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Investigating the Effect of Additional Sodium Bicarbonate Solution on Hemodynamic Management in the First Three Hours in Patients with Severe Sepsis and Septic Shock

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ABSTRACT

Background & Objective: Sepsis is one of the the main global causes of morbidity and mortality. Acute acidemia is often observed during critical illness, which reduces the effectiveness of catecholamines. Sodium bicarbonate injection is a management choice for severe metabolic acidemia. Determining the probability of hemodynamic stability by restoring intravascular volumes along with the administration of sodium bicarbonate within the first three hours in severe sepsis and septic shock management.

Materials & Methods: 72 patients with severe sepsis or septic shock were randomly allocated into two groups. In the control group, initial targeted treatment with 30 cc/kg of isotonic crystalloid serum was done in the first 3 hours. In the intervention group, sodium bicarbonate was added to the serum volume, similar to the control group, in the amount equal to half of the calculated deficiency. All orders, such as obtaining blood samples for necessary data and monitoring at the beginning and end of the intervention, were the same for both groups.

Results: There was no meaningful difference among groups in demographic information, hemodynamic variables and arterial blood gas analysis variables before treatment, duration of hospitalization, and patient mortality; The recorded data of average arterial pressure, systolic and diastolic blood pressure, central venous pressure, PH, HCO3, BE and Lactate at the end of the treatment recorded, a significant difference was observed in the two groups.

Conclusion: Adding SB to Early Goal-Directed Therapy may offer clinical and hemodynamic benefits, the limited sample size reduces generalizability. Further large-scale studies are required to confirm the safety and efficacy.

Keywords: EGDT, Sepsis, Shock, Sodium Bicarbonate

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1. Introduction

Sepsis, a life-threatening organ dysfunction (1, 2) characterized by infection-induced dysregulated host response (3, 4). Sepsis is conventionally defined as a suspected infection associated with at least two of the four criteria for Systemic Inflammatory Response Syndrome (SIRS) (5). Septic shock is a severe type of sepsis characterized by cellular, circulatory, and metabolic dysfunctions, high in-hospital mortality, and long-term morbidity for survivors, and considerable economic consequences (1, 5, 6).

Timely management of sepsis/septic shock is essential for patients' prognosis and early recognition and timely intervention (1).

From a hemodynamic standpoint, septic shock involves simultaneous disruptions in macrocirculation and microcirculation, resulting in an imbalance between oxygen supply and demand (1, 7-9).

General hypoxia of tissues as an indicator of critical illness predicts multi-organ failure and death. This process of disease progression occurs in the early [golden] hours, when definitive diagnosis and treatment and support of the cardiovascular system receive the most help in terms of the outcome of the disease. These golden hours may be spent in the ICU, emergency department (ED), or hospital ward. Additionally, numerous studies have identified lactate levels as a diagnostic, therapeutic, and predictor of tissue hypoxia in distributed shocks (9-11).

Early goal-directed therapy (EGDT) protocol has been used according to international guidelines to manage severe sepsis/septic shock in the ICU. This therapeutic process includes adjusting the preload, afterload, and heart contraction strength to create a balance between oxygen supply and oxygen consumption (10-12).

Acute acidemia is often observed during critical illnesses (13), defined herein as a plasma pH below 7.20 (6, 13), which disrupts the normal function of the cardiovascular system (14). Patients who do not survive tend to have lower pH levels compared to survivors. Notably, the underlying cause of acidosis in non-survivors is predominantly metabolic in origin rather than respiratory (15). Conversely, if acidemia itself were a critical factor contributing to patient mortality, one would anticipate that interventions such as the direct administration of sodium bicarbonate ($NaHCO_3$) would result in a substantial decrease in mortality rates (16).

Because H+ ion accumulation reduces the effectiveness of endogenous and exogenous catecholamines, sodium bicarbonate infusion is a therapeutic option for the administration of severe metabolic acidemia. Despite its frequent use in ICUs worldwide, the effect of SB infusion for managing metabolic acidemia remains debated (17).

Considering the importance of early diagnosis and targeted treatment of subjects suffering from severe sepsis and septic shock, we assessed the effectiveness of prescribing sodium bicarbonate as an initial treatment in the early hours in the ICU.

