ISSN 0025-7680

SHOCK 1998: OXYGEN, NITRIC OXIDE
AND THERAPEUTIC PERSPECTIVES
International Symposium, Academia Nacional de Medicina
Buenos Aires, 30 April 1998

MEDICINA (Buenos Aires) 1998; 58: 393-402

# HYPERTONIC SALINE RESUSCITATION

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**Abstract** Treatment of severe hemorrhage offers few theoretical problems, but in practice, severe blood loss usually occurs out of hospital, often in more or less inaccessible scenarios. Controversy rages over ideal fluid, ideal volume, and minimum $O_2$ carrying capacity, but all agree that pre-hospital, isotonic resuscitation is unfeasible. The effects of highly hypertonic 7.5% NaCl (HS) was first described in 1980, when we showed that it induced immediate and long lasting hemodynamic restoration. The addition of 6% dextran-70 to (HSD) significantly enhances the duration and intensity of volume expansion, with no loss of hemodynamic effects. HS/HSD restores cardiac output, arterial pressure, base excess and oxygen availability, induce pre-capillary vasodialtion, moderate hyperosmolarity and hypernatremia, reversal of high glucose and lactate. It interferes with endocrine secretions when administered to animals in hemorrhagic hypotension. HS acts through transient plasma volume expansion, positive inotropic effect on cardiac contractility, precapillary vasodilation through a direct action on vascular smooth muscle. Expansion of circulating volume is part of the mechanism, the extra volume coming from the intracellular compartment fluid, especially from endothelial and red blood cells, which facilitate microcirculatory flow. The new field of interactions of hypertonicity with the immune mechanisms may provide insight into the long lasting effects of hypertonic solutions. Randomized double blind prospective studies on the effects of HS, or HSD, used as first treatment of shock show that both are safe and free from collateral, toxic effects. These studies show an early significant rise in arterial blood pressure and a non-significant trend towards higher levels of survival. HSD administration to patients about to undergo cardiopulmonary bypass for cardiac surgery results in higher cardiac output before, and immediately following cardiopulmonary bypass, as well as zero fluid balance.

**Resumen** ***Resucitación con solución salina hipertónica.*** El tratamiento de una hemorragia severa presenta pocos problemas teóricos, pero en la práctica, la pérdida abundante de sangre se presenta generalmente lejos del hospital y a menudo en escenarios poco accesibles. Hay mucha controversia en cuanto al fluido de reposición ideal, al volumen ideal y a la capacidad mínima de transporte de $O_2$, pero hay un acuerdo tácito en que la resucitación isotónica pre-hospitalaria no es factible. Los efectos de la solución salina hipertónica (HS) al 7.5% fueron descriptos inicialmente en 1980 cuando demostramos que es capaz de conducir a una restauración hemodinámica inmediata y de larga duración. La adición de dextran 70 al 6% a la solución hipertónica (HSD) aumenta significativamente la duración y la intensidad del volumen de expansión, sin pérdida de los efectos hemodinámicos. HS/HSD restaura el volumen mínimo, aumenta la presión arterial, corrige el exceso de bases y aumenta la disponibilidad de oxígeno además de inducir vasodilatación precapilar, hiperosmolaridad moderada e hipernatremia, disminuyendo los altos niveles de glucosa y de lactato. Administrado a animales en hipotensión hemorrágica, HS/HSD interfiere también con las secreciones endocrinas. HS actúa a través de la expansión del volumen plasmático con un efecto inotrópico positivo sobre la contractilidad cardíaca, y sobre la vasodilatación precapilar mediante una acción directa sobre el músculo liso vascular. La expansión del volumen circulante es parte del mecanismo a expensas del fluido de los compartimientos intracelulares en especial de las células endoteliales y de los glóbulos rojos, lo que facilita el flujo microcirculatorio. El reciente campo de interacciones de la hipertonicidad con los mecanismos inmunes abre horizontes nuevos en el estudio de los efectos a largo plazo de las soluciones hipertónicas. Los estudios prospectivos doble ciego randomizados de los efectos de HS o de HSD empleados como primer tratamiento del shock muestran que ambas soluciones son seguras y sin efectos tóxicos colaterales. Se obtuvo un aumento temprano y significativo de la presión arterial y una tendencia no significativa hacia mayores niveles de sobrevida. La administración de HSD a pacientes en cirugía cardíaca antes de un by-pass cardiovascular resultó en un aumento del volumen mínimo, antes e inmediatamente después del by-pass cardiopulmonar alcanzando un perfecto equilibrio de los fluidos orgánicos.

**Key words:** hemorrhage, hypertonic saline, shