachievable, phenomenon that stems from the mechanism of action of antibiotics and the evolution of bacteria. Strategies can be used, nonetheless, to lessen resistance's emergence and effects. Adjuvant antibiotics provide such a method. These are the substances that, albeit having little or no active antibiotic properties of their own, function as antibiotic enhancers or resistance blockers. Therefore, the antibiotics given are combined with adjuvant and further classified into two groups: Class 1 agents which act on the pathogen, and class 2 agents which act on the host. Adjuvants offer an opportunity both to suppress the emergence of resistance and to rescue the effect of existing drugs.[12] Meropenem is a broad-spectrum carbapenem antibiotic that acts against gram-negative, gram-positive, and anaerobic bacteria. Like other carbapenems, meropenem is stable against chromosomal and extended-spectrum beta-lactamase. Meropenem is more stable to renal dehydropeptidase and does not require concomitant administration of a dehydropeptidase inhibitor such as cilastatin to achieve appropriate concentration.[13] Meropenem's ability to kill bacteria is due to its suppression of cell wall synthesis. Most Gram-positive and Gram-negative bacteria's cell walls are easily penetrated by meropenem, allowing it to access its penicillin-binding protein (PBP) targets. It has a substantial affinity for PBPs 1, 2, and 4 of Staphylococcus aureus as well as PBPs 2, 3, and 4 of Escherichia coli and Pseudomonas aeruginosa.[14] Meropenem when paired with EDTA may exhibit more potent antimicrobial activity against ESBL-producing pathogens than either meropenem or EDTA alone. EDTA has been confirmed to remove Mg2+ and Ca2+ ions from the outer cell wall of gram-negative bacteria, releasing up to 50% of the LPS molecules and exposing inner membrane phospholipids, thereby enhancing the effectiveness of the antimicrobial agent.[15]

MATERIALS AND METHOD

PARTICIPANTS

After reviewing the case records in Critical Care department, we concluded that the sample size of 60 for the study.

INCLUSION CRITERIA:

Patient from 18-70 years of age.
Both male and female.
Patient with presumed or confirmed sepsis, being treated with meropenem or meropenem-EDTA.
Patients should be admitted in critical care unit.

EXCLUSION CRITERIA:

Age ≤ 18 years.
Pregnant ladies
Immuno-compromised patient
CKD

METHODOLOGY

This study was performed based on prospective observational method. The patients with diseases falling in the category of presumed or confirmed septicemia with age criteria of above 18 years are taken into consideration and the role of both the drugs meropenem and meropenem + EDTA in treating the disorders and comparing their effects are involved in this study. All the required demographic details, vitals before and after the administration of drugs, the appearance of symptoms, and required laboratory investigations has been collected in the format of study proforma.

RESULTS

This study involved 30 subjects divided into two groups based on patients prescribed with meropenem (group 1) or meropenem-EDTA (group2)

Gender	No of patients	Percentage
Male	19	63.3%
Female	11	36.7%

Table 1: Distribution of patients according to gender

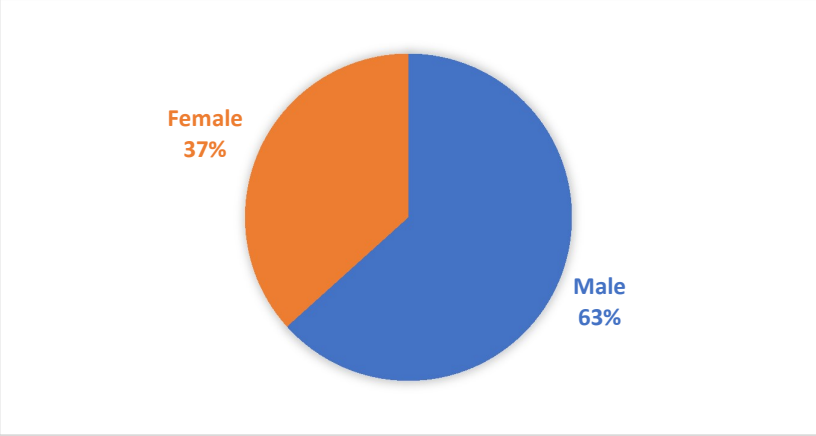

Fig 1: pie chart distribution according to gender

Fig-1 and **Table-1** shows the percentage distribution of gender in the study, out of which 36.7% where female and 63.3% were male.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group 1 (N=14)	Group 2 (N=15)	
	Median (IQR)	Median (IQR)	
Calcium (Baseline)	8.30 (7.55 to 8.9)	8.40 (7.7 to 8.85)	0.5000
	Group1 (N=11)	Group2 (N=15)	
Calcium (Follow up)	8.20 (7.95 to 8.9)	8.10 (7.95 to 8.6)	0.2659

