Effect of Hypertonic Saline on Adequacy of Resuscitation, Progression of Inflammation and Outcome of Critically Ill Septic Patients.

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Abstract: Background: Many studies discussed the use of hypertonic solutions (HTS) for treatment of septic shock; however, they do not refer to the possible prophylactic benefit of early use of such solutions (before development of severe sepsis or septic shock). **Aim of the work:** to evaluate the effect of early administration of hypertonic saline on adequacy of resuscitation, progression of inflammation and outcome of critically ill septic patients. **Patients and methods:** Thirty patients with sepsis were enrolled in our prospective study in El-helal hospital. Patients were divided into two groups: The study group(group A) (15 patients) with sepsis received 4ml/kg b.wt 7.5% hypertonic saline over 15 minutes plus standard medical therapy, compared to the control group(group B) (15 patients) with sepsis received standard medical therapy alone. Both groups were monitored as regard to hemodynamics (MAP, HR, UOP, CVP), respiratory parameters (R.R, ABG, CVSO2) and laboratory parameters (WBCs, CRP, TNF-α). **Results:** group A showed significant reduction in heart rate(P=0.049) and respiratory rate(P=0.001), occurrence of metabolic acidosis (p= 0.019), inflammatory markers (WBCs, CRP) (P=0.019, 0.034, respectively) , TNFα (p= 0.001), the rate of occurrence of septic shock (p = 0.006), need for mechanical ventilation (p = 0.006), the mean ICU length of stay (p = 0.001) , ICU mortality (p =0.032) and increase in CVSO2 (P = 0.034) compared to group B. **Conclusion:** HTS 7.5% has no inferior results on critically ill septic patients, but it has superior results in comparison to other fluids as it decrease inflammatory markers (WBCs, CRP), inflammatory mediator TNF-α and improve secondary outcome (occurrence of septic shock, need for mechanical ventilation, ICU mortality) with significant reduction of the mean ICU length of stay when given in early sepsis.

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Abbreviations: MAP (mean arterial pressure), HR (heart rate), UOP (urine output), CVP (central venous pressure), R.R (respiratory rate), ABG (arterial blood gases, CVSO2 (central venous oxygen saturation),WBCs (white blood cell count), CRP (C reactive protein), TNF-α (tumor necrosis factor α).

1. Introduction:

Widespread activation of cells responsive to pathogens results in uncontrolled systemic inflammation. The release of inflammatory mediators induces vascular dilatation and increase in permeability with leakage of plasma components, extravasations and activation of leucocytes to tissues and organs [(1)]. The cytokines tissue necrosis factor-α (TNF-α) and Interleukin (IL)-1 are released first and initiate several cascades. TNF-α and IL-1 have been shown to be released in large quantities within 1 hour of an insult and have both local and systemic effects (2).

The infusion of several liters of isotonic fluids is associated with the adverse effects of extravasation into the interstial space. In sepsis, in particular, this may result in peripheral and/or pulmonary edema (3). Several studies have been performed that used small volume resuscitation which is defined as a rapid infusion of hypertonic solution (NaCl 7.5%) at a dose of 2-4 ml/kg into a peripheral vein and have some demonstrated promising beneficial effects (4). Most of the studies found that HTS infusion caused a rapid and significant increase in oxygen delivery, elevated cardiac output, increased oxygen extraction and redistribution of fluids from the perivascular to the intravascular space (5).

Improvement in myocardial contractility by HTS may be related to direct hyperosmolar effect, restoring transmembrane potentials or decreasing myocardial edema (6).

A large number of very interesting experiments highlighted that HTS resuscitation may decrease susceptibility to post-traumatic sepsis; modulate trauma and sepsis-induced immune dysfunction, inflammatory response and apoptosis (7) .

During small volume resuscitation by HTS, the intracellular fluid is primarily mobilized from microvascular endothelial cells and erythrocytes; this produces a reduction in hydraulic resistance and an

improvement in tissue perfusion(8). HTS may also improve immune function with control of neutrophils migration; reduce pro-inflammatory mediators and free radicals with increased antibacterial activity and decreased susceptibility to bacterial toxins (**9**).

Data have been reported which indicate that HTS augments interleukin-10 induction by lipopolysaccharide in the bacterial cell-wall and reduces tumor necrosis factor α level. These actions may explain the lesser degree of injury following HTS administration. However, because HTS reduces but does not completely abrogate proinflammatory pathways, there is an adequate balance between proinflammatory and anti inflammatory cytokines, thus maintaining the ability to fight bacteria efficiently (10).

Aim of the work:

To evaluate the effect of early administration of hypertonic saline on adequacy of resuscitation, progression of inflammation and outcome of critically ill septic patients.

