A PROSPECTIVE STUDY ON CORRELATION OF HYPERCHLOREMIA WITH MORTALITY IN INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL.

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Abstract

Introduction :

Serum chloride (Cl−) is a crucial extracellular anion with significant medical importance. Hypochloremia has been identified as an autonomous predictor of mortality based on emerging evidence gathered from patients diagnosed with kidney or heart disease. However, an overabundance of chloride ions (Cl−) can lead to fatality in critically unwell individuals. The objective of the research was to assess the frequency of hyperchloremia among deceased patients, with the aim of modifying our clinical approach by replacing chloride-rich solutions with solutions containing appropriate chloride levels (such as lactated ringer or plasmalyte) to prevent this iatrogenic complication. This may have potential benefits for our patients in the future.

Methods :

This prospective study was conducted at the Indira Gandhi Institute of Medical Sciences, Patna over a period of one year, from October 2021 to November 2022. This study comprised a sample size of 100 patients who were classified into two distinct groups based on their medical diagnosis.

Results:

The study's findings indicate that among the Non sepsis Groups, patients aged <=40 years accounted for 16.0% of the sample, while patients aged 41-60 years accounted for 30.0%, patients aged 61-80 years accounted for 46.0%, and patients aged >80 years accounted for 8.0%. The findings of the study indicate that there was no statistically significant variance in the average Chloride Value across the various time intervals.

Conclusion :

The administration of chloride-rich solutions in ICU patients necessitating large volume fluid resuscitation should be approached with caution to mitigate the effects of hyperchloremia.

Keywords: Serum chloride, extracellular anions, heart disease, hypochloremia, Submitted: 2023-06-26 Accepted: 2023-06-27

1. Introduction:

Chloride is a vital and abundant anion present in the extracellular fluid, which contributes approximately 33% of the fluid's tonicity [1]. Chloride plays a crucial role in numerous physiologically significant functions within the human body, such as maintaining acid-base balance, regulating the immune system, facilitating osmosis, and enabling proper muscle function [2]. The principal

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function of chloride in the human body is to maintain the acid-base equilibrium. The chloride levels exhibit an inverse relationship with bicarbonate, which is considered to be the principal buffering agent in the human physiological system. The alteration of chloride levels in the body has a significant impact on the acid-base equilibrium, leading to metabolic acidosis and metabolic alkalosis when decreased or increased, respectively, in the absence of an anion gap.

Chloride plays a dual role in the gastrointestinal tract. Firstly, it is secreted as a constituent of hydrochloric acid in the stomach, which assists in the digestion of proteins, inhibits the proliferation of microorganisms, and promotes the absorption of specific essential nutrients and minerals. Secondly, it sustains the osmotic gradient and fluid secretion in the gastrointestinal tract. Chloride ions have been found to exert significant influence on the process of oxygen unloading from haemoglobin, as well as on the regulation of the immune system and the maintenance of cardiovascular stability.

The homeostasis of serum chloride levels is predominantly regulated by the renal and gastrointestinal systems. Dyschloremia, an electrolyte disturbance characterised by an abnormal serum chloride concentration, is frequently observed in patients admitted to the intensive care unit (ICU) who are undergoing intravenous fluid therapy or diuretic treatment. Hyperchloremia is a relatively more common electrolyte disturbance than hypochloremia among patients admitted to the intensive care unit (ICU). Despite its physiological significance, chloride has been a relatively understudied ion in the medical field until recent years [3]. However, the discovery of a correlation between chloride-rich solutions and hyperchloremia metabolic acidosis has brought attention to this topic [4,5]. The medical condition of elevated chloride levels in the blood, known as hyperchloremia, has been documented to have a significant impact on short-term mortality rates following non-cardiac surgical procedures, as evidenced by multiple academic studies [6,7].