Table 2: Comparison of Calcium at Baseline and Follow up with Study group in the study population.

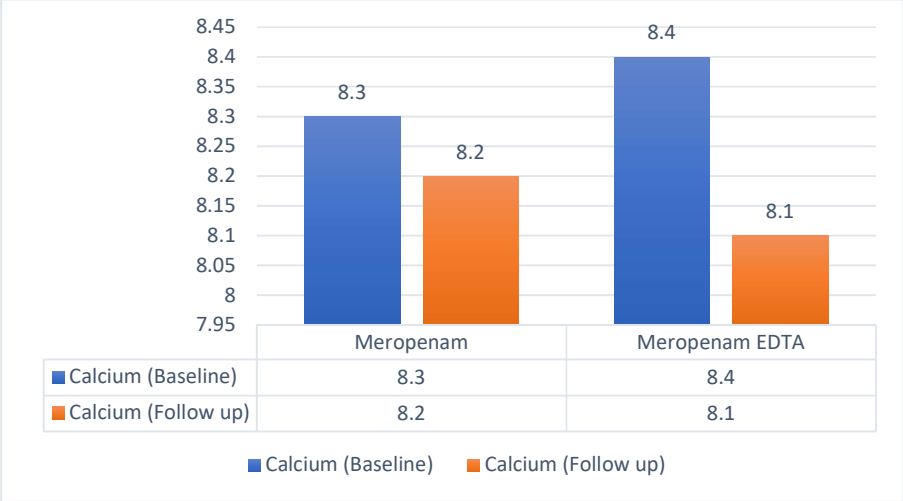

Fig 2: Effect of Meropenam Vs Meropenam EDTA on Calcium levels

Fig-2 and **Table-2** illustrates the median calcium (follow up) within Group 1 was 8.20(7.95 to 8.9) and within group 2 was 8.10(7.95 to 8.6). The median difference of calcium (post) in
study groups were found to be statistically not significant with P value 0.2659.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group1 (N=15)	Group2 (N=15)	
	Median (IQR)	Median (IQR)	
cCa (Baseline)	1.16(1.1 to 1.19)	1.18(1.1 to 1.2)	0.3310
cCa (Follow up)	1.16(1.11 to 1.23)	1.15(1.12 to 1.16)	0.2334

Table 3: Comparison of ionized calcium at Baseline and Follow up with Study group

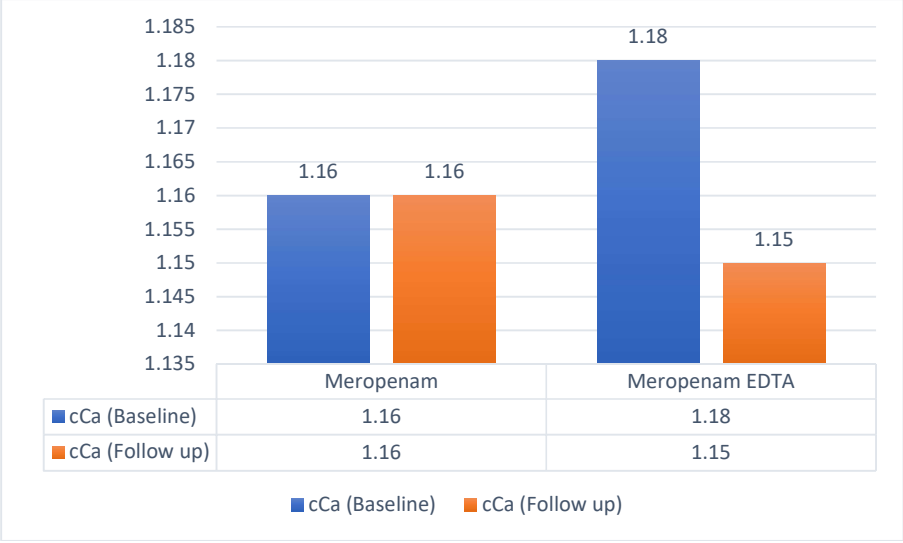

Fig 3: Effects of Meropenam Vs Meropenam EDTA on Ionised Calcium

Fig-3 and **Table-3** shows the median ionized calcium (follow up) within Group 1 was 1.16(1.11 to 1.23) and within group 2 was 1.15(1.12 to 1.16). The median difference of ionized calcium (follow up) in study groups was statistically not significant with P value 0.2334.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group1 (N=13)	Group2 (N=15)	
	Median (IQR)	Median (IQR)	
Magnesium (Baseline)	1.80(1.69 to 2.0)	1.90(1.75 to 2.05)	0.2730
	Group1 (N=9)	**Group2 (N=15)**	
Magnesium (Follow up)	1.70(1.6 to 2.0)	1.70(1.7 to 2.1)	0.2353

Table 4: Comparison of Serum magnesium at baseline and follow up with Study group

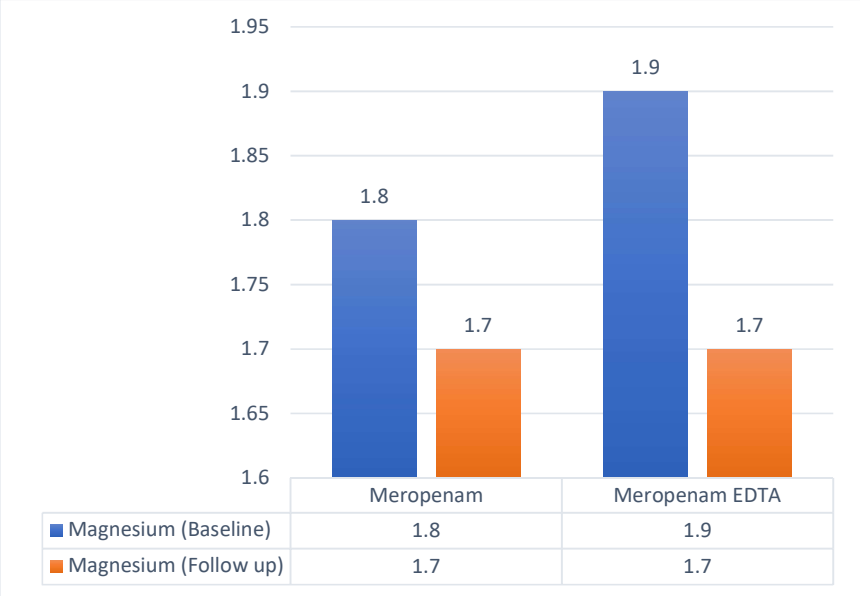

Fig 4: Impact of Meropenam Vs Meropenam EDTA on Magnesium levels

Fig-4 and **Table-4** shows the median Magnesium (follow up) within Group 1 was 1.70(1.6 to 2.0) and within group 2 was 1.70(1.7 to 2.1). The median difference of magnesium (follow up) in study groups was statistically not significant with P value 0.2353.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Median (IQR)	Median (IQR)	
	Group1(N=9)	Group2(N=7)	
Phosphorus (Baseline)	4.30(2.9 to 4.7)	3.20(2.25 to 4.25)	0.2135
	Group1(N=5)	**Group2(N=2)**	
Phosphorus (Follow up)	4.00(2.3 to 5.6)	2.90(2.45 to 3.35)	0.2806