2. Materials and Methods

This clinical trial was conducted in 2023 with a selected cohort of hospitalized patients in the Intensive Care Units (ICUs) of Imam Reza Hospital. The research obtained authorization from the Medical Ethics Committee of Mashhad University of Medical Sciences (permission number: IR.MUMS.MEDICAL.REC.1401.230) and the Clinical Trial Center of Iran (registration number: IRCT20220310054246N1). Using a qualitative trait analysis in two populations and referencing the findings of Chen et al (18), we determined that at least 33 patients were required in each group, based on an alpha of 0.05 and a beta of 0.20 (80% power). To accommodate a 10% dropout rate, we augmented the sample size to 36 patients in each group. To account for an expected dropout rate of 10%, we increased the sample size to 36 patients per group, resulting in 72 participants randomly allocated to the intervention and control groups.

Randomization was performed utilizing a blocked strategy to guarantee that patients, analyzers, and sample allocators remained unaware of group allocations. All participants were non-septic patients admitted to the ICU who developed signs and symptoms of severe sepsis during their ICU stay. Severe sepsis was characterized as sepsis accompanied by hypotension, organ failure, or hypoperfusion. Septic shock was defined as persistent hypotension requiring vasopressor support to maintain a mean arterial pressure of 65 mmHg or higher. Whenever possible, sepsis workup and echocardiography were promptly performed for all participants to exclude patients with other causes of hypotension.The Inclusion criteria comprised participants aged 18–80 years, with blood lactate levels exceeding 2 mmol/L despite adequate volume resuscitation. Exclusion criteria included patients with unsatisfactory responses, untreatable disseminated malignancies, alkalotic gasometry, hypernatremia, colloidal solutions, any volume restriction, and severe bleeding. Fasting protocols were implemented for all patients, along with the administration of empirical antibiotics in accordance with our hospital's stewardship rules. After securing reliable central venous access and necessary monitoring, tissue samples consisting of blood, urine, and secretions from the airway and each suspicious collection were obtained for sepsis workup and other valuable data relevant to patient care. The disease severity was evaluated via the Acute Physiology and Chronic Health Evaluation II score. Demographic characteristics, including age, weight, height, body mass index (BMI), and gender, were documented, alongside parameters for assessing and comparing the intervention's initiation and conclusion, such as respiratory rate, gasometric results, blood pressure, central venous pressure, and heart rate. For all participants, a low dose of norepinephrine, diluted in 5% dextrose solution, was administered at a rate of 0.05 μg per kilogram of body weight via central venous infusion. The control group received conventional treatment based on the Early Goal-Directed Therapy (EGDT) protocol, which included 30 cc/kg of isotonic saline as a crystalloid solution intravenously during the first three hours. In the intervention group, a 7.5% SB solution was administered at a rate of half the deficit calculated using the formula [Base Excess x Weight of Patient in Kilograms x 0.30], in addition to the same volume as the control group over three hours. All data, including reasons for hospitalization and sources of infection, were collected using a standardized questionnaire.

All findings obtained at the beginning of the entry and after three hours post-intervention were compared using statistical methods.

3. Result

The results of this study demonstrated that there was no significant difference in demographic information, including age [P=0.158], gender [P=0.811], height [P=0.737], weight [P=0.125], and body mass index [P=0.145] (Table 1). Also, according to the obtained data, it was observed that in the studied groups, the patients in terms of respiratory status [P=0.206], reason for hospitalization [P=0.053], source of infection [P=0.567] and the result of APACHI2 criteria evaluation To reject the bias of the severity of the illness in the intervention [P= 0.614] were not significantly different from each other. All data were summarized in Table 1.

In this study, hemodynamic variables including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, mean arterial pressure, and central venous pressure were recorded before and after treatment. According to the T-Test, there was a significant difference in the pre-treatment data including SBP [P=0.859], diastolic blood pressure [P=0.526], mean arterial pressure [P=0.683], heart rate [P=0.924] and central venous pressure [P=0.334] were not seen between the two groups. Still, between the recorded data of SBP [P<0.001] and DBS [P<0.001], mean arterial pressure [P<0.001] and central venous pressure [P<0.001] at the end of the treatment, there was a significant difference in the two groups. All data were summarized in Table 2.

