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Sepsis volume reposition with hypertonic saline solution

Reposição de volume na sepse com solução salina hipertônica

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ABSTRACT

The present review discusses the hemodynamic and immune-modulatory effects of hypertonic saline in experimental shock and in patients with sepsis. We comment on the mechanisms of action of hypertonic saline, calling upon data in hemorrhagic and septic shock. Specific actions of hypertonic saline applicable to severe sepsis and septic shock are highlighted. Data available support potential benefits of hypertonic saline infusion in various aspects of the pathophysiology of sepsis, including tissue hypoperfusion, decreased oxygen consumption, endothelial dysfunction, cardiac depression, and the presence of a broad array of pro-inflammatory cytokines and various oxidant species. A therapy that simultaneously blocks the damaging components of sepsis will have an impact on the management of sepsis. Proper designed prospective studies may prove a beneficial role for hypertonic saline solution in the future.

Keywords: Saline solution, hypertonic/pharmacology; Shock, septic/therapy; Sepsis/therapy

INTRODUCTION

In spite of advances in diagnosis and treatment, sepsis maintain high rates of mortality, around 30-80%.[1-3] Patients with severe sepsis experience marked cardiovascular disturbances that can compromise oxygen delivery to the tissues and consequently are in part responsible for the organ dysfunction and the high mortality rate observed in those patients.[4,5]

Sepsis is a severe systemic inflammatory syndrome which is followed by vasodilatation, myocardial depression, intravascular volume reduction and increased metabolism.[4] Sepsis and septic shock induces an intense release of inflammatory mediators, associated with inadequate tissue blood flow.[6,7]Advances in the understanding of pathophysiology of sepsis started after World War II when Beecher (1952) used volume reposition in a fast way as a therapy for hypovolemic condition.[8] The hemodynamic approach for severe sepsis and septic shock includes a rapidly restoration of intravascular volume and an adequate balance of delivery and demand of oxygen. In order to reach hemodynamic and tissue perfusion goals in the treatment of septic patients the use of fluids is a routine clinical practice.[9,10]

Infusion of great amounts of fluids (colloids or crystalloids) to reach the adequate tissue perfusion is common.[9] However, infusion of great amount of volume is associated to adverse event of interstitial extravasation that may result in tissue edema, particularly the lung and contributing or worsening

acute lung injury.

In 1952, Parkins et al.[11] showed that isotonic solutions were effective for recovery of hemodynamic in dogs submitted to hemorrhagic shock, if the volume used was the double of blood shaded. Saline solutions were also efficient in the correction of interstitial dehydration caused by the exit of water and sodium to intracellular space that happens during shock.[12] However the use of isotonic solutions in order to normalize arterial blood pressure may cause the worsening of respiratory function.[13-16]

Nonetheless, global resuscitation may not be sufficient for prevent microcirculatory dysfunction with consequent ischemia and tissue damage[9,17-19] and most of cell lesions occur after volume reanimation.[13,20-23]

Hypertonic solution has been showed as an interesting therapeutic tool for experimental hemorrhagic shock since 1917.[24,25] In the hemorrhagic shock was demonstrated that hypertonic sodium chloride injection followed by the reinfusion of blood reduced tissue damage and increase survival.[26,27] Rowe et al.[28] demonstrated in 1972 that NaCl 30% resulted in cardiac output and systolic volume increase, reduction of vascular systemic and pulmonary resistance and hemodilution in dogs.

Velasco et al. described the use of 7.5 % hypertonic saline solution (HSS) in experimental hemorrhagic shock.[29] The authors observed immediate recovery of blood arterial pressure and cardiac output, increase in plasma osmolarity, plasma sodium, correction of metabolic acidosis, transitory expansion of plasma volume and increased survival. Since that study many authors have studied the effects of hypertonic solution and its superiority compared to others fluid for volume reposition.[30,31] In the 80', de Felippe et al.[32] showed hemodynamic benefits in patients with hypovolemic shock refractory to conventional volume, corticoid and dopamine treatment. Other clinical studies realized in 1988 by Younes et al.[33] showed that the hypertonic solution, administrated in a peripheral vein, was effective in improve blood arterial pressure of patients admitted in the emergency room. Mattox et al.,[34] realized a multicentric prospective clinical trial for pre hospital treatment, they demonstrated that conventional treatment with isotonic solution was followed with higher rates of respiratory and renal failure, and coagulophaty compared to the group of patients treated with hypertonic. In 1984, Nakayama et al.,[35] showed an improvement of blood arterial pressure, cardiac output, increase in plasma volume and reduction of vascular resistance and consequent circulatory improvement.