Table 5: Comparison of Phosphorus at baseline and follow up with Study group

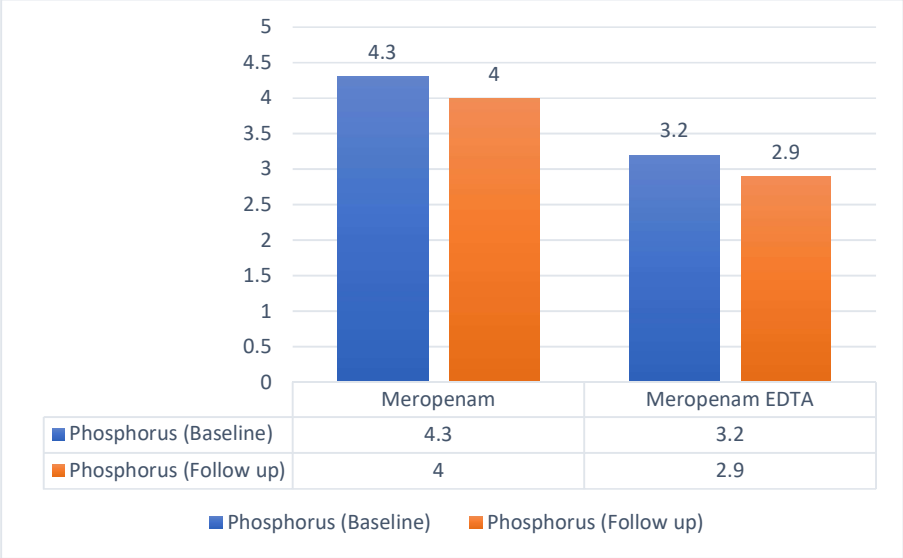

Fig 5: Effect of Meropenam Meropenam on Phosphorus levels

Fig-5 and **Table-5** illustrates the median Phosphorus (follow up) within Group 1 was 4.00 (2.3 to 5.6) and within group 2 was 2.90(2.45 to 3.35). The median difference of Phosphorus (follow up) in study groups was statistically not significant with P value 0.2806.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group1 (N=15)	Group2 (N=15)	
	Median (IQR)	Median (IQR)	
Potassium (Baseline)	4.10(3.55 to 4.55)	4.10(3.8 to 4.45)	0.4339
Potassium (Follow up)	3.40(3.2 to 3.65)	3.70(3.4 to 4.3)	0.0754

Table 6: Comparison of Potassium (K+) at Baseline and Follow up with Study group in the study population.

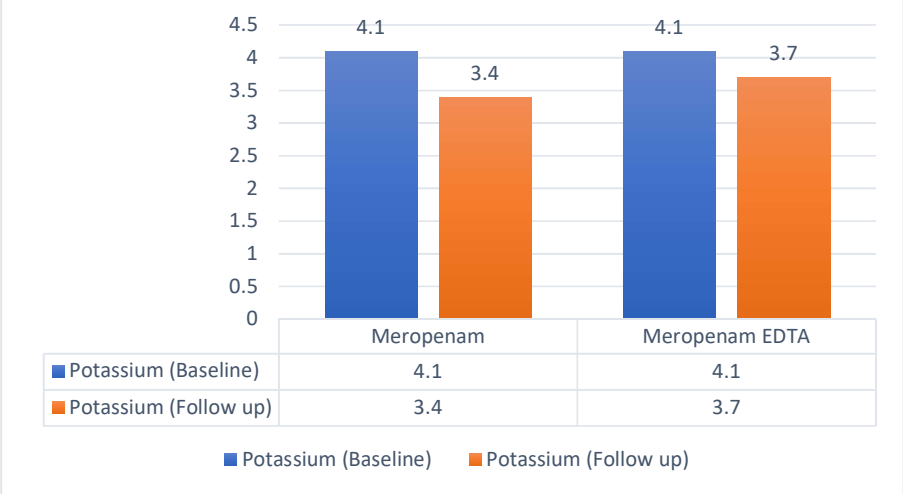

Fig 6: Effects of Meropenam Vs Meropenam EDTA on Potassium levels

Fig-6 and **Table-6** shows the median Potassium (follow up) within Group 1 was 3.40(3.2 to 3.65) and within group 2 was 3.70(3.4 to 4.3). The median difference of Potassium (follow up) in study groups was statistically not significant with P value 0.0754.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group1(N=15)	Group2(N=15)	
	Median (IQR)	Median (IQR)	
cK (Baseline)	4.30(3.76 to 4.66)	4.20(3.9 to 4.5)	0.4917
cK (Follow up)	3.40(2.95 to 3.8)	3.50(3.4 to 4.1)	0.1399