Patients' Population and data collection:

Thirty patients with sepsis were prospectively enrolled in our study, which performed in ICU of El-helal hospital (Cairo, Egypt).

A-Inclusion criteria:

-Age between 30 and 50 years old, both sexes.
-Evidence of SIRS: 3 or more of the following:
-Fever of more than 38 ^{o}C or less than 36 ^{o}C.
-Heart rate of more than 90 bpm.
-Respiratory rate of more than 20 breaths per minute or a $PaCo_2$ level of less than 32 mm Hg.
-Abnormal WBCs count (>12,000/μL or <4,000/μL or >10% bands)
-Presence of documented infection (11).

B. Exclusion criteria:

-Patient with septic shock or end-organ dysfunction (altered organ function such that normal physiology cannot be maintained without support)
-Patients on circulatory support or mechanical ventilation.
-Patients with pre existing severe organ system dysfunction.
-Patients with poorly controlled blood sugar or uncontrolled blood pressure.

Our patients were divided into two groups;

(Group A)Study group (n = 15): These patients will be administered 4 mL / kg of hypertonic saline 7.5 % over 15 minutes every 24 hours. Maintenance of the same hemodynamic parameters will be achieved with isotonic fluids when needed, in addition to the same lines of treatment of Control group.

Group B (Control group, n = 15):

These patients will be managed with isotonic solution (Ringer acetate, or normal saline) to maintain the following hemodynamic values (central venous pressure 8 – 12 mm Hg, mean arterial pressure ≥ 65 mm Hg, urine output > 0.5 mL / kg / h) in addition to the other lines of treatment of septic patients in ICU.

Both groups are subjected to:

I- Full history from patient relatives and full clinical examination.

II- Hemodynamic monitoring (MAP, HR, UOP, CVP):

Will be measured at the start of the study (base line) then every 2 hours for 48 hours.

III-Respiratory parameters monitoring (RR, ABG, CVSO2):

Will be measured at the start, then every 24 hours for 48 hours.

IV-Laboratory parameters (CRP, WBCS, TNF-α):

Will be measured before resuscitation and after 48 hours.

All patients were followed up during period of hospitalization from the date of ICU admission for.

Need for mechanical ventilation.
Occurrence of septic shock and need for circulatory support.
Length of stay in ICU.
Death.

2. Method of statistical analysis:

The sample was selected by simple random sample so all members of the population have an equal chance of being selected as part of the sample. Every patient with sepsis admitted to the hospital and matching the inclusion and exclusion criteria. Data collection using textular, tabular and graphical method. Our primary data is master tables and our secondary data is the statistical results. Data was statistically analyzed using SPSS (statistical package for social science) program version 13 for windows and Epi info program version for all the analysis a p value < 0.05 was considered statistically significant Data are shown as mean, range or value and 95% confidence interval (95% CI) and frequency and percent.

3. Results:

Patient characteristics on admission:

In randomised controlled trial, 30 patients, 16 (53.3%) males and 14 (46.7%) females with sepsis were enrolled in the study with mean age 41.8 ± 3.7 years.

Patient divided randomly into two groups:

(Group A) Study group: 15 patients with sepsis received hypertonic saline plus standard medical therapy (SMT),

(Group B) Control group: 15 patients with sepsis received standard medical therapy (SMT) alone.

A. Comparison of baseline characteristics between both groups according to demographic data (age, gender), vital signs (MAP, HR, R.R), hemodynamic monitoring parameters (CVP, UOP), ABG, CVSO2 and laboratory parameters (CRP, WBCs, TNF-α):

There were no statistically significant differences in baseline characteristics among the two groups of patients regarding demographic data (age, gender) and patient characteristics before treatment as regard to (vital signs, hemodynamic monitoring parameters(CVP, UOP), ABG and Laboratory parameters), **(Table1).**

Table (1): Comparison of baseline characteristics on admission between both groups

Characteristic	HTS(study group)=15	SMT (control group)=15	*P*-value
Age(yrs)	41.8 ± 4.1	41.7 ± 3.4	0. 9
Male gender%	53% (8)	53% (8)	1. 0
MAP	88.3 ± 3.6	86.3 ± 3.9	0.162
HR(beats/min)	113.3 ± 3.6	113 ± 4.1	0.816
RR(breaths/min)	26.1 ± 3.2	25.4 ± 2.6	0.500
CVP	7.45 ± 0.01	7.45 ± 0.009	0.377
UOP	72.4 ± 10.2	72.3 ± 11.2	0.980
PH	27.8 ± 2.4	27.1 ± 2.4	0.465
HCO_3(mmole/L)	21.4 ± 1.2	21.1 ± 1.5	0.492
PaO_2(mmHg)	9.9 ± 0.4	9.9 ± 0.4	1.000
$PaCO_2$(mmHg)	106.7 ± 14.8	98.3 ± 17.6	0.172
SPO_2	94 ± 2.4	94.2 ± 2.2	0.787
$CVSO_2$	65.2 ± 2.4	65.3 ± 2.07	0.899
CRP	84.2 ± 11.2	82.8 ± 10.4	0.726
WBCs	21.2 ± 4.8	22.8 ± 5.0	0.401
TNF-α	289 ± 207	172 ± 89	0.06