From these studies several authors have shown the HSS effects on different experimental as well as clinical studies for treatment of different pathologies as: trauma, cardiogenic shock, septic shock and volemic support of surgeries.[36-39] The hemodynamic and immunomodulatory effects of hypertonic solution have been shown beneficial in sepsis.[31,39,47]

Thus, hypertonic saline solutions emerge as potential beneficial alternatives in fast global and microcirculatory hemodynamic resuscitation and in diminishing the inflammatory insult.

EXPERIMENTAL STUDIES WITH HYPERTONIC SALINE SOLUTION (HSS)

Hypertonic solution has been largely studied in its efficacy for hemorrhagic shock.[48] However there are a few studies in the field of sepsis and septic shock using hypertonic saline solution.[39,46,49-50]

The main beneficial effects of HSS reanimation in septic shock models are the intravascular volume expansion and consequent improvement of cardiovascular function as well as hemodynamic parameters, better blood redistribution and improvement of microcirculation. Particularly in sepsis, the relevant anti-inflammatory effect of hypertonic solution that may reduce SIRS and attenuated MODS suggest that this is the most intriguing beneficial effect.[31]

Septic shock studies in animals' models confirm that hypertonic solution can be a helpful tool, Shi et al.[51] showed reduction of lung and gut damage with hypertonic saline solution compared to Ringer lactate. The protection on gut also was followed by lower intestinal bacteria translocation. Another study confirmed that the susceptibility to occur sepsis was reduced in hemorrhagic shock after hypertonic solution.[52] Two hit model studies were able to show that hypertonic solution after the first aggression presented a protective action against the second hit event.[8,40,42,53-57]

Lagoa et al.[58] used an intravenous injection of live bacteria in dogs, Ringer Lactate Solution restored the systemic hemodynamic parameters, but was not efficient in restore an adequate tissue perfusion. Also using the same septic model, Garrido et al.[59] showed that hypertonic and Ringer Lactate solutions promoted hemodynamic beneficial, however only the hypertonic increased the mesenteric and systemic oxygen extraction, what suggest that hypertonic was able in improve blood flow redistribution and microcirculatory perfusion. Other authors have shown an improvement of microcirculation

when was used an association of hypertonic solution and colloid in sepsis.[44,47,60-62]

Oi et al.[61] showed in septic pigs an improvement in cardiac output, portal and intestinal as well as a reduction of pCO2 gradient of intestinal mucosal-arterial when hypertonic solution and 6% Dextran was infused in the animals compared to an isotonic solution. Like others using a pig model of sepsis, the authors observed that hypertonic solution reduced mortality.[61,63]

The mechanism evolved in the action of hypertonic solution in sepsis have been related to hemodynamic effects[39,44-47,52,64,65] and immunomodulatory reducing release of proinflammatory cytokines, expression of L-selectin as well as the oxidative burst in the neutrophil.[43,45,66-73] Other kind of effects have been reported, Parreira et al.[41] showed that hypertonic solution changes brown fat tissue protecting from hemorrhagic shock and it has been also demonstrated in sepsis and MODS.[74]

CLINICAL STUDIES WITH HYPERTONIC SOLUTION

Over 300 papers have been published in the last decade about hypertonic solution in hemorrhagic shock.[75] However, for sepsis and septic shock the clinical trials using hypertonic solution are rare. An important observational clinical study related to the effects of resuscitation with 2 or 4 ml/kg of hypertonic solution in 21 patients in septic shock was published by Hannemann et al.[46] The authors observed increased oxygen transport, cardiac output, and pulmonary capillary wedge pressure in patients treated with HSS. Except for the increase in pulmonary capillary wedge pressure, none of the cardiovascular changes lasted for longer than 60 min. Plasma sodium levels increased and normalized within 24 hours after HSS infusion.

Oliveira et al.[39] studied the hemodynamic effects of a hypertonic saline/dextran solution as compared with those of a normal saline solution in severe sepsis. Patients were randomly assigned, in a blinded manner, to receive 250 ml of a solution of either normal saline (n = 16) or hypertonic saline (NaCl 7.5%/dextran 8%; n = 13). Before they received normal saline or HSS, patients had to have been stable for at least 60 min. Over the 180 min following infusion of normal saline or HSS, the rate of infusion of regular fluid or vasoactive drug was not changed. The cardiac and stroke volume indices increased, and systemic vascular resistance decreased only in the HSS group, without any change in arterial pressure. The increase in plasma sodium levels lasted for 6 hours in the HSS group. Those investigators concluded that hypertonic saline/dextran solution improved cardiovascular performance and resuscitated severely septic patients through a volume effect, but may also directly improve cardiac function.

Muller et al. observed similar hemodynamic effects in 12 mechanically ventilated patients with severe sepsis or septic shock requiring a pulmonary artery catheter and volume loading but using a pure 250 ml hypertonic 7.5% saline solution.[50]

All previous studies showed that 7.5% hypertonic saline solution improved cardiovascular function mainly because of volume expansion.[39,46,50] Similarly in all studies, the effects of a small volume of HSS almost doubled the cardiac index and the effect lasted up to two hours. However, the magnitude of the effect on blood flow was probably due to a combination of increase in filling pressures, a reduction on vascular resistance, hemodilution and an increase on myocardial contractility.

HYPERTONIC SOLUTION MECHANISMS

The most important actions reported in the literature for hypertonic solution are: (a) restore of plasmatic volume and blood arterial pressure as a direct consequence of mobilization of fluid from intracellular to extracellular compartments by the osmotic gradient produced;[76] (b) improvement of cardiac output by increase of preload;[30] (c) reduction of endothelial and tissue edema;[30,77,78] (d) arteriolar vasodilatation;[60,79,80] (e) reversion of refractory hemorrhagic shock;[29,81-84] (f) correction of metabolic acidosis;[82,85] (g) modulation of cytokines release;[55,86] (h) fast blood flow restore and function recovery of kidney, liver and intestine;[60,87,88] (i) improvement of microcirculation;[77,89-91] (j) immunomodulatory effects.[13,14,52,55,86,87,92-94]

Intravascular volume expansion

Hypertonic solution promotes and keeps intravascular expansion for long period of time[36,95,96] also maintaining hemodynamic and metabolic actions. However, other authors showed a transient duration of the effects on oxygen delivery and extraction as well as increase in cardiac performance.[39,45,46,65] The osmotic strength of hypertonic solution generates fluid[48] and this effect produces plasma expansion.[29,96,97] In sepsis the same effects have been studied and reported.[39,45,46,64] The usual 4 mL/kg of 7.5% NaCl dosage adds a load of 5.12 mEq Na+/kg body weight which, if diluted exclusively into the plasma volume, it should significantly increase plasma sodium.[48]

Such values have never been observed in any laboratory or clinical trials and indicate that water has been osmotically drawn into the intravascular space.

Effects on the cardiac contractility

Myocardial function is depressed in the hyperdynamic phase of sepsis.[98,99] Cardiac contractility has been showed increased after hypertonic solution infusion, that effect has been related to the hemodynamic action (volume expansion and reduced afterload),[44,100] direct hyperosmolar effect, restoring transmembrane potentials or to a decreased myocardial edema.[101] *In vivo* and *in vitro* studies indicated an increase in the ventricular contractile force with mild and severe hyperosmolarity.[44,102,103] HSS has been shown to increase left ventricular dP/dtmax, cardiac output, and stroke work at equivalent or lower atrial filling pressures than with isotonic solutions.[82,104,105] A recent study with hypertonic solution and pentoxifiline showed increase in cardiac performance and mucosal gastric oxygenation.[56]

