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Research Article

Non-Nutritional Sodium and Carbapenems Associated Hypernatraemia Significance in Infected Mal-Nourished Patients Who Are On Parenteral Nutrition Support

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Abstract: ***Objectives*****:** Non-nutritional sources of sodium are commonly encountered in hospitalized patients who are used carbapenems to treat non-carbapenemase producing multi-drug resistant gram-negative bacteria. Meropenem and Imipenem/Cilastatin are the most two widely used carbapenems in most medical centers including our institution. The non-nutritional sources of sodium from both tested carbapenems may have a detrimental effect on critically ill patient's organ functions and may be an independent risk factor for mortality. The primary objective of our study is to investigate the significance difference of non-nutritional associated hypernatremia (NNAH) risk between Meropenem (Group I) versus Imipenem/Cilastatin (Group II). ***Methods*****:** Our study was retrospectively carried out for critically ill patients admitted to King Hussein Medical Hospital (KHMH) wards between April 2017 and Dec 2019 Patients were excluded if they discharged or died before completed 2 days of the tested ABs during their admission. Collected continuous data were analyzed using Independent T-Test while Chi Square Test were used for dichotomous data analysis and to determine the NNAH risk in both tested groups. Corrected sodium level (cNa^+) level of 145 mEq/l will be considered the cutoff point for hypernatremia. ***Results:*** The mean overall age was 59.62±1.59 years, and 57 subjects (71.25%) were male. The overall risk of NNAH was 5.1% (4 patients). Critically ill patients who were on Meropenem had the highest risk of NNAH (7.9%, 3 patients) contrast on Imipenem /Cilastatin (2.4%, 1 patient).***Conclusion*****:** Our results demonstrate that empirical or targeted use of β-lactam Carbapenems either Meropenem or Imipenem/Cilastatin is an independent risk of NNAH especially in case of high dose Meropenem.

Keywords: Carbapenems; Non-Nutritional Associated Hypernatremia; Infected Mal-Nourished patients; Parenteral Nutrition Support

INTRODUCTION

In hospitalized patients, hypernatremia is less common and less studied than hyponatremia also its very dangerous and poor prognosis, the development of it about (1% - 2%).[1-3] One study showed that 2.6% observed hypernatremia during hospitalized and 61% from observed cases were acquired.[4] In contrast, hypernatremia is more common in critically ill patients with a prevalence of (2% to 6%) upon admission and (4% to 10%) for surgical ICU patients or (6% to 26%) for medical ICU patients attributed to the administration of hypertonic solutions, resuscitation crystalloids, irrigation solutions, enteral and parenteral feeding, maintenance crystalloids fluids, and administration of sodium-rich antibiotics.[5-8] Meropenem and Imipenem/Cilastatin are formulated with sodium carbonate to control the pH of solution in which the sodium load per gram is 3.92 mEq/g for Meropenem and 3.2 mEq/g for Imipenem/Cilastatin.[9-10] The consequences of this carbapenems-associated hypernatremia, as a non-nutritional sources of sodium, may have detrimental effects on infected critically ill patient's organ functions and may be an independent risk factor for mortality. The objective of this study is to investigate the clinically significance of carbapenems associated hypernatremia in the two most widely used

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carbapenems, Meropenem **(Group I)** and Imipenem/ Cilastatin **(Group II),** in critically ill patients on total or partial parenteral nutrition who are infected with carbapenems-sensitive multi-drug resistant gram-negative bacteria.

METHODS

Study design and setting

The study protocol was approved by our Institutional Review Board (IRB), we design it as observational retrospective cohort study in single center, the department of adult ICU of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan to investigate the significance difference of non-nutritional associated hypernatremia (NNAH) risk between Meropenem (Group I) versus Imipenem/Cilastatin (Group II)., it included critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem. Flow chart of critically ill patient's selection and data collection process is fully illustrated in **Figure 1.**

