Journal of Anesthesia and Patient Care
Volume 5 | Issue 1
ISSN: 2456-5490

Research Article Open Access

The Effect of Hypertonic Saline on Volume Resuscitation and Intracranial Pressure in Septic Patients

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Citation: Ahmad Bagheri Moghadam, Mahdi Khodadadzadeh, Ali Feizi Lain, Raheleganjali, Arashpeivandiyazdi (2023) The Effect of Hypertonic Saline on Volume Resuscitation and Intracranial Pressure in Septic Patients J Anesth Pati Care 5(1): 101

Received Date: August 04, 2023 **Accepted Date:** September 04, 2023 **Published Date:** September 07, 2023

Abstract

Background and Objective: Septic shock remains an impatient cause of morbidity and mortality. Early restitution of the circulation improve tissue oxygen delivery and increase survival. This study is a prospective randomized single center study its main objective is to investigate the therapeutic value of hypertonic saline in patients with septic shock.

Methods: Fifty-two critically ill patients admitted with septic shock divided into two groups, the first group received isotonic saline (control group) starch, while the second received hypertonic saline 5%.

Results: The mean central venous pressure in the first and third hours of the intervention in the isotonic saline group was significantly higher than the hypertonic saline group. (Respectively, P=0.024 and P=0.014). The average pH and BE in the second and third hours of the intervention in the isotonic saline group were significantly higher than the hypertonic saline group. (Respectively, P=0.032 and P=0.040). The average bicarbonate in the third hour of the intervention in the isotonic saline group was significantly higher than the saline group. (P=0.008). Also, the average optic nerve diameter in the third hour of the intervention was 4.4±0.1 in the isotonic saline group and 4.2±0.2 in the hypertonic saline group, and there was a significant difference between the two groups in this hour.

Conclusion: Our study results showed that hypertonic saline administration in septic shock patients is safe and can be used as an adjuvant resuscitation fluid therapy as i it has a preventive ability in causing tissue edema compared to isotonic crystalloid solutions.

Keywords: Saline Solution; Hypertonic; Shock; Septic; Optic Nerve; Resuscitation

Introduction

Severe sepsis and septic shock are a major cause of death in the whole world. Its treatment costs are high and it has a mortality rate of 40-20%. Increasing intravascular volume is an important component of sepsis management and the best initial treatment for stabilization of Cardio vascular status in septic shock. Primary hypotension caused by cardiovascular instability can be treated with volume infusion alone in many patients. Although this type of intravenous fluid is ideal for the management of septic shock, it is debated[1]. Only a quarter of the crystalloid fluid remains in the intravascular space and the remaining three quarters enters the extra vascular space, thus leading to a transient increase in plasma volume. In recent years, hypertonic crystalloids have been used as a resuscitation fluid and have many advantages over conventional fluids[2]. Hypertonic crystalloid infusion helps to improve the circulatory condition not only by increasing the intravascular volume but also by drawing water from the extra vascular space by the osmotic gradient. Hypertonic crystalloid also improves the heart's contractility, reduces endothelial edema, and has immune modulating effects. Therefore, it has an important role in the treatment of septic shock[3]. In a number of studies on patients with brain trauma, the use of hypertonic saline has been effective in reducing intra cerebral pressure[4]. Limited clinical trials have been conducted to compare the effects of isotonic and hypertonic crystalloids for the treatment of septic shock[5]. This study helps us to determine the complications associated with isotonic crystalloid (tissue edema, etc.) that can be prevented by using hypertonic crystalloid.

Method and Materials

This clinical trial study was conducted among patients with septic shock in the ICUs of Imam Reza Hospital between 2021 and 2022. The local ethical committee approved this study (no.IR.MUMS.MEDICAL.REC.1400.665), and it was registered in the Iranian registration center (no. IRCT20111212008384N7 on 22/02/2022). The inclusion criteria included patients with septic shock, and the age between 18-80 years, and the exclusion criteria included patients' dissatisfaction, patients with untreatable diffuse malignancy, patients with hyper natremia, patients receiving colloidal solutions such as albumin, etc. and any type of volume restriction such as uncompensated heart failure.