Physiological saline, which contains 0.9% sodium chloride, is a commonly employed chloride-rich solution in medical settings, particularly for patients who are critically ill or undergoing preoperative procedures. In contrast to its nomenclature, the 0.9% saline solution is deemed as atypical and non-neutral in the medical and academic spheres [8]. In comparison to plasma, its chloride concentration is higher than the physiological range (154 vs. 100 mEq/L, respectively) as reported in medical literature. The administration of a chloride-rich solution in a liberal manner can result in the development of hyperchloremic metabolic acidosis in critically ill patients, as evidenced by medical research [11,12]. This condition can lead to a range of adverse effects [13,14], particularly in patients who are experiencing severe sepsis and septic shock [15]. The association between elevated chloride levels and the development of acute kidney injury in patients admitted to the intensive care unit has been established. Additionally, the presence of severe acidosis can impede the effectiveness of inotropic agents and result in cardiovascular collapse. The deleterious consequences of hyperchloremia are associated with a rise in mortality rates. In the phase of salvage for septic shock, patients who are critically ill and septic are commonly subjected to 0.9% saline, which puts them at risk for hyperchloremic metabolic acidosis and other unfavourable outcomes of hyperchloremia during the post-resuscitation phase. Observational studies examining the correlation between hyperchloremia and hospital mortality have yielded inconsistent results and have included a limited sample size of septic patients in the intensive care unit [16-18].

In our intensive care unit (ICU), isotonic saline solution (0.9% NaCl) is routinely administered for fluid resuscitation of patients. The objective of the research was to investigate the frequency of hyperchloremia in postmortem patients, with the aim of modifying our clinical approach by opting for solutions with chloride levels within acceptable limits (such as lactated ringer or plasmalyte) instead of chloride-rich solutions, in order to prevent this iatrogenic complication and potentially enhance patient outcomes.

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2. Methods:

2.1. Study Design:

The prospective study was carried out at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India within a year from October 2021 to November 2022.

2.2. Methodology:

The demographic characteristics including age, sex, and body mass index (BMI) were documented, along with the aetiology of intensive care unit (ICU) admission and mortality. The study participants were classified into two distinct cohorts based on their medical diagnosis. 27 Group-I: Individuals with a medical diagnosis of sepsis or septic shock. Group-II: Individuals with a medical diagnosis that differs from sepsis. After death of patients we were find out from their medical records the serum chloride levels of last 5 days and correlate their relation with death. The nature and aggregate volume of fluid administered in the intensive care unit over the past five days were also documented.

2.3. Sample Size:

Patients were enrolled in this study.

2.4. Inclusion criteria:

Patient ≥8 years of age of either sex who died in ICU after minimum 3 days of ICU admission, irrespective of etiology.
Receiving intravenous fluid.

2.5. Exclusion criteria:

Patients transferred from another ICU
Patient on dialysis
Patient requiring plasmapheresis
Patients having creatinine level at admission>1.3mg/dL
Non-consenting patient

2.6. Statistical analysis:

All the data were analyzed using SPSS package (Stata, version 26.0 SPSS INC, Chicago, IL, USA) for windows. The data were presented as descriptive statistics for continuous variables and percentage for categorical variables and was subjected Chi-square test, ANOVA test and t test. Other values were represented in number, proportions (%) and mean ± SD.

3. Results:

Only 100 of the 170 patients initially enrolled in this study met the inclusion criteria and comprised the study's sample population. Patients in the investigation were evenly divided into two groups, Nonsepsis and Sepsis. 50% of patients were found in the Nonsepsis Group and the Sepsis Group, respectively.

The table 1 compares the age distribution of patients participating in the investigation between two groups. Under Non-sepsis Groups, it was observed that 16.0% of the patients were aged =40 years, 30.0% of the patients were aged 41-60 years, 46.0% of the patients were aged 61-80 years, and 8.0% of the patients were aged >80 years. Similarly, under Sepsis Groups, it was observed that 22.0% of the patients were aged =40 years, 56.0% of the patients were aged 41-60 years, 14.0% of the patients were aged 61-80 years, and 8.0% of the patients were aged >80 years. Moreover, it was observed that the distribution of patients by age group differed significantly between the two categories (p = 0.005).