(N.B).Reference range of TNF-α (10-50 pg/ml), ideal range (<8.1 pg/ml)

B. Primary outcome:

♦ **Mean changes in patient characteristics 48 hours after treatment:**

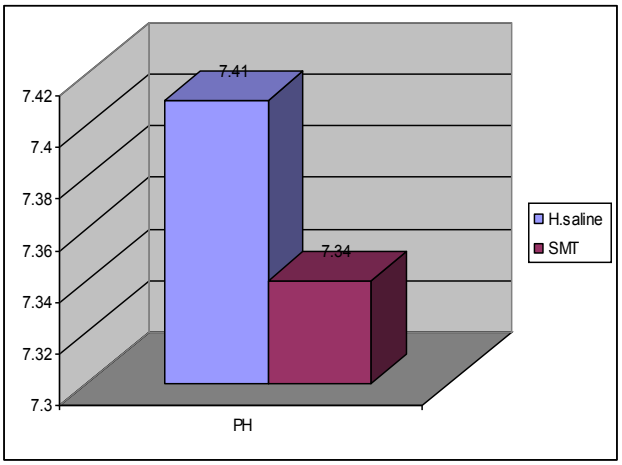
Comparison between two groups regarding mean changes in vital signs, hemodynamic monitoring parameters (CVP, UOP), ABG, CVSO2 and laboratory parameters (CRP, WBCs, TNF-α) 48h after treatment:

Showed significant reduction in heart rate (HR) , respiratory rate (RR), significant changes in PH , $PaCO_2$ and HCO_3 , significant changes of $SCVO2$ and significant reduction of CRP, $WBCs$ and $TNF\alpha$ in **(group A)** which receive hypertonic saline plus standard medical treatment compared with **(group B)** which receive standard medical therapy alone(Table 2; Figs. 1-4).

Table (2) Comparison between two groups regarding mean changes in vital signs, hemodynamic monitoring parameters (CVP, UOP), ABG, $CVSO_2$ and laboratory parameters (CRP, WBCs, TNF-α) 48hrs after treatment.

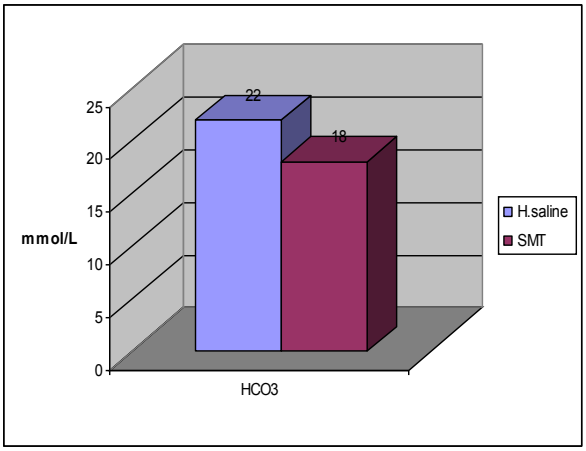
Characteristic	HTS(study group)=15	SMT (control group)=15	*P*-value
MAP	89.67 ± 3.52	87 ± 4.14	0.068
HR(beats/min)	91 ± 9	100 ± 14	0.049*
RR(breaths/min)	18 ± 1	22 ± 2	0.001*
CVP	9.9 ± 0.4	10 ± 0.3	0.667
UOP	105 ± 14	101 ± 17	0.571
PH	7.41 ± 0.02	7.34 ± 0.10	0.019*
HCO_3(mmole/L)	22.5 ± 1.5	18.7 ± 4.4	0.006*
PaO_2(mmHg)	75.8 ± 6.6	75.8 ± 6.6	0.477
$PaCO_2$(mmHg)	35.6 ± 3.0	29.6 ± 4.6	0.001*
SPO_2	95 ± 1	94 ± 2	0.415
$CVSO_2$	66.1 ± 1.5	62.7 ± 5.4	0.034*
CRP	59.6 ± 8.1	71.5 ± 18.4	0.034*
WBCs	14.6 ± 4.2	19.5 ± 6.2	0.019*
TNF-α	12.4 ± 9.8	171.7 ± 89.4	0.001*

Significant *p*- value<0.05.