Procedure

In this study, using random sampling and in intensive care units, patients with severe sepsis or septic shock (due to the delay of culture results, first all suspected patients were included in the study, and if the culture results were negative, they were excluded from the study) and started Blood pressure reduction to MAP<65, after obtaining informed consent, randomly (using sealed envelopes) were divided into two control and intervention groups. For all patients after entering the study, demographic characteristics including age, sex, BMI, reason for admission to ICU (medical or surgical), severity score with APACHI 2 scoring system (to eliminate the effect of distortion of patient severity), parameters Hemo dynamics and gasometry (mentioned below) were all recorded. Broad-spectrum empirical antibiotics for gram-positive and gram-negative bacteria were prescribed for all patients and patients in control group received the same conventional method of treatment (30 cc of isotonic saline serum per kilogram of body weight during the first 3 hours), and in the intervention group, 5% hypertonic saline was prescribed at the rate of 5 cc per kilogram of body weight during the first 3 hours. Hemodynamic parameters (HR, SBP, DBP, MAP, CVP) and gasometric parameters (PH, PaCO2, PaO2, HCO3, BE, Lactate) were recorded in the first, second and third hour of treatment for comparison in two groups. To investigate tissue edema caused by resuscitation, optic nerve diameter was measured and recorded by ultrasound in both groups before the start of treatment and at the end of 3 hours.

APACHE II score provides an objective assessment of disease severity in patients hospitalized in the intensive care unit. APACHE II score consists of three components: 1-Acute physiology score (APS) 2-Age adjustment 3-Chronic health evaluation (CHE).

APS Includes 12 Parameters

1. Central body temperature

2. Mean arterial blood pressure

3. Heart rate

4. Respiration rate

5. Arterial oxygen pressure

6. Arterial pH or serum bicarbonate (if arterial blood gas analysis is not available)

7. Serum sodium

8. Serum potassium

9. Serum creatinine

10. Hematocrit

11. White blood cells

12. GCS

The values of these parameters are related to the first 24 hours of the patient's hospitalization. These parameters are scored from zero to four based on its value, and if we do not have the value of a parameter in the first 24 hours, we give it zero points, and on the other hand, if we have several values of the same parameter, we enter the worst value (that value which gets the highest score). Regarding GCS in patients who underwent elective surgery; GCS should be calculated after waking up and removing the effects of anesthetics.

- The second part is related to the age of the patients: based on the age, a score is given to the patient in such a way that the age of less than 44 years gets 0 points, the age of 45 to 54 years gets 2 points, the age of 55 to 64 years gets 3 points, the age of 65 to 74 years gets 5 points and age older than or equal to 75 years gets 6 points

- The third part is related to the person's chronic disease status, which includes: biopsy-proven cirrhosis, class 4 chronic heart failure, severe chronic obstructive pulmonary disease, chronic dialysis, immunodeficiency such as: AIDS, leukemia, radiotherapy, chemotherapy, Long-term high-dose steroid therapy, pulmonary hypertension.

If the patient has a history of any of the above-mentioned chronic diseases and currently no surgery has been performed on him or emergency surgery was performed on him, 5 points will be given to the patient, but if elective surgery was performed for the patient, 2 points will be given to the patient. Finally, we added the points obtained from all three components together. In general, patients may receive from 0 to 71 points.

Method of Optic Nerve Sheath Diameter Measurement

- A linear probe having a high frequency (5–10 MHz) is used to perform an ocular ultrasound exam. Depth is adjusted to visualize structures up to 5–6 cm deep.
- The patient is placed and examined in the supine position, and cooperative patients can be directed to maintain the midline position of the eye.
- Apply a copious amount of ultrasound gel over the upper closed eyelid.
- Place the transducer softly over the superior aspect of the closed eye avoiding too much of pressure (Figure 1). 6, 7.The probe is adjusted, so that cross-section of the globe, as well as optic nerve, can be seen.
- The optic nerve sheath visualized as a tubular hypo echoic band, shifting away from the eyeball.
- ONSD measurement is taken 3 mm posterior to the globe.
- For the assessment of ONSD, two lines are drawn (Figure 2).