The comparison of two groups' ages. It was observed that the mean age of non-sepsis groups was 58.80 19.20 years, whereas the mean age of sepsis groups was 53.60 15.72 years. Moreover, it was observed that there was a statistically significant difference in the mean age of patients between the two categories (p = 0.042). The preceding table and graph compare the Weight between two categories. The non-sepsis groups had a mean weight of 58.18 6.75 kg while the sepsis groups had a mean weight of 56.64 8.33 kg. Moreover, there was no statistically significant difference in the

Table 1: Age group distribution of patients

Age Groups	Non sepsis Frequency	%	Sepsis Frequency	%	p value
<=40 yrs	8	16.0%	11	22.0%	
41 - 60 yrs	15	30.0%	28	56.0%	
61 - 80 yrs	23	46.0%	7	14.0%	0.005
>80 yrs	4	8.0%	4	8.0%	
Total	50	100%	50	100%	

mean weight of patients between the two groups (p = 0.260).

The comparison of chloride values between two groups at various time points is shown in Table 2. In addition, there was no significant difference in the mean Chloride Value on the Day of Death (p = 0.774), 1 Day Before Death (p = 0.832), 2 Day Before Death (p = 0.945), 3 Day Before Death (p = 0.554), or 4 Day Before Death (p = 0.926) between the two groups.

The Chloride Value at different time intervals for the Non-Sepsis Group. It was observed that the mean chloride value on the day of death was 105.93 11.45, whereas it was 105.15 9.74 one day before death, 104.95 9.90 two days before death, 106.20 7.85 three days before death, and 106.55 6.12 four days before death. Further, it was observed that there was no discernible trend in Chloride concentrations.

The pairwise comparison of Chloride levels across multiple time points in the Non-Sepsis Group. Observations revealed that there was no significant difference in mean Chloride Value between any two time points. Table 3 displays the Chloride Value at various time intervals for the Sepsis Group. It was observed that the mean chloride value on the day of death was 105.31 9.82, whereas it was 104.73 10.10 one day before death, 104.83 7.34 two days before death, 107.14 7.75 three days before death, and 106.43 7.04 four days before death. In addition, a significant trend was observed in the Chloride values (p value < 0.001).

The pair-wise comparison of Chloride concentrations at various time intervals for the Sepsis Group. It was observed that the Chloride Value was substantially higher at 2 days before death compared to 3 days before death (p = 0.046). Comparison of Fluid Type Administered (i.e., NS and RL) between Two Groups at Various Time Points. Comparing the two groups, it was found that there was no significant difference in the mean Type of Fluid administered (i.e. NS and RL) on the Day of Death (p = 0.414), 1 Day Before Death (p = 0.414), 2 Day Before Death (p = 0.192), 3 Day Before Death (p = 0.534), and 4 Day Before Death (p = 0.576).

The Comparison of Fluid Amount Administered to Two Groups at Different Times. Further, there was no significant difference in the mean amount of fluid administered (i.e. NS and RL) on the Day of Death (p = 0.568), 1 Day Before Death (p = 0.348), 2 Day Before Death (p = 0.901), 3 Day Before Death (p = 0.345), or 4 Day Before Death (p = 0.134) when comparing the two groups. the Quantity of Fluid at Different Time Points in the Non-Sepsis Group. It was observed that the mean amount of fluid on the day of death was 1958.00±78.48, whereas it was 1759.18 ± 122.34 one day before death, 1773.47 ± 99.53 two days before death, 1777.55± 134.27 three days before death, and 1783.67± 144.84 four days before death. In addition, a significant trend was observed in the amount of fluid used in the non-sepsis group. (p value <0.001).