The variables of arterial blood gas analysis, such as PH, PaCO2, PaO2, HCO3, BE and Lactate, before and after the studied treatment, were also recorded, and based on the T-Test, there was a significant difference in the data before the treatment, including PH [P=0.617], PaO2 [P=0.676], PaCO2 [P=0.525], HCO3 [P=0.550], BE [P=0.077] and Lactate [P=0.754] were not seen between the two groups; But between the recorded data of PH [P=0.028], HCO3 [P=0.047], BE [P<0.001] and Lactate [P=0.005] at the end of treatment, a significant difference was observed in both groups (Table 3).

In the end, it was noted that there was no significant difference between the two groups in terms of ICU hospital duration stay [P=0.880] and hospital [P=0.142], as well as the final patient status [P=0.070].

Table 1. Demographic characteristics.

Variables		Groups		p-value
		Intervention	Control	
Age, year		56.75±12.07	60.72±11.54	0.158[1]
Sex	Male	20[55.6]	22[61.1]	0.811[2]
	Female	16[44.4]	14[38.9]	
Height cm		167.94±10.13	167.17±9.46	0.737[1]
Weight cm		74.28±12.30	78.83±12.60	0.125[1]
Body mass Index kg/m^2		26.58±5.26	28.56±6.08	0.145[1]
Respiratory status	Non-intubated	22[61.1]	27[75]	0.206 [2]
	Intubated	14[38.9]	9[25]	
Hospitalization outcome	Death	7[19.4]	14[38.9]	0.206[2]
	Discharge	29[80.6]	22[61.1]	
Source of infection	Abdominal	6[16.7]	9[25]	0.567[2]
	soft texture	3[8.3]	5[13.9]	
	Pulmonary	14[38.9]	15[41.7]	
	Urinary	9[25]	5[13.9]	
	Catheter	4[11.1]	2[5.6]	
APACHI2		26.18±4.99	26.75±4.77	0.614[1]

Data presented as mean ± SD or N [%] for quantitative and qualitative variables, respectively; 1. t-test; 2. Chi-square [χ2] test

Table 2. Comparison of hemodynamic variables before and after treatment in 2 groups.

Hemodynamic variables		Groups		p-value
		Intervention	Control	
Before treatment	SBP	74.17±6.68	73.86±7.86	0.859
	DBP	52±4.83	52.72±4.78	0.526
	HR	112.39±14.38	112.06±15.06	0.924
	MAP mm Hg	59.39±4.04	59.77±3.82	0.683
	CVP cm H_2O	6.83±1.4	7.17±1.5	0.33
After treatment	SBP	91.53±7.25	83.31±7.94	0.0001
	DBP	61.36±5.32	69.33±4.99	0.0001
	HR	101.03±12.72	103.81±14.11	0.383
	MAP mm Hg	76.73±4.42	68.68±4.77	0.0001
	CVP cm H_2O	14.19±1.63	12.44±1.79	0.0001

Abbreviations: Systolic blood pressure (SBP); Diastolic blood pressure (DBP); Heart rate (HR); Central venous pressure (CVP); Mean arterial pressure (MAP); Data presented as mean± SD.

Table 3. Comparison of hemodynamic variables before and after treatment in 2 groups.

Arterial blood gas analysis		Groups		p-value
		Intervention	Control	
Before	PH	7.22±0.04	7.21±0.05	0.617
	$PaCO_2$	72.33±13.97	70.75±17.80	0.676
	PaO_2	53.53±11.00	51.83±11.47	0.525
	HCO_3	16±2.74	15.61±2.74	0.55
	BE	-7.98±2.90	-9.16±2.66	0.077
	Lactate	4.09±1.24	4±1.15	0.754
After	PH	7.29±0.04	7.26±0.05	0.028
	PaO_2	19.33±76.36	77.39±14.56	0.8
	$PaCO_2$	59.22±12.34	55.67±12.22	0.223
	HCO_3	18.04±3.19	16.6±2.85	0.047
	BE	-5.01±1.89	-7.49±2.16	0.0001
	Lactate	2.08±0.68	2.57±0.77	0.005

Data presented as mean± SD

4. Discussion

This study investigated the additional impact of the SB solution alongside the initial targeted treatment during the first three hours of hemodynamic management in participants with severe sepsis/septic shock. Our findings demonstrated that the addition of SB significantly improves hemodynamic parameters and the analysis of arterial blood gases, which statistically compares the data of central venous pressure, SBP and DBP, mean arterial pressure, pH, HCO3, BE, and plasma lactate after treatment between the two studied groups; this superiority was significant. The existing data in this area are limited and inconsistent.