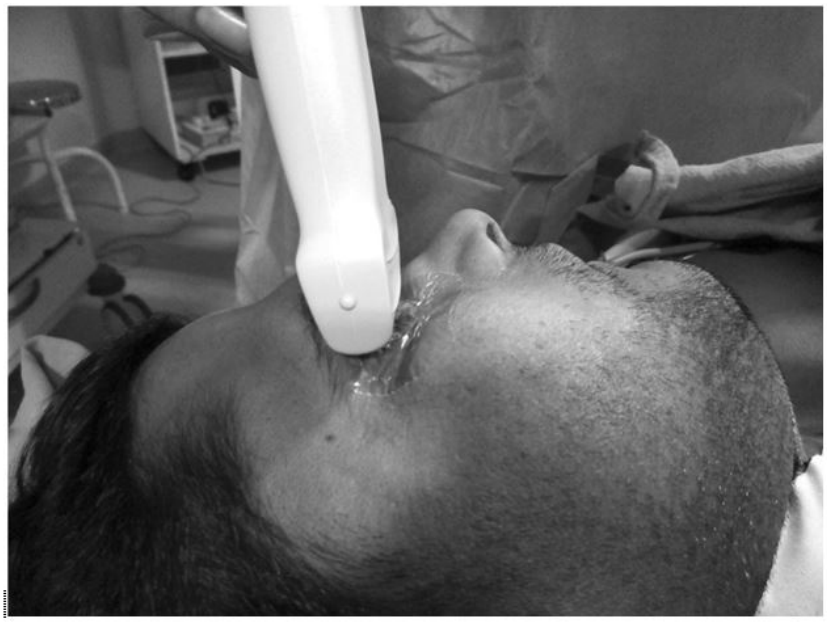

Figure 1: Placement of probe over the upper eyelid.

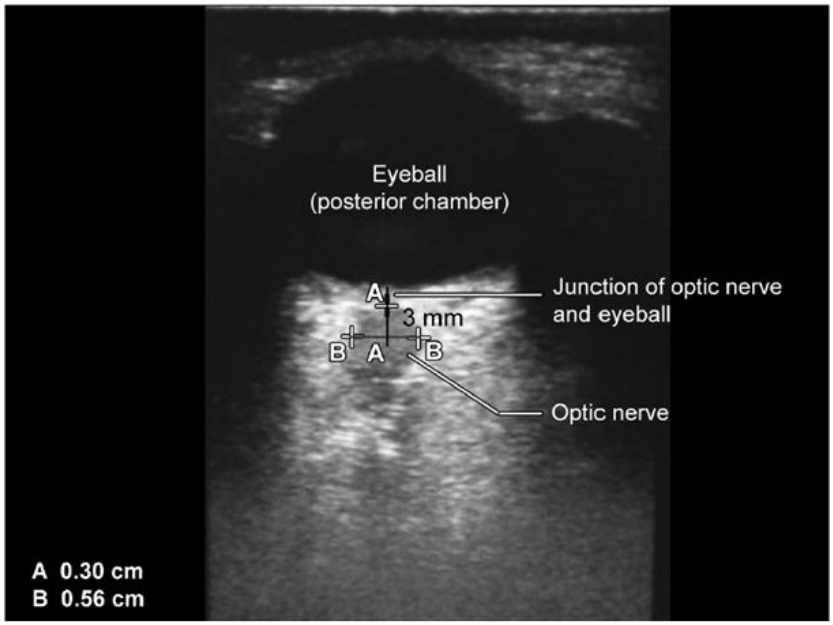

Figure 2: Sonographic image of optic nerve and eyeball. For measurement of optic nerve sheath diameter (ONSD) a 3 mm line (A-A) is drawn from junction of eyeball and optic nerve. At this point another line is drawn perpendicular to the first line (B-B) to measure the ONSD.

1st line: From the junction of the optic nerve and the eyeball, a straight line is drawn 3 mm long (Figure 2; A-A) that is the reference point for next measurement.

2nd line: At the 3 mm reference point, a second perpendicular line is drawn across the optic nerve, which provides ONSD measurement (Figure 2; B-B). 3,4

The normal value of ONSD in adults is 4.5 mm. There is a wide range of cut off values to denote raised ICP however, a value of more than 5.0 mm is usually considered to denote raised ICP.