A pair-wise comparison of the Amount of Fluid at various time points within the Non-Sepsis Group. It was observed that the Amount of Fluid on the Day of Death was substantially greater than a) 1 Day Before Death, b) 2 Day Before Death, c) 3 Day Before Death, and d) 4 Day Before Death (p value 0.001).

The Quantity of Fluid at Various Times within

Table 2: **Mean difference of Sepsis with Day of death**

Chloride Value	Non sepsis (n=50)			Sepsis (n=50)			p value
	Mean ± SD	Min - Max	Median (IQR)	Mean ± SD	Min - Max	Median (IQR)	
Day of Death	105.93 ± 11.45	77 - 143	104 (100 - 112.25)	105.31 ± 9.82	81.5 - 128.0	105 (100 - 112)	0.774
1 Day Before Death	105.15 ± 9.74	85 - 129	105 (97.50 - 111)	104.73 ± 10.10	80 - 126	106.50 (98 - 110)	0.832
2 Day Before Death	104.95 ± 9.90	84 - 137	103 (99.50 - 110)	104.83 ± 7.34	83 - 120	105 (101.50 - 109)	0.945
3 Day Before Death	106.20 ± 7.85	80 - 128	107 (103 - 109.50)	107.14 ± 7.75	85.0 - 123.6	107 (103.75 - 111)	0.554
4 Day Before Death	106.55 ± 6.12	90 - 123	107 (102.50 - 110)	106.43 ± 7.04	85 - 118	108 (102 - 110)	0.926

Table 3: **Mean difference between 1st Day before Death, 2nd Day before Death, 3rd Day before Death and 4th Day before Death**

Chloride Value	n	Mean ± SD	p value
Day of Death	50	105.31 ± 9.82	
1 Day Before Death	50	104.73 ± 10.10	
2 Day Before Death	50	104.83 ± 7.34	<0.001
3 Day Before Death	50	107.14 ± 7.75	
4 Day Before Death	50	106.43 ± 7.04	

the Sepsis Group. It was observed that the mean amount of fluid on the day of death was 1948 95.28, whereas it was 1784± 139.04 at 1 day before death, 1776 ± 102.14 at 2 days before death, 1740 ± 119.52 at 3 days before death, and 1828 ± 147.28 at 4 days before death. In addition, a substantial trend was observed in the amount of fluid used in the sepsis group. (p value <0.001).

ompares the Amount of Fluid between various time periods within the Sepsis Group. It was observed that the Amount of Fluid on the Day of Death was substantially greater than on the Day of Death and a) 1 Day Before Death, b) 2 Day Before Death, c) 3 Day Before Death, and d) 4 Day Before Death (p < 0.001; Table 4).

4. Discussion:

Hypochloremia occurrence in the ICU is frequent and is associated with a twofold increase in mortality compared to patients who do not develop hypochloremia. After adjusting for severity of illness at ICU admission, age, development of renal failure, dysnatremia, sepsis, and neurocritical illness, this association remains.

Chloride is one of the most important and abundant anions in extracellular fluid, contributing approximately one-third of the tonicity [19]. Multiple physiologically significant functions of chloride within the body include acid-base balance, immune modulation, osmosis, and muscular activity [18]. Chloride's principal function in the body is acid-base homeostasis. In the ICU, large-volume fluid resuscitation is common, and fluid type selection is essential. When resuscitating septic patients with large volumes of chloride-rich solutions, hyperchloremia and its adverse effects may occur.

Several studies have identified the dangers of hyperchloremia in critically ill patients. Neyra

Table 4: **pair wise comparison of Amount of Fluid between various time points under Sepsis Group**