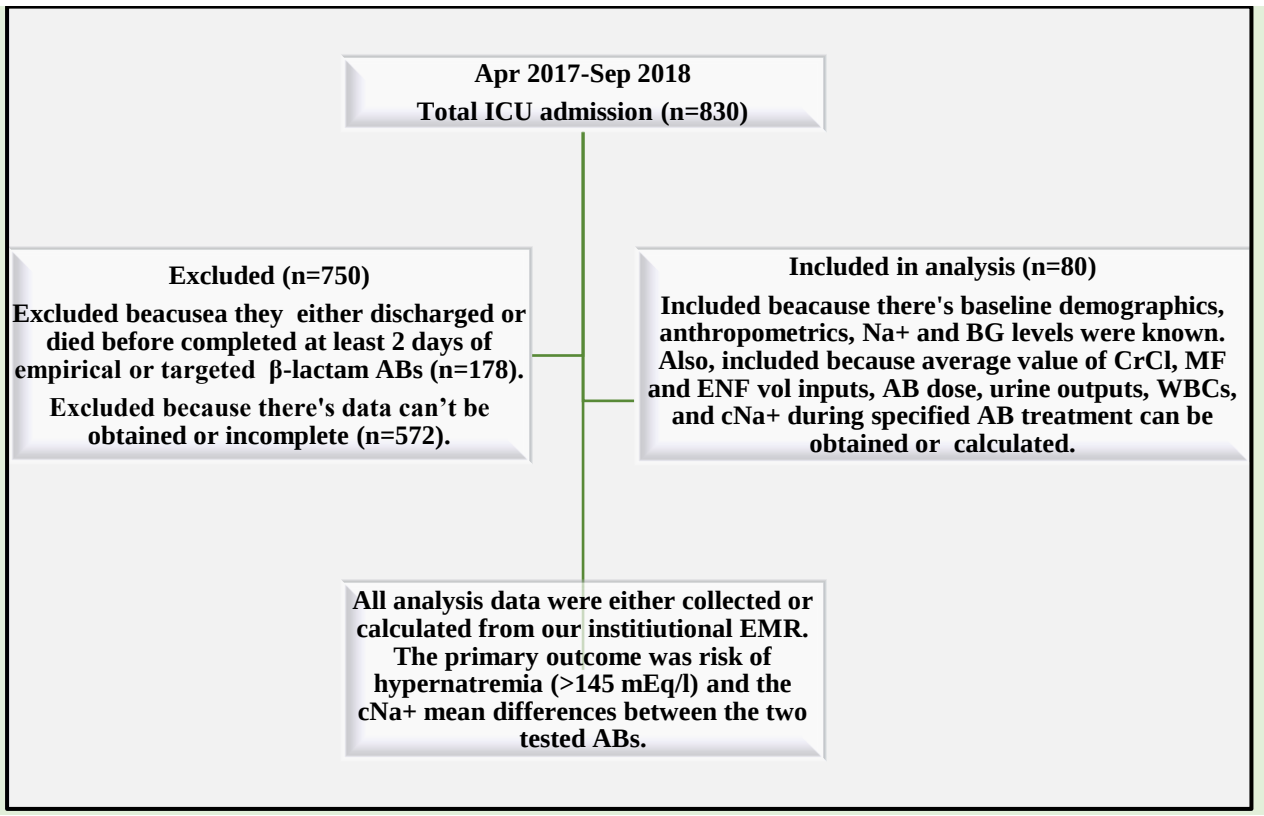

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April. ABs: Antibiotics. CrCl: Creatinine clearance.
Sep: September. Na+: Sodium. MF: Maintenance fluid.

Statistical analysis

Independent T-Test was used to analyzed the desired outcomes of the two groups data by compare the Mean±SD of independent variables among two tested groups. In case of gender (male or female) and risk of NNAH were presented as number (percentage) using chi square analysis. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

The mean overall age was 59.62±1.59 years, and 57 subjects (71.25%) were male. The overall risk of NNAH was 5.1% (4 patients). Critically ill patients who were on Meropenem had the highest risk of NNAH (7.9%, 3 patients) contrast on Imipenem /Cilastatin (2.4%, 1 patient). The mean difference of corrected average sodium levels (cNa^{+}_{avg}) was significant between two tested groups with Mean differences±SEM of 1.42±0.21 mEq/l. Demographics, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarized in **Table 1.**

Table-1. Demographics, anthropometrics, and follow-up comparison data of the study's critically ill patients