Statistical Analyzes

The recorded data were analyzed by SPSS version 26 software. The characteristics of the studied subjects were presented by descriptive statistical methods, including central indices, dispersion and frequency distribution in the form of suitable tables. To compare the quantitative variables between the two groups, if the data were normally distributed, the independent T-test was used, otherwise, the Mann-Whitney test was used. To compare qualitative variables between two groups, chi-square test and Fisher's exact test were used if necessary. In all calculations, a value of 0.05 was considered as a significant level.

Results

This study was conducted to investigate and compare the effect of hypertonic saline and isotonic saline on the success of resuscitation of patients with septic shock in the first three hours of treatment. In this study, 52 patients with septic shock were examined from 2021 to 2022 in the ICUs of Imam Reza Hospital, 26 patients in the isotonic saline group (12 men and 14 women) and 26 in the hypertonic saline group (17 men and 9 women). and based on Chi-square test, the two groups were similar in terms of gender and there was no significant difference (P=0.202). According to the Mann-Whitney test, the average age of the patients in the isotonic saline group was 62.3 ± 16.6 years and in the hypertonic saline group was 60.7 ± 16.6 years, which in terms of the average age difference between these two groups was not significant (P = 0.641).

Also, the mean BMI in the isotonic saline group was 24.0 ± 2.4 and in the hypertonic saline group was 23.6 ± 1.9, the difference between the two groups was not significant (P=0.325) (Table 1).

Table 1: Demographic characteristics in the two study groups.

Variables		Isotonic (%)	Hypertonic (%)	P value
Gender	Male	12 (23.1)	17 (32.7)	0.202 *
	Female	14 (26.9)	9 (17.3)	
Age		62.3±16.6	60.7±16.6	0.641 †
BMI		24.0±2.4	23.6±1.9	0.325 †

According to the data in Table 2, none of the hemodynamic parameters (HR, SBP, DBP, MAP, CVP), primary outcomes and gasometric parameters (PH, PaCO2, PaO2, HCO3, BE, Lactate) and optic nerve diameter had significant differences between isotonic saline and hypertonic saline groups at the time of arrival (P<0.053).

Table 2: The average of the investigated variables in the two studied groups.

Variables	Isotonic	Hypertonic	P value
APACHE II	.2 ± 22.19	3.0 ± 23.1	0.205 *
CVP 0	0.8 ± 3 .5	0.6± 5.2	0.692 *
MAP 0	7.2 ± 48.5	3.8 ±47.9	0.709 *
DBP 0	6.9 ± 37.8	3.4 ± 37.9	0.959 *
SBP 0	7.3 ± 67.8	3.7 ± 66.8	0.502 *
HR 0	7.1 ± 127.2	6.2 ± 128.7	0.409 †
PH 0	0.0 ± 7.2	0.0 ± 7.2	0.204 *
PaCO2 0	3.4 ± 31.4	3.8 ± 31.2	0.789 †
PaO2 0	20.2 ± 141.1	18.1 ± 143.3	0.687 *
HCO3 0	1.9 ± 12.5	1.9 ± 12.2	0.569 *
BE 0	2.6 ± 12.9	2.6 ± 13.3	0.567 *
Lactate 0	1.0 ± 10.6	0.8 ± 10.8	0.412 †
Optic 0	0.2 ± 4.1	7.6 ± 5.6	0.311 *

Values are presented as mean ± SD,

* Mann-Whitney Test

† Independent Sample T-Test

According to the data in Table 3, the mean central venous pressure in the first hour of the intervention was 5.8 ± 0.7 in the isotonicsaline group and 5.5 ± 0.5 in the hypertonic saline group, also in the third hour of the intervention in the isotonicsaline group was 7.0 ± 0.1 and in the hypertonic saline group was 6.4 ± 0.5, there was a significant difference between the two groups in these hours. And the isotonicsaline group had significantly higher central venous pressure than the hypertonic saline group (respectively, P=0.024 and P=0.014). Also, based on the results of the Friedman test, there is a significant difference between the first and last samples in each group (P<0.001). Also, in the comparison of two groups of hypertonic saline and isotonicsaline, there is a significant difference between the first and last samples (P=0.007). Also, the mean arterial pressure, diastolic and systolic blood pressure and average heart rate were not significantly different in any of the hours in the isotonicsaline and hypertonic saline groups (P<0.053).