		Mean Difference	Std. Error	p value	95% Confdence Interval for Difference [b]	
					Lower Bound	Upper Bound
Day of Death	1 Day Before Death	164.000[*]	23.169	<.001	117.44	210.56
	2 Day Before Death	172.000[*]	18.525	<.001	134.772	209.228
	3 Day Before Death	208.000[*]	21.916	<.001	163.957	252.043
	4 Day Before Death	120.000[*]	26.954	<.001	65.833	174.167
1 Day Before Death	2 Day Before Death	8	28.691	0.782	-49.657	65.657
	3 Day Before Death	44	26.521	0.103	-9.295	97.295
	4 Day Before Death	-44	29.299	0.140	-102.879	14.879
2 Day Before Death	3 Day Before Death	36	24.704	0.151	-13.644	85.644
	4 Day Before Death	-52	27.883	0.068	-108.033	4.033
3 Day Before Death	4 Day Before Death	-88.000[*]	26.286	0.002	-140.823	-35.177

et al. examined the negative effects of hyperchloremia in ICU patients in a large retrospective study. The research involved 1940 patients. 615 (31.7%) of these patients had hyperchloremia upon ICU admission, while 1325 (68.3%) had no hyperchloremia at the time of ICU admission. Patients were monitored from the time of ICU admission until hospital discharge or mortality. During the observation period, 431 (23.9%) patients passed away, including 147 (23.9%) patients with hyperchloremia and 284 (21.4%) patients without hyperchloremia. This significant difference in mortality between the two groups suggests that hyperchloremia increases the mortality of ICU patients. In addition, hyperchloremic patients required more vasopressors, more blood transfusions, a prolonged ICU stay due to more days of mechanical ventilation, and exhibited more oliguria. The significance of maintaining a physiological serum chloride range in ICU patients is demonstrated by these observations and other investigations [20].

A extensive cluster-randomized multiple-crossover comparison of normal saline and balanced crystalloids (lactated ringer or plasma lyte A) for fluid resuscitation in the ICU. In this study, 15802 patients were randomly assigned to receive either normal saline (0.9% sodium chloride solution) or balanced crystalloid fluids (lactated Ringer's solution or Plasma-Lyte A) in five intensive care units. The primary outcome was the occurrence of a significant adverse kidney event within 30 days, the initiation of renal replacement therapy (RRT), the development of persistent renal dysfunction 58 defined as an increase in serum creatinine level to 200% of baseline, or death. All data was analysed within 30 days of the patient's discharge or demise, whichever came first. The subgroup administered balanced crystalloids as opposed to conventional saline performed better. 14.3% (1139 patients) of the 7942 patients in the balanced-crystalloid group and 15.4% (1211 patients) of the 7860 patients in the normal saline group experienced a significant kidney-related event. In the balanced saline group, the 30-day hospital mortality rate was 10.3% and in the saline group it was 11.1% (p = 0.06). The incidence of new renal replacement therapy was 2.5% in the balanced saline group and 2.9% in the normal saline group (p-value = 0.08), and the incidence of persistent renal dysfunction was 6.4% in the balanced saline group and 6.4% in the normal saline group (p-value = 0.60), respectively. The results indicate that

balanced crystalloid solution induces less organ dysfunction than normal saline [21].

In our study, we found that 16.0% of the patients in the Non-sepsis Groups were aged =40 years, 30.0% of the patients were aged 41-60 years, 46.0% of the patients were aged 61-80 years, and 8.0% of the patients were aged >80 years. Similarly, under the Sepsis Groups, it was observed that 22.0% of the patients were aged =40 years, 56.0% of the patients were aged 41-60 years, 14.0% of the 59 patients were aged 61-80 years, and 8.0% of the patients were aged >80 years. In addition, the distribution of patients by age group varied considerably between two groups. (p value < 0.005).

In our study, the non-sepsis groups had a mean weight of 58.18±6.75 kg while the sepsis groups had a mean weight of 56.64± 8.33 kg. Despite the fact that there was no statistically significant difference in the mean weight of patients between the two groups, no difference was observed. (p value < 0.260).

In our investigation, we compared the chloride concentrations of two distinct groups over time. In addition, there was no significant difference in the mean Chloride Value on the Day of Death (p = 0.774), 1 Day Before Death (p = 0.832), 2 Day Before Death (p = 0.945), 3 Day Before Death (p = 0.554), or 4 Day Before Death (p = 0.926) between the two groups.

In our investigation, we present the Chloride Value for the Non-Sepsis Group at various time points. It was observed that the mean chloride value on the day of death was 105.93± 11.45, while it was 105.15 9.74 one day before death, 104.95 ± 9.90 two days before death, 106.20 ± 7.85 three days before death, and 106.5± 6.12 four days before death. Further, it was observed that there was no discernible trend in Chloride concentrations.

Within the Non-Sepsis Group, we present a pairwise comparison of Chloride levels at various time periods in our study. Observations revealed that the mean Chloride Value did not differ significantly between any two time points.

In our investigation, we present the Chloride Value at different time points for the Sepsis Group. It was observed that the mean chloride value on the day of death was 105.31 ± 9.82, whereas it was 104.73 ± 10.10 one day before death, 104.83 ± 7.34 two days before death, 107.14 ± 7.75 three days before death, and 106.43 ± 7.04 four days before death. In addition, a significant trend was observed in the Chloride values (p value = 0.046).

In our investigation, we compare the types of fluids (i.e., NS and RL) administered to two groups at various time points. Comparing the two groups, it was found that there was no significant difference in the mean Type of Fluid administered (i.e. NS and RL) on the Day of Death (p = 0.414), 1 Day Before Death (p = 0.414), 2 Day Before Death (p = 0.192), 3 Day Before Death (p = 0.534), and 4 Day Before Death (p = 0.576).

In our study, we analysed the mortality rates of patients who received intravenous fluids for the majority of their intensive care unit (ICU) stay and died at least 72 hours after admission. The liquid consisted entirely of regular saline. The objective was to determine the number of ICU patients who developed hyperchloremia after 72 hours of receiving intravenous fluids. After 72 hours, the incidence of hyperchloremia among intensive care unit (ICU) patients was substantially higher (50.5%). It suggests that we overuse chloride-rich solutions: almost exclusively 0.9% saline, whose chloride concentrations exceed physiological levels and can cause dose-dependent hyperchloremic metabolic acidosis and other hazards. Reviewing the available literature on the effects of hyperchloremia in critically ill patients, the situation appears alarming and reinforces the need for caution in fluid selection when resuscitating our patients with large volumes of fluid 62. The lower incidence of hyperchloremia in patients with diagnoses other than sepsis, which included all patients other than those with sepsis or septic shock, was an intriguing finding of the study. In comparison to the sepsis group, fluid administration was reduced overall.

5. Conclusion:

In light of the study's findings, chloride-rich solutions should be administered with caution to ICU patients requiring large-volume fluid resuscitation in order to counteract the effects of hyperchloremia. For large-volume resuscitations in critically ill patients, balanced crystalloids (lactated ringer or plasmalyte) are equally efficacious with a lower risk of hyperchloremia and its consequences. Concerning the relationship between hyperchloremia and the total volume of fluids administered, the study has certain limitations. However, the higher incidence of hyperchloremia in ICU-deceased patients strongly suggests the use of intravenous solutions with a low chloride concentration in order to prevent the avoidable Iatrogenic side effect of fluid resuscitation when necessary.

6. Limitation:

The limitation of this study was that a small sample size was used for the study, due to which the findings cannot be generalized for a larger population.

7. Recommendation:

Chloride-rich solutions should be used with caution to counteract the effects of hyperchloremia in ICU patients requiring large volume fluid resuscitation.

8. ACKNOWLEDGEMENT-

None

9. List of Abbreviations:

ICU : Intensive care unit
CI : Confidence Interval
HRR : Higher Relative Risk
RRT : Renal replacement therapy
LOS : Length of stay
H : Hypertension
CD : Cardiovascular dysfunction
HBS : High Blood sugar

CBC : Complete Blood Count
IV : Intravenous
BMI : Body Mass Index

10. Conflict of Interest:

The authors state that they have no conflicts of interest.

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12. Publisher details:

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