Microcirculatory effects of hypertonic solution

Besides hemodynamic improvement, a rapidly recovery of ischemia is determinant of clinical evolution.[88,106] Microvascular alterations related to hypertonic solution have received special attention and intense debate.[107] There are data showing increase in blood flow to peripheral vessels, due to reduction in vascular resistance as secondary effect of hemodilution and muscular vessel relaxation from hypertonicity action.[48]

Hypovolemia conditions including hemorrhagic shock and severe sepsis, course with endothelial cell edema secondary to hypoxia and neutrophil activation. The vessel lumen is partially occluded what produce blood flow obstruction and reduction in oxygen delivery.[77,83] The effect of intracellular fluid mobilization to extracellular during hypertonic infusion occurs first in the erythrocytes and endothelial cell, the direct consequence is lower vascular resistance and improved tissue perfusion.[77,88] Endogenous vasodilators substances may be released during hypertonic solution infusion also producing improved cardiac function and better peripheral blood flow distribution.[108] Hypertonic solution plus dextran used in pigs submitted to hemorrhagic shock resulted in hemodilution what also diluted some hormones as cortisol and aldostherone, as well as plasma levels of noradrenaline, adrenaline, vasopressin and renin.[31,109] Victorino et al.[110] showed that hypertonic solution acts on endothelial cells in the states of elevated microvascular permeability reducing fluid extravasation.

Immunomodulatory Effects

In the last years has been shown that one of the most important actions of hypertonic solution is the immunologic improvement,[111,112] intensely compromised in hemorrhage and sepsis.[93] It has been shown that an early infusion of hypertonic solution is able in protection of tissues from inflammation and improve immune response.[49]

The immunomodulatory effects of HSS start at the level of gene activation,[53,113,114] protein regulation,[54,66,115] activation of kinases of intracellular signaling,[116-118] free radical, heat shock protein and cytokines production and release[53,117] and finally the mechanism of cell adhesion.[68,119]

The chain of events for the lung damage reduction after hypertonic solution infusion[120] is explained by a reduced neutrophil infiltration in broncoalveolar lavage, reduction in albumin extravasation and lower histopathologic lesion.[40,66,72,87,93] Rhee et al.[14] observed that Ringer lactate produced higher activation of neutrophil compared to HS. However, hypertonic solution interferes in a favorable fashion in the neutrophil-endothelium interaction in the way that less PMN are marginated[14], that effect was shown related to a lower expression of L-selectin[93]. Following this line of thought, Rizoli et al. showed that hypertonic solution prevents expression and activation of CD11b by the cells after lipopolyssacharide challenge.[67] Intercellular adhesion molecule–1 (ICAM-1) has been showed reduced after hypertonic solution in the ischemic liver tissue.[121] Also the combined HSS and pentoxifiline were efficient in reduce neutrophil activation and pro-inflammatory mediators.[122] One clinical study confirmed that early treatment with hypertonic solution prevents activation of neutrophils.[75]

In 2003, Powers et al.[123] published the first study of immunomodulatory effects of HSS in macrophage. Lipopolyssacharide is a common tool to stimulate the production of tumor necrosis factor-α (TNF-α), in studies about hypertonic was showed that TNF-α was lower and HS induces the production of the anti-inflammatory cytokine IL-10. Rizoli et al.[94] in a recent clinical study showed that hypertonic solution changes monocyte distribution and modulate the balance of pro and anti-inflammatory cytokines. Many authors have verified that the immunomodulatory effects are due of high tonicity caused by sodium, as well plasma patients reanimated with hypertonic solutions as in animals and cell cultures experiments.[92,124]

Hypertonicity modulate cell signaling pathways

Hypertonicity simulating a clinical situation blocked degranulation and superoxide production in response to N-formil-methilonil-leucil-fenilalanine (fMLP), and impaired MAPKs activation: ERK1/2 and p38.[72,73,118] However, the oxidative burst was not suppressed by hypertonic solution when the stimulus was miristate phorbol acetate.[118] Taken together the conclusion is that hypertonic solution suppresses neutrophile function blocking the cell signaling upstream C kinase protein.