Table 7: Comparison of ionized potassium at Baseline and Follow up with Study group

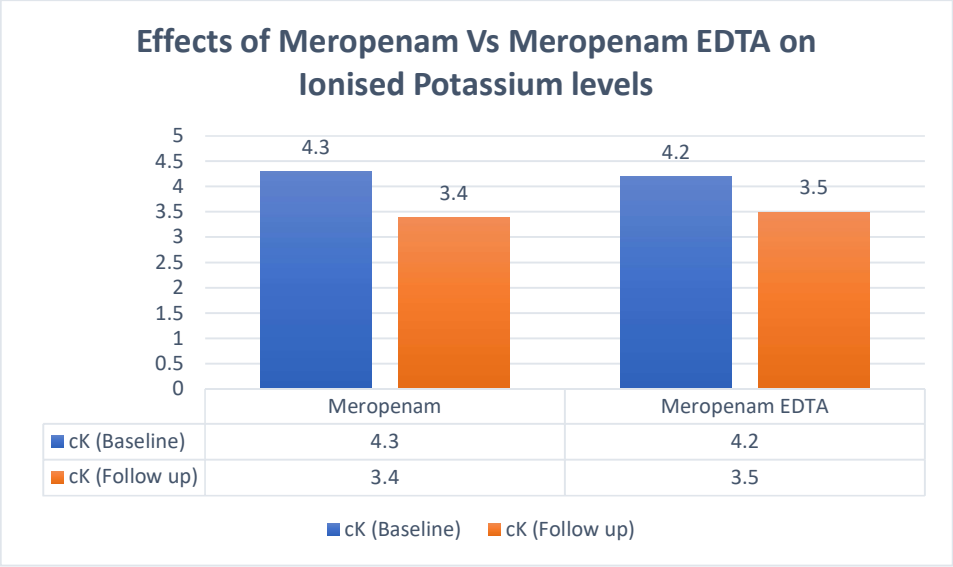

Fig 7: Effects of Meropenam Vs Meropenam EDTA on Ionised Potassium levels

Fig-7 and **Table-7** illustrates the median ionized potassium (follow up) within Group 1 was 3.40(2.95 to 3.8) and within group 2 was 3.50(3.4 to 4.1). The median difference of ionized potassium (follow up) in study groups was statistically not significant with P value 0.1399.

Parameter	Study groups		P Value (Mann Whitney U Test)
	Group1 (N=15)	Group2 (N=15)	
	Median (IQR)	Median (IQR)	
Total leucocyte count (Baseline)	14900.00(10550.0-25300.0)	18300.00(11300.0- 22650.0)	0.3165
Total leucocyte count (Follow up)	12800.00(7600.0 to 14450.0)	12000.00(10100.0- 15100.0)	0.4669

Table 8: Comparison of Total leucocyte count (TLC) at Baseline and Follow up with Study group.

Table-8 Illustrates the median total leucocyte count (follow up) within Group 1 was12800.00(7600.0 to 14450.0) and within group 2 was 12000.00(10100.0 to 15100.0). The median difference of total leucocyte count (follow up) in study groups was statistically not significant with P value 0.4669.

Study groups	Mean hospital stays (Days)	Percentage
Group 1	10.73	58%

Group 2	7.93	42%

Table 9: Comparison of Hospital stay (in days) with Study group in the study population.

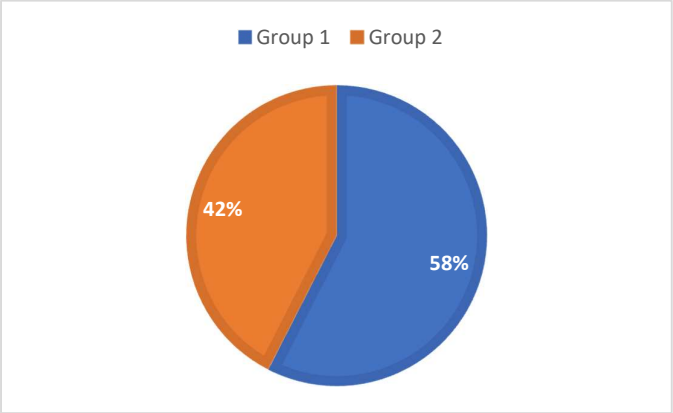

Fig 8: Pie chart distribution of mean hospital stays

Table-9 and **Fig-8** present the comparison of hospital stay (in days) between the two study groups, demonstrating that patients in **Group 2** required a significantly shorter hospital stay than those in **Group 1.**