P value 0.01

Figure (1): PH 48hrs after treatment



p value 0.006

Figure (2): HCO_3 48hrs after treatment

C. Secondary outcome:

There was statistically significant reduction in the rate of occurrence of septic shock, need for mechanical ventilation, ICU mortality and the mean ICU length of stay in group A(study group) patients compared to group B (control group) , (Table 3; Fig. 5).

Table (3): Secondary outcome

Characteristic	HTS(study)**N = 15**	SMT(control)**N = 15**	P **- value**
Septic Shock No %	0 (0%)	6 (40%)	0.006*
Mechanical ventilation No %	0 (0%)	6 (40%)	0.006*
ICU **mortality No %**	0 (0%)	4 (26%)	0.032*
Mean ICU **length of stay (days)**	9.8 ± 3.8	17.2 ± 5.0	0.001*

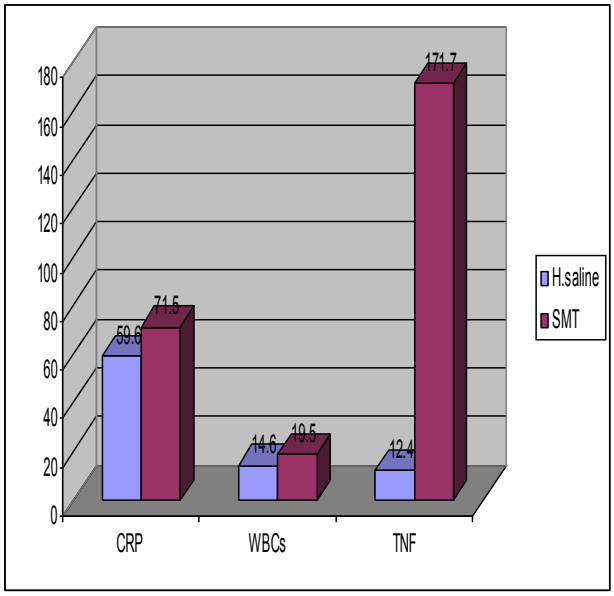


Figure (4): Laboratory data 48hrs after treatment

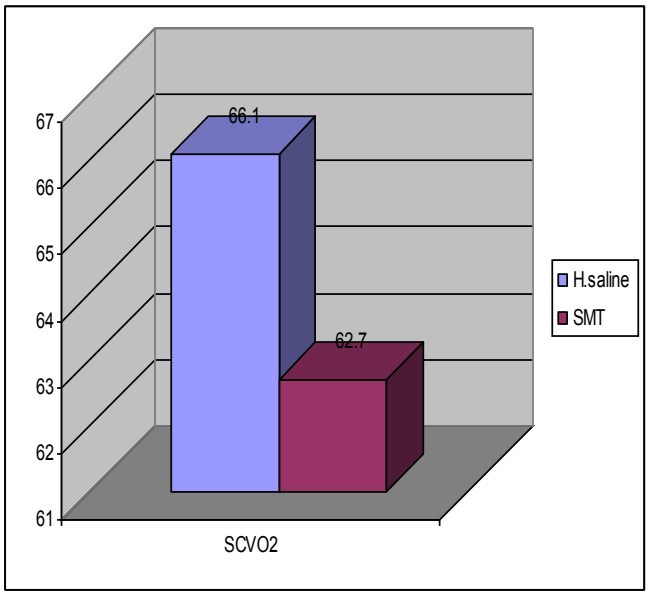


Figure (3): SCVO2 48hrs after treatment

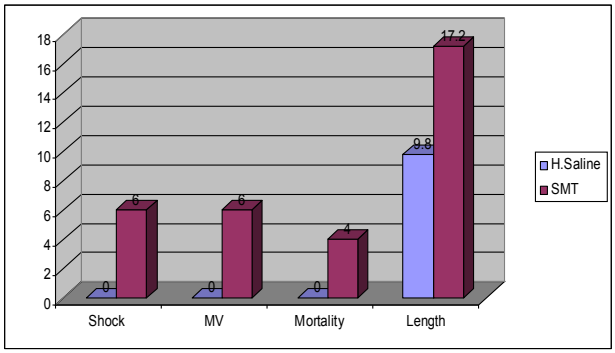


Figure (5): Secondary outcome and complication

4. Discussion:

In their review, Oliveira and coworkers discussed the use of hypertonic solutions for treatment of septic shock; however, they do not refer to the possible prophylactic benefit of early use of these solutions (before development of severe sepsis or septic shock) (8).