Dependent Variable		Group I N=38 Mean±SD	Group II N=42 Mean±SD	Total N=80 Mean±SD	*P*-Value
Age (Yrs)		57.79±1.46	61.45±1.73	59.62±1.59	0.056 (NS)
Gender	Male	27 (71.1%)	30 (71.4%)	57 (71.25%)	0.284 (NS)
	Female	11 (28.9%)	12 (28.6%)	23 (28.75%)	
BW_0 (Kg)		78.16±1.70	74.21±1.44	76.19±1.57	0.003 (S)
BMI_0 (Kg/m^2)		28.04±0.52	26.02±0.59	27.03±0.55	0.000 (S)
Na^+_0 (mEq/l)		138.08±0.17	137.97±0.12	138.03±0.145	0.404 (NS)
BG_0 (mg/dl)		148.50±1.43	176.14±1.29	162.32±1.36	0.000 (S)
c Na^+_0 (mEq/l)		138.85±0.17	139.19±0.12	139.02±0.145	0.090 (NS)
$WBCs_{avg}$ (Cells/µl)		11152±1851	9883±1254	10517.5±1552.3	0.640 (NS)
$CrCl_{avg}$ (ml/min)		51.07±7.58	55.06±7.52	53.065±7.55	0.332 (NS)
Urine $Output_{avg}$ (ml/d)		865.5±73.1	884.9±73.2	875±73.15	0.203(NS)
AB $Dose_{avg}$ (mg/d)		4158±263	1976±117	3067±190	0.000 (S)
AB $Duration_{avg}$ (Days)		7.55±0.58	7.26±0.49	7.40±0535	0.732 (NS)
AB Na+ $Input_{avg}$ (mEq/d)		16.29±1.03	6.32±0.37	11.31±0.7	0.000 (S)
MF vol_{avg} (ml/d)		2904±8	2899±6	2901±7	0.405 (NS)
MF Na+ $Input_{avg}$ (mEq/d)		223.59±0.66	223.19±0.47	228.39±0.89	0.406 (NS)
ENF Vol_{avg} (ml/d)		407.6±15.5	403.1±15.1	405.2±15.3	0.171 (NS)
ENF Na+ $Input_{avg}$ (mEq/d)		14.88±0.57	14.71±0.55	14.79±0.56	0.171 (NS)
Na^+_{avg} (mEq/l)		142.63±0.17	141.23±0.12	141.93±0.145	0.000 (S)
BG_{avg} (mg/dl)		162.97±3.25	162.43±1.81	162.7±2.53	0.011 (S)
c Na^+_{avg} (mEq/l)		143.31±0.17	141.89±0.12	142.6±0.145	0.000 (S)
Risk of AAH	Positive (>145 mEq/l)	3 (7.9%))	1 (2.4%)	4 (5.1%)	0.000 (S)
	Negative (≤145 mEq/l)	35 (92.1%)	41 (97.6%)	76 (94.9%)	
ALB $level_{avg}$ (g/dl)		2.63±0.02	2.66±0.02	2.645±0.02	0.006 (S)
H.ALB infused avg (g/d)		19.47±0.37	19.52±0.33	19.5±0.35	0.510 (NS)

Data are analyzed by either Independent T-Test and presented as Mean±SD or Chi Square Test and presented as Number (%) (at p-value< 0.05).
Group I: Critically ill patients who were on Meropenem (Meronem®).
Group II: Critically ill patients who were on Imipenem/Cilastatin (Tienam®).

S: Significant.
IBW: Ideal body weight.
BMI: Body mass index.
AB: Specified antibiotic.
AAH: Antibiotic associated hypernatremia.
Na^+: Sodium.
ALB: Albumin.
0: Baseline dependent variable before intervention.
CrCl: Creatinine clearance.
NS: Non-significant.
BW: Body weight.
BG: Blood glucose.
MF: Maintenance fluid.
H.ALB: Human albumin 20% IV.
cNa^+: Corrected sodium.
Avg: Average during antibiotic administration.
ENF: Enteral nutritional formula (Ensure® in this study).
WBCs: White blood cells.

DISCUSSION

The present study included septic mechanically ventilated critically ill patients who were taking either empirical or targeted Carbapenems ABs for at least 2 days at overall duration of 7.40±0.27 days. Because the major sources of Na^+ inputs in this study were maintenance fluid (MF), enteral nutritional formula (ENF), human albumin (H.ALB), and broad spectrum β-lactam ABs and there were insignificant differences between the two groups regarding average MFs, ENFs, and H.ALB, the significant changes in Na^+ during antibiotics administration were likely from β-lactam ABs. Meropenem **(Group I)** has the highest Na^+ load than Imipenem/Cilastatin **(Group II).**

In our study we showed that the greatest impact of NNAH was more in Meropenem studied

critically ill patients (Group I) compared with Imipenem/Cilastatin studied critically ill patients (Group II). These results can be explained by the high variability of AB renal adjusted dose inputs, which was highest in Group I (4158±263 mg AB/day) than Group II (1976±117 mg AB/day) and by higher sodium load per gram in Meropenem vs Imipenem/Cilastatin (3.92 mEq/g vs 3.2 mEq/g, respectively). To calculate AB Na^+ input (mEq Na^+/day), we multiplied AB Na^+ load (mEq Na^+ /g AB) by AB dose input (g AB/day). The AB Na^+ input in our study was significantly higher in Group I (16.29±1.03 mEq Na^+/day) than Group II (6.32±0.37 mEq Na^+/day).

CONCLUSION

In summary, our results demonstrate that empirical or targeted use of β-lactam Carbapenems is an independent risk of NNAH especially in case of high dose Meropenem (2 g TID) for treatment carbapenem sensitive multi-drug resistant gram-negative bacteria. This study is limited by its retrospective design, using single-center data, including only ICU patients. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

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Conflicts of interest: None declared.

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