DISCUSSION

India is one among the largest consumers of antibiotics, as such many cases have been reported of resistance to gram negative bacteria. The emergence of resistant microbial pathogens threatens the efficacy of some antibiotics.[16] A broad-spectrum beta-lactam antibiotic called meropenem is used in health facilities to treat life-threatening infections. It is frequently employed in the targeted therapy of multidrug-resistant gram-negative bacteria, additionally, the empiric treatment of sepsis or complex infections.[17] A comparative study on two drugs that are commonly prescribed in treating septicemia was performed in tertiary care hospitals to observe their effects on serum electrolytes and hematological parameters.

In our prospective observational study, over 6 months, we observed 30 cases of patients suffering from septicemia. During the study, the following parameters were observed, and any changes found were recorded after administration of drugs. For our study, we selected the mostly prescribed drugs for septicemia which are meropenem and meropenem EDTA and the changes in the below parameters were observed-

In patients who are receiving with meropenem EDTA, a minor drop in calcium levels on serum and ABG is shown, however in patients who are categorized as group-1 receiving meropenem, no such decrease was seen in comparison to meropenem EDTA. According to a statistical analysis that is insignificant. When meropenem EDTA is used excessively, it might cause hypocalcemia as opposed to meropenem.

According to the study, taking meropenem EDTA causes a reduction in certain individuals' magnesium levels. By the statistical analysis, P value is insignificant. The meropenem EDTA does not impact serum magnesium levels.

By analyzing the median phosphorus values in the study groups, we found that in group-2 there is some minor decreased in the phosphorus levels compared to group-1. Highly use of meropenem EDTA can lead to decrease the phosphorus level in serum.

A slight decreased in potassium levels on serum and ABG in both groups. However, meropenem EDTA had a lesser impact on serum and ionized potassium compared with meropenem.

After observing the Total Leucocyte count it shows that there is more decreased TLC level in group-2 compared to group-1. This indicates that meropenem EDTA shows more effectiveness in the treating bacterial infection.

By comparing both the groups, it is observed that patients grouped under meropenem EDTA are required to stay in the hospital for a low duration of time.

LIMITATIONS

The allotted study duration and sample size was limited and brief.

The patients with the disease- Septicaemia were found to be very low compared with other infectious and communicable diseases which are very regular and large.

The reliability of these findings cannot be assumed to apply to the community at large.

The patient`s database was used exclusively for the maintenance of laboratory values, any flaws in the patient`s database could lead to less accurate values.

Due to a lack of communication with the patients after they are discharged, a small number of cases were not followed up further.

CONCLUSION

It is concluded from the study that the impact of meropenem EDTA on serum and ionized electrolyte showed minor decrease in the calcium level and didn't have any impact on the magnesium or potassium levels. Meropenem EDTA showed slight decrease in the Total Leucocyte Count. By comparing the two groups of meropenem and meropenem EDTA, it was shown that meropenem needed a hospital stay

of 58% and meropenem EDTA needed a hospital stay of 42%. This indicates that in Septicemia patients, Meropenem EDTA requires a shorter hospital stay than meropenem. Therefore, its concluded that **Meropenem EDTA** is considered to be **better** compared to meropenem in **Septicemia**.

Ethical approval
The present study was conducted in compliance with the Helsinki Declaration and received approval from the Ethics Committee at the Dept of Lab Medicine, CARE Hospital, In-Patient Building, Ground Floor, Road No. 1, Banjara Hills, Hyderabad- 500034 (Ref. no. IEC/CARE/21461/2023/PharmD).

Conflict of interest
The authors declare no conflict of interest.

Ethical statements
The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that written/verbal informed consent was obtained from the participants enrolled in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Use of AI
In order to improve the structure of two sections of the article and check the text's grammar, the authors employed an AI tool during the preparation of this work. The authors then accepted full responsibility for the publication's content and reviewed and edited it as necessary.

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Data availability
All data used are referenced or included in the article.

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