In our study we gave HTS 7.5% early in sepsis before development of multiple organ dysfunction syndrome or septic shock unlike other studies which were always looking for the effect of HTS 7.5% on septic patients after development of multiple organ dysfunction syndrome or septic shock, and this explains the differences in results according to hemodynamics , respiratory parameters, laboratory parameters (WBCs, CRP, TNFα) and secondary outcome (ICU mortality or ICU length of stay) because of delayed use of HTS 7.5% in other studies.

Our study supported that HTS 7.5% when given in early sepsis avoid progression of inflammation (from sepsis to septic shock), and improve outcome of critically ill septic patient. This was proved in our study which showed significant reduction in heart rate (20% versus 11%) and respiratory rate (31% versus 12%) (P=0.049, 0.001, respectively) , significant reduction in occurrence of metabolic acidosis((p=0.019), significant reduction of WBCs (29% versus 17%; P=0.019), CRP(29% versus 13%; P=0.034) and TNFα (95% versus 0% reduction; P=0.001) and significant reduction in the rate of occurrence of septic shock(zero versus 40% septic shock; P=0.006), need for mechanical ventilation(zero versus 40% mechanical ventilation; p = 0.006), ICU mortality(zero versus 26% mortality; p =0.032) and the mean ICU length of stay(10 days versus 17; p = 0.001) in study group(group A) which receive hypertonic saline plus standard medical treatment compared to control group (group B) which receive standard medical therapy alone. These results explained by **early improvement in hemodynamic status** (6), cardiac contractility may also improve (12), **immune modulating effect** (13) and reducing tumor necrosis α factor level (10).

Since, the prediction of outcome is one of the major problems associated with critical illness. Investigations have been performed on the potential use of TNF-α and other proinflammatory mediators as prognostic indicators for severity of disease and for mortality in previously healthy immunocompetent patients with well-documented sepsis or severe sepsis and was found that non survival from sepsis or septic shock had been mainly associated with higher levels and persistant high serum TNF-α, Also patient with an early haemodynamic deterioration associated with higher levels of TNF-α (14). This come in agree with our study which showed that septic shock, need for mechanical ventilation, ICU mortality and prolonged ICU length of stay associated with higher levels and persistent high TNF-α which observed in group B(control group), not received HTS .

Also in a study performed by **Chih-Chin *et al.*, 2008** who investigated the effect of (HTS 7.5% 4ml/kg) on the hemodynamics (MAP, HR) and 18 hours mortality results from the development of multiple organ dysfunction syndrome) on 128 rats having sepsis induced by cecal ligation and puncture, and the animals observed another 18 hours. The result was that hypertonic saline prevented circulatory failure, alleviated multiple organ dysfunction syndrome, and decreased the mortality rate (15). This comes in agree with our study which showed significant reduction in the rate of occurrence of septic shock, *ICU* mortality (P=0.006, 0.034, respectively).

In a study performed by **Gurfinkel et al., 2003** who compared the effect of hypertonic saline (HTS 5ml/kg) and isotonic saline (IS) solutions on tumor necrosis factor-alpha and survival benefit on Wister rats having endotoxic shock. The result was that, patients treatment with HTS have decrease in tumor necrosis factor-alpha (p < 0.0001) and lower mortality with (p < 0.01) (16). This comes in agree with our study which showed that the early use of HTS significantly decreases TNF-α (p = 0.001) and decreases ICU mortality with (p =0.032).

While **Maciel et al., 1998,** who investigated the effect of HTS 7.5% on MAP, and mortality in patients with septic shock on 14 patients, and shows that no significant difference in MAP between the two groups and there was no survival benefit of HTS (5). This comes in agree with our study which showed that there was no statistically significant difference in patient MAP among the two groups (p 0.068), but this was not in agreement with our study which showed that HTS 7.5% decrease mortality due to sepsis with significant p value 0.032.This is can be explained by delayed use of HTS in this study.

Conclusion and recommendation:

HTS 7.5% has no inferior results on critically ill septic patients, but it has superior results in comparison to other fluids as it decrease inflammatory markers (WBCs, CRP), inflammatory mediator TNF-α and improve secondary outcome (occurrence of septic shock, need for mechanical ventilation, ICU mortality) with significant reduction of the mean ICU length of stay when given in early sepsis. So we recommend further studies to evaluate prophylactic benefit of HTS when used early (before development of severe sepsis or septic shock).

Limitations:

Small number of patients of both study and control group.

Cardiac output and ejection fraction are not used as comparing parameters.

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