Hypertonic solution attenuated the expression of integrine β2 mediated by platelet activating factor (PAF), the production of free radical, and the release of elastase.[43,72,125] Cytoskeleton reorganize is a critical point for signal transduction mediated by receptor.[126] The alteration of cytoskeleton produced by hypertonic media prevents the reduction in MAPK p38 activation.

Effect on inflammatory mediators

Specific studies on cell effects of hypertonic solution showed a regulation on expression and release of elastase, cytokines, free radical and adhesion molecules. T cell incubated with NaCl in compatible levels found at the end of *in vivo* studies, i.e. 180 mmol/l, exhibited doubled proliferation. T cell function has been showed depressed in trauma by many factors. Prostaglandin–E2 is a substance that suppress T cell interfering in cell signaling pathway calciumnerin-dependent, finally inhibiting interleukin–2 production and consequent T cell proliferation.[108,124,127-129] A mononuclear cell was also inhibited by prostaglandin-E2 in culture. On the other hand, T cell showed a significant increase in proliferation when exposed to hypertonic medium. After a trauma immunologic cellular function is reduced and hypertonic solution restored spleen cells and T cell activity.[129] In a model of hemorrhagic shock with rats was showed a reduction of bacteremia, and that fact was related to T cell activity recovery with hypertonic solution.[86]

Recent data indicate that HSS can increase gene transcription of IL-10, reduce TNF from peritoneal macrophages, in spite of nuclear factor κB.[121] In several cell lineages have been shown that hypertonic solution reduces the production of TNF-α, IL-1β e IL-6.[55,130]

Probably most of immunologic and anti-inflammatory effects of hypertonic solution may be explained by data from a recent paper, the authors found an increase in the expression of heat shock proteins by the HS.[54,131] HSP 70 has an effect in reducing inflammatory response, demonstrated in sepsis and pancreatites models,[132,133] was showed that HSP reduces the expression of cytokines like as TNF-α, and HSP can reduce intercellular adhesion molecule.[134]

CONCLUSION

Resuscitation with HSS, which has been extensively studied in hypovolemic shock, appears to be reproducible in various models of experimental septic shock and present potential to immune-modulate septic response.

Hemodynamic effects are probably interesting mainly in the early phase of severe sepsis resuscitation. However, in spite of short time action of hypertonic saline solution, the modulation of immune functions promotes long time and latter effects, improving hemodynamic pattern and producing lower levels of inflammatory cytokines, and consequently reduction in tissue damage with reduced mortality in animal models. The anti-inflammatory effects of hypertonic solution, mainly in neutrophil, oxidative burst and cytokines release may reduce the excessive proinflammatory activation in sepsis. A therapy, that simultaneously blocks both of the damaging components of sepsis, namely ischemia and inflammation, will probably have an enormous impact on the management of sepsis. Proper designed prospective studies may prove a beneficial role for HSS in the future.

RESUMO

Esta revisão discute os efeitos hemodinâmicos e imunomoduladores da solução hipertônica em choque experimental e em pacientes com sepse. Comentamos sobre os mecanismos de ação da solução hipertônica, recorrendo a dados sobre choque hemorrágico e séptico. Atuações específicas da solução salina hipertônica aplicáveis a sepse grave e choque séptico são enfatizadas. Os dados disponíveis corroboram os benefícios em potencial da infusão de solução salina hipertônica em vários aspetos da fisiopatologia da sepse, inclusive hiperperfusão dos tecidos, consumo reduzido de oxigênio, disfunção endotelial, depressão miocárdica e presença de um amplo elenco de citosinas pró-inflamatórias e várias espécies de oxidantes. Uma terapia que, ao mesmo tempo, bloqueia os componentes prejudiciais da sepse terá um impacto no seu tratamento. Estudos prospectivos adequadamente desenhados poderão no futuro comprovar o papel benéfico da solução salina hipertônica.

Descritores: Solução salina hipertônica/farmacologia; Choque séptico/terapia; Sepse/terapia

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