# EFFECT OF HYPERTONIC SALINE ON ADEQUACY OF RESUSCITATION, PROGRESSION OF INFLAMMATION AND OUTCOME OF CRITICALLY ILL SEPTIC PATIENTS

## Thesis

**For partial fulfillment of master degree in Critical care.**


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**Abstract:**

The present study was designed to evaluate the effect of early administration of hypertonic saline on adequacy of resuscitation, progression of inflammation and outcome of critically ill septic patients.

The result of the study showed that HTS 7.5% has prophylactic role in progression of inflammation in septic patients as HTS 7.5% 4ml/kg infusion lead to significant reduction in laboratory parameters of inflammation (CRP, WBCs and TNFα) with significant improvement of tachycardia and tachypnea induced by sepsis and reduction of occurrence of metabolic acidosis, so HTS infusion lead to improvement of outcome of critically ill septic patient according to occurrence of septic shock, need for mechanical ventilation, ICU mortality and the mean ICU length of stay.

**Keywords:** Hypertonic saline, inflammation, critically- ill septic patients.

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# List of Abbreviations

| | |
|---|---|
| **ACCP** | American Collegue Of Chest Physicians. |
| **APACHE** | Acute Physiology and Chronic Health Evaluation. |
| **APC** | Activated Protein C |
| **ASK1** | Apoptosis signal-regulating kinase 1 |
| **ATF2** | Activating transcription factor 2 |
| **BNP** . | Brain or (B-type) Natriuretic Peptide. |
| **CBC** | Complete Blood Count. |
| **c-Jun** | Is the name of a gene and protein that, in combination with c-Fos, forms the AP-1 early response transcription factor. |
| **CRP** | C-Reactive Protein. |
| **C.V.P** | Central venous pressure |
| **CXCR** | Chemokine Receptors. |
| **CXC** | Chemokines |
| **DIC** | Disseminated Intravascular Coagulation. |
| **EC** | Endothelial cells |
| **ELISA** | Enzyme Linked Immunosorbant Assay. |
| **ERKs** | Extracellular-signal-regulated kinases |
| **FDP** | Fibrin Degradation Products. |
| **GCKs** | One of enzymes of signal transduction and intracellular pathways |
| **HR** | Heart rate |
| **IKK** | Inhibitors of NF-Kb protein kinase |
| **IL** | Interleukin. |
| **iNOS** | Inducible Nitric Oxide.Synthase. |
| **INR** | International Normalized Ratio. |

| | |
|---|---|
| **JNK** | Jun N-terminal kinase. |
| **LT** | Lymphotoxin |
| **MAP** | Mean arterial Pressure. |
| **MAP2K** | One of 3 enzymes of mitogen activated protein kinase kinase |
| **MAP3K** | One of 3 enzymes of mitogen activated protein kinase kinase |
| **MAPK** | Mitogen activated protein kinase |
| **MEK** | One of 3 enzymes of mitogen activated protein kinase kinase |
| **MEKK** | One of 3 enzymes of mitogen activated protein kinase kinase kinase |
| **MIF** | Macrophage migration Inhibitory Factor. |
| **MKK** | One of 3 enzymes of mitogen activated protein kinase kinase |
| **MKKK** | One of 3 enzymes of mitogen activated protein kinase kinase kinase |
| **MOD score** | Multiple Organ Dysfunction score. |
| **MODS** | Multi Organ Dysfunction Syndrome. |
| **NF-κB** | Nuclear factor kappa B |
| **NOS** | Nitric Oxide.Synthase |
| **PaCO2** | Partial Carbon dioxide tension. |
| **PAF** | Platelet Activatig Factor |
| **PAI-1** | Plasminogen Activator Inhibitor-1 |
| **PaO2** | Partial Oxygen tension |
| **PCR** | Polymerase Chain Reaction. |
| **RIP** | Receptor inhibitory protein |
| **R.R** | Respiratory rate |
| **RR** | Relative risk |
| **SAPS** | Simplified Acute Physiology Score |
| **SAFE study** | analysis of data from the saline versus albumin fluid evaluation |

| | |
|---|---|
| **SCCM** | Society of Critical Care Medicine. |
| **SD** | Standard Deviation. |
| **SIRS** | Systemic Inflammatory Response Syndrome. |
| **SODD** | Superoxide dismutase associated death domain protein |
| **SOFA** | Sequential Organ Failure Assessment |
| **SVO2** | mixed Venous Oxygen Saturation. |
| **ScvO2** | central venous oxygen saturation |
| **TACE** | TNF alpha converting enzyme |
| **TF** | Tissue Factor |
| **TISS** | Theraputic Intervention Scoring System |
| **TLRs** | Toll Like Receptors |
| **TM** | Thrombomodulin. |
| **TNF-RA** | Tumor Necrosis Factor-Receptor Antagonist |
| **TNFα** | Tumor Necrosis Factor α. |
| **TRADD** | Tumor necrosis factor receptor type 1 associated death domain protein |
| **TRAF2** | TNF receptor-associated factor 2 |
| **Trks(Trx)** | One of enzymes of signal transduction and intracellular pathways(activating receptor tyrosine kinases) |
| **WBCs** | White Blood Cells. |

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# Introduction

Sepsis and the systemic inflammatory response syndrome (SIRS) are common and represent a major factor in morbidity and mortality in intensive care units and the critically ill. The pathogenesis of these syndromes is becoming increasingly understood and it is hoped that this will result in improved outcome ***(R I Paterson et al., 2000).***

SIRS is the clinical response to infection manifested by two or more of the Following:

-Temperature ≥ 38 C or ≤36 C.

- HR> 90 bpm.

- Respiration ≥ 20 breaths/ min.

- WBC count ≥12,000/micro liter or ≤4,000/micro liter or ≥ 10% immature Neutrophils.

Sepsis is defined as confirmed or suspected infection plus ≥ 2 SIRS criteria.

Severe sepsis is sepsis and ≥ one organ dysfunction, while septic shock is defined as sepsis plus hypotension (≤90 mm Hg) despite fluid resuscitation ***(Annane D et al., 2002)***.

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, and extravasations and activation of leucocytes to tissues and organs ***(Van Amersfoort ES et al., 2003)***.

The cytokines tumor 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 ***(Casey LC et al., 2000)***.

Rivers and colleagues demonstrated that early resuscitation strategy, which was goal oriented with respect to manipulation of cardiac preload, afterload and contractility, reduced the incidence of multiple organ dysfunction and mortality ***(Rivers E et al., 2001)***.

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 ***(Astiz ME et al., 1993)***.

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 some promising beneficial effects ***( Hannemann L et al., 1996).***

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 ***(Maciel F et al., 1998)***.

Improvement in myocardial contractility may be related to direct hyperosmolar effect, restoring transmembrane potentials or decreasing myocardial edema ***(mouren S et al., 1995)***.

A large number of very interesting experiments highlighted that hypertonic saline resuscitation may decrease susceptibility to post-

traumatic sepsis, modulate trauma and sepsis-induced immune dysfunction, inflammatory response and apoptosis ***(Oliveira et al., 2002)***.

During small volume resuscitation, 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 ***(Roselaine P Oliveira et al., 2002).***

Also, reduction in Plasma concentration of nor epinephrine (noradrenaline), epinephrine (adrenaline), vasopressin, and renin were greater with hemodilution combined plasma volume expansion than with hemodilution alone, indicating that alteration in hormone release have a role to play in cardiovascular response to HTS ***(Wade CE et al., 1991)***.

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 (***Zalen G et al., 2000)***.

Data have been reported that indicate that HTS augments interleukin-10 induction by lipopolysaccharide in the bacterial cell-wall and reduces tumor necrosis factor 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 ***(Oreopoulos GD et al., 2001)***.

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) ***(Roselaine P Oliveira et al., 2002).***

# Aim of the work

This study is designed to evaluate the effect of the early administration of hypertonic saline on adequacy of resuscitation, progression of inflammation and outcome of critically ill septic patients.