Table 3: Average hemodynamic parameters (HR, SBP, DBP, MAP, CVP) during ICU.

Variables		Isotonic	Hypertonic	P value
CVP	CVP 0	0.8±5.3	0.6±5.2	0.692 *
	CVP 1	0.7±5.8	0.5 ±5.5	0.024 *
	CVP 2	0.9±6.5	0.6 ±6.2	0.296 *
	CVP 3	1.0±7.0	0.5 ±6.4	0.014 *
P-value		0.001>†	0.001>†	
CVP0-CVP3		0.7±1.6	0.4 ±1.2	0.007 *
MAP	MAP0	7.2±48.5	3.8 ±47.9	0.709 *
	MAP1	6.3 ±51.3	2.8 ±51.5	0.933 *
	MAP2	5.6 ±58.0	3.1 ±57.2	0.504 *
	MAP3	6.9±65.4	2.7 ±64.3	0.473 *
P-value		0.001>†	0.001>†	
difMAP		8.5 ±16.9	4.1 ±16.4	1.000 *
DBP	DBP0	6.9±37.8	3.4±37.9	0.959 *
	DBP1	7.5 ±40.9	3.1±40.0	0.811 *
	DBP2	8.6 ±46.8	3.0 ±44.0	0.117 *
	DBP3	6.9 ±53.5	3.5±52.7	0.598 *
P-value		0.001>†	0.001>†	
difDBP		9.9±15.7	4.9 ±14.8	0.820 *
SBP	SBP0	7.3 ±67.8	3.7±66.8	0.503 *
	SBP1	8.7 ±73.0	4.0 ±71.8	0.503 *
	SBP2	9.1 ±81.5	2.6 ±78.8	0 .153 *
	SBP3	6.8 ±88.7	2.3 ±86.2	0.077 *
P-value		0.001>†	0.001>†	
difSBP		6.2 ±20.9	3.7 ±19.4	0.910*
HR	HR0	7.1 ±127.2	6.2 ±128.7	0.409 ‡
	HR1	6.5 ±119.0	5.1 ±120.1	0.341 *
	HR2	6.4 ±110.7	3.8 ±112.0	0.053 *
	HR3	3.6±102.2	3.0 ±102.5	0.773 *
P-value		0.001>†	0.001>†	
difHR		5.9 ±25.0-	4.0 ±26.2-	0.301 ‡

Values are presented as mean ± SD ,

* Mann-Whitney Test

†Friedman Test

‡ Independent Sample T-Test

According to the data in Table 4, the average pH in the second hour of the intervention was 7.2 ± 0.0 in the isotonicsaline group and was 7.2 ± 0.0 in the hypertonic saline group, and in the third hour of the intervention in the isotonicsaline group was 7.3 ± 0.0 and in the hypertonic saline group was 7.2 ± 0.0, so there was a significant difference between the two groups in these hours. And the isotonic saline group had significantly higher pH than the hypertonic saline group (Respectively, P=0.032 and P=0.040). Also, based on the results of the Friedman test, there is a significant difference between the first and last samples in each group (P<0.001). Also, comparing two groups of hypertonic and isotonicsaline, there is no significant difference between the first and last samples (P=0.150).The mean PaCo2 and PaO2 and mean lactate were not significantly different in any of the hours in the two groups of isotonic saline and hypertonic saline (P<0.051). Also, the average bicarbonate in the third hour of the intervention was 17.1 ± 2.1 in the isotonic saline group and 15.6 ± 1.9 in the hypertonic saline group, and there was a significant difference between the two groups in this hour. And the isotonic saline group had significantly more bicarbonate than the hypertonic saline group in the third hour of intervention. (P=0.008).The average Base Excess in the second hour of the intervention in the isotonic saline group was 10.3 ± 2.0 and in the hypertonic saline group was 11.5 ± 1.8, also in the third hour of the intervention in the isotonicsaline group was 9.2 ± 1.9 and in the hypertonic saline group was 10.6 ± 1.6, and there was a significant difference between the two groups in these hours. And the isotonic saline group had significantly less Base Excess than the hypertonic saline group (Respectively, P=0.024 and P=0.001).