El-Solh et al (19) observed that bicarbonate replacement is associated with a reduced time of ventilation and a shorter hospital stay. Furthermore, according to findings of a retrospective study, administration of SB may enhance survival rates in septic patients experiencing acute moderate lactic acidosis (MLA) in both ICU and hospital environments. Additionally, it was found to lower hospital mortality rates in septic shock patients who suffer from acute MLA. However, SB therapy was found to raise pH and PCO2 without benefits in cardiac output or blood pressure. Chen et al (18) explored the use of SB for treatment of hypoperfusion-induced lactic acidemia secondary to septic shock, and results demonstrated that using SB can improve the increase in lactic acidemia, the decrease in occurrence rate of multiple organ dysfunction, less duration of ventilation and ICU stay, and eventually less mortality rate.

Although different studies have represented insufficient evidence of SB administration affecting mortality rate in critically ill patients suffering from septic shock/sepsis **(20-22)**, Mathieu and Farr **(23)** found no changes in hemodynamic parameters after SB therapy. Another study investigated the effect of SB infusion on the mortality rate of sepsis patients with metabolic acidosis and found no significant difference between the two groups. While the pH and concentration of SB in the control group were significantly lower than those in the treatment group **(24)**, a similar study by Jaber and colleagues showed that mortality rates over 28 days were comparable between the two groups **(17)**.

Recently, the role of SB in metabolic acidosis was evaluated **(25)**. It was noted that there is limited evidence regarding the usefulness of SB intake in patients with pH < 7.2 and its beneficial effects in acute kidney injury. Still, no outcome was detected in patients with pH > 7.2. The administration of SB in the initial management of severe sepsis/septic shock may offer several potential benefits. By directly addressing lactic acidosis, bicarbonate may mitigate the detrimental effects of acidosis on myocardial contractility and vascular tone. Severe acidosis can impair cardiac performance, leading to reduced cardiac output and further exacerbation of shock. By correcting acidosis with $NaHCO_3$, myocardial performance may be restored, vascular responsiveness to catecholamines may be enhanced, and ultimately, mean arterial pressure (MAP) and organ perfusion may improve. Moreover, SB may enhance oxygen delivery to tissues. As tissue pH is restored, the affinity of hemoglobin for oxygen may increase, supporting better oxygen release at the cellular level. In critically ill patients, even moderate improvements in tissue oxygenation can yield significant advantages, including reduced rates of organ failure and an improved overall prognosis.

There were some limitations in our study. Firstly, the population examined was limited to a single institution. One of the most significant limitations was the insufficient number of prior studies on the use and effectiveness of primary targeted treatment, as well as the use of SB infusion as an adjunctive treatment to help reduce complications associated with sepsis and septic shock. Consequently, our researchers focused solely on studies that addressed the objectives of this investigation. Although previous research has explored primary targeted treatment and the use of SB infusion, there is a lack of studies examining the combination of these two treatments, including their benefits and potential side effects, which remain unproven in existing evidence. This issue warrants further discussion.

5. Conclusion

Although our initial results suggest that adding SB to Early Goal-Directed Therapy may provide clinical and hemodynamic benefits, the small sample size limits the generalizability of these findings. Further large, randomized controlled trials would be required to confirm such potential benefits and to perform a more comprehensive examination of the safety profile.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study was approved under the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1401.230). Clinical Trial Registration Code is IRCT20220310054246N1.

6.3 Authors' Contributions

Conceptualization, Arash Peivandi Yazdi. And Leila Mashhadi.; methodology, Ehsan Noori.; software, Saeed Akhlaghi.; validation, Saeed Akhlaghi., Arash Peivandi Yazdi. and Leila Mashhadi.; formal analysis, Saeed Akhlaghi.; investigation, Andia Peivandi Yazdi.; resources, Andia Peivandi Yazdi.; data curation, Andia Peivandi Yazdi.; writing—original draft preparation, Leila Mashhadi.; writing—review and editing, X.X.; visualization, Saeed Akhlaghi.; supervision, Arash Peivandi Yazdi.; project administration, Leila Mashhadi. All authors participated in reviewing the manuscript and its revision, and they were involved in research, interpretation, and finalizing the manuscript.

6.4 Conflict of Interest

The authors declare no conflict of interest.

6.5 Fund or Financial Support

This research received no external funding.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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