Table 4: Average gasometrical parameters (PH, PaCO2, PaO2, HCO3, BE, Lactate) during ICU.

Variables		Isotonic	Hypertonic	P value
PH	PH0	0.0±7.2	0.0 ±7.2	0.204 *
	PH1	0.0 ±7.2	0.0 ±7.2	0.102 †
	PH2	0.0 ±7.2	0.0±7.2	0.032 †
	PH3	0.0 ±7.3	0.0±7.2	0.040 *
P-value		0.001 >‡	0.001 >‡	
Dif PH		0.0 ±0.1	0.0±0.1	0.150 †
PaCO2	PaCO20	3.4 ±31.4	3.8 ±31.2	0.789 †
	PaCO21	3.3±34.1	3.4±33.8	0.741 †
	PaCO22	2.7 ±36.9	3.1 ±36.6	0.672 †
	PaCO23	2.9 ±40.1	3.5±39.5	0.05 *
P-value		0.001 >‡	0.001 >‡	
DifPaCO2		1.7±8.7	2.0±8.4	0.741 †
PaO2	PaO20	20.2 ±141.1	18.1±143.3	0.501 †
	PaO21	20.6±141.7	18.1 ±143.7	0.710 †
	PaO22	202 ±143.3	18.1 ±145.0	0.631 †
	PaO23	20.4 ±143.8	18.0 ±146.3	0.625 *
P-value		0.001 >‡	0.001 >‡	
DifPaO2		1.5±2.7	1.7±3.0	0.480 †
HCO3	HCO30	1.9 ±12.5	1.9±12.2	0.569 †
	HCO31	1.9 ±14.0	1.8±13.3	0.172 *
	HCO32	2.1 ±15.7	1.8±14.4	0.702 †
	HCO33	2.1±17.1	1.9 ±15.6	0.008 *

P-value		0.001 >‡	0.001 >‡	
difHCO3		1.5±4.6	0.8 ±3.4	0.001 > †
BE	BE0	2.6±12.9	2.6 ±13.3	0.567 †
	BE1	2.3±11.7	2.1±12.5	0.187 *
	BE2	2.0±10.3	1.8±11.5	0.024 *
	BE3	1.9±9.2	1.6±10.6	001/0 *
P-value		0.001 >‡	0.001 >‡	
DifBE		2.1±3.7-	19.3±1.1	0.001 †
Lactate	Lactate0	1.0±10.6	0.8±10.8	0.412 *
	Lactate1	0.9±10.1	0.7±10.4	0.175 *
	Lactate2	0.8±9.6	0.7±9.9	0.127 *
	Lactate3	0.7±9.1	0.5±9.4	0.116 *
P-value		< 0.001 §		
DifLactate		0.6±1.5-	0.4 ±1.5-	0.601 †

Values are presented as mean ± SD ,

† Mann-Whitney Test

* Independent Sample T-Test

‡ Friedman Test

§ Repeated Measure ANOVA

According to the data in Table 5, the mean diameter of the optic nerve in the third hour of the intervention was 4.4 ± 0.1 in the isotonicsaline group and 4.2 ± 0.2 in the hypertonic saline group, which had a significant difference between the two groups at this hour. And the optic nerve in the isotonicsaline group had a significantly larger diameter than the hypertonic saline group in the third hour of intervention (P<0.001). Also, based on the results of the Wilcoxon Signed Ranks Test, there is a significant difference between the first and last samples in each group (P<0.001). Also, in the comparison of two groups of hypertonic and isotonicsaline, there is a significant difference between the first and last samples (P<0.001).

Table 5: Mean optic nerve diameter during ICU.

Variables	Isotonic	Hypertonic	P value
Optic0	4.1 ± 0.1	4.1 ± 0.2	0.311*
Optic3	4.4 ± 0.1	4.2 ± 0.2	< 0.001 *
P-value	< 0.001 †	< 0.001 †	
difOptic	0.2 ± 0.07	0.5 ± 0.5	< 0.001 *

Values are presented as mean ± SD,

* Mann-Whitney Test

†Wilcoxon Signed Ranks Test

Discussion

This study was conducted to compare the effect of hypertonic and isotonicsaline on the success of resuscitation of patients with septic shock during the first three hours of treatment. In this clinical trial study, 52 patients with septic shock were examined from 2021 to 2022 in the ICUs of Imam Reza Hospital, 26 patients in the isotonicsaline group (12 men and 14 women) and 26 patients in the hypertonic saline group (17 men and 9 women) were located. In this part, we will explain the effective mechanisms on the resuscitation of patients with septic shock and analyze the results of the studies. The main disorder in sepsis is the mal distribution of blood flow. A triggering event leads to a local inflammatory response characterized by vasodilation, increased capillary permeability, and migration of inflammatory cells into tissues. Neutrophil activation leads to the release of vaso regulatory mediators (eg, nitric oxide and arachidonic acid metabolites) and proteases (eg, elastase and matrix metallo protein ases), which in turn lead to increased endothelial permeability[6]. In an attempt to overcome this complex cascade of events leading to these hemodynamic disturbances, high-volume resuscitation with crystalloid solutions (from 6 to 10 L) is often used during the initial resuscitation of a patient with sepsis. It has been shown that early resuscitation of a patient with sepsis and septic shock leads to a reduction in morbidity and mortality and a faster recovery of patients. Hypertonic saline (HTS) is theoretically a suitable option for volume resuscitation in patients[6]. However, potential changes in hemodynamic stability can occur.In our study, according to the analyzes performed, the central venous pressure at 1 hour and 3 hours and during the study in the isotonicsaline group was significantly higher than the hypertonic saline group, which indicates the greater effect of isotonic saline in increasing the central venous pressure compared to the hypertonic saline. In general, the increase in plasma volume leads to a decrease in the plasma levels of various neuro hormones(such as ACTH, cortisol, and aldosterone) and endogenous vaso pressors (such as norepinephrine, epinephrine, cortisol, vasopressin, and renin), which contribute to changes in hemodynamic stability. Recent studies have shown that HTS has the ability to rapidly expand plasma volume by moving fluid from the intracellular space to the intravascular space. This leads to an increase in plasma volume up to 4 times than the actual injected volume, while the effects are short-lived. The addition of colloids to HTS prolongs the duration of volume expansion, thus exacerbating these effects on the central and local circulatory systems[6]. According to the results of our study, the diameter of the optic nerve in the isotonicsaline group was significantly higher than the hypertonic saline group, and the possibility of increased ICP in the isotonicsaline group was higher than the hypertonic saline group according to the average diameter of the optic nerve. One of the concerns of volume restoration is tissue edema and compartment syndrome, which is less likely with hypertonic solutions. In our study, the increase of ICP was investigated as a variable indicating edema, and obvious edema was not evident, and less edema occurred in the hypertonic saline group. Studies have shown that HTS mixed with dextran has been studied in fluid resuscitation of laboratory animals and humans with hemorrhagic or traumatic shock[7]. The mechanisms behind the improved outcome in hemodynamic status are likely to be multi factorial. The rapid increase in intravascular volume occurs through the movement of water (from the intracellular space, micro vascular endothelium, and red blood cell [RBC]) into the interstitial and intravascular space. A decrease in endothelial edema and a decrease in vascular resistance occur, all of which increase tissue perfusion. Cardiac contractility may also be improved through a direct hyper osmolar effect and through a reduction in myocardial edema unrelated to changes in coronary blood flow[8]. Silvestein et al. [9] calculated efficiency ratios to represent the change in plasma volume relative to infused volume and found that HTS resulted in the greatest increase in plasma volume at 30 min post-infusion with an efficiency ratio 2 to 3 times greater than either liquid. The researchers also concluded that HTS has the highest effect on increasing blood volume (approximately three times more than the injected volume), which is explained by absorption of fluid from other compartments into the intravascular space. In the reviewed study, the volume-enhancing effects of HTS were short-lived and lasted for 30 minutes, while synthetic colloids were added resulted in significant plasma volume expansion lasting 240 minutes. The increase in plasma volume appears to be dose-related because a dose of 6 ml/kg resulted in a greater volume increase than a dose of 4 ml/kg[9]. Improvement in cardiovascular function and tissue perfusion as demonstrated by splanchnic perfusion was also observed. Also, according to the results obtained from our study, in the comparison between hypertonic saline and isotonic saline, the amount of PH and HCO3 in the isotonic saline group was significantly higher than the hypertonic saline group, and the BE level in the isotonic saline group was significantly lower than the hypertonic saline group which indicates an increase in the amount of bas excess in patients with hypertonic saline resuscitation.

The mechanism of this result can be explained as follows: firstly, we had a metabolic acidosis with hypocapnia in the direction of compensation, which in the third hour is reasonable by correcting the increase in PH, PCO2 and bicarbonate and decreasing BE, and as a result, in the pathological range, isotonic saline is towards correction. Also, on the other hand, in our study, due to the higher osmolarity of hypertonic saline, we expect ICP to decrease more compared to isotonic saline, which the results of the study have also shown. Comparing isotonic saline and hypertonic saline, both transiently improve systemic and regional blood flow. However, hypertonic saline was associated with a significant (and sustained) reduction in systemic and mesenteric oxygen extraction without worsening other markers of tissue perfusion[10]. Other studies have explained the positive inotropic effect by volume-expanding effects (increased preload) and vascular effects (decreased after load, decreased pulmonary and systemic vascular resistance), the latter of which may temporarily lower blood pressure following bolus doses of hypertonic saline. Myocardial function may be improved directly by reducing myocyte edema, or by increasing myocardial calcium uptake by restoring membrane potential[11]. Various immune modulatory effects have also been described following the use of HTS in the treatment of sepsis. A significant reduction in the number of bacterial colonies along with increased killing of intracellular bacteria and superoxide production was observed in animals resuscitated with HTS compared to the control group resuscitated with ISS[12]. A recent study in 2011 by Frank et al. [13] inseptic shock patients, hypertonic saline solutions, compared to isotonic fluid, may modulate the expression of several measured genes involved in neutrophil-endothelial interaction and capillary leakage. This was the first study to report the effects of hypertonic saline on inflammatory gene expression in septic shock patients.Bunn et al. [14] published in the Cochrance database a study of hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients, which showed no improvement in the relative risk of death for hypertonic saline patients. A study was done in 1999 that looked at colloids versus crystalloids and was recently updated by Pearl and Roberts[15]. Very few studies have considered adverse effects of hypertonic saline as a primary outcome measure. The use of hypertonic saline causes a dangerous complication called ODS (Osmotic Demyelination Syndrome), an acute hyperosmolar state (the most dreaded complication) that leads to central myelinolysis of the pons. Especially when the sodium level in hyponatremia is corrected quickly and when the patient is not fed properly[16]. Other potential side effects include hyperchloremic acidosis and hyperosmolar renal failure.Vassar et al. [17] evaluated the potential side effects of rapid infusion of 7.5% hypertonic saline with and without dextran. 8 patients out of 166 had significant hyper chloremic acidosis. However, it was felt that the cause of their dying condition was acidosis rather than high chloride load. The vast majority of trials with bolus injection of hypertonic saline have reported on side effects, and no significant side effects have been reported, and no evidence of osmotic demyelination syndrome has been found.

Based on the obtained results, hypertonic saline can be used as an adjuvant resuscitation treatment with routine resuscitation protocols in critically ill patients with septic shock, and considering the close results in these two groups in the resuscitation of patients with septic shock in cases where the patient is faced with an increase in ICP, hypertonic saline can be used as a more appropriate choice to revive patients.

Limitations

One of the limitations of this study was its relatively small sample size and the lack of use of advance monitoring systems. For better investigations, studies in the form of clinical trials with a larger sample size can be used.

Suggestion

Studies in the form of clinical trials, with a larger sample size, increase the validity of the results. Also, the measurement of various parameters in the first 3 hours has been analyzed in our study, which should be measured and compared with advanced hemodynamic parameters in a longer period of time.

Funding Statement

Financial supported by Mashhad University of Medicine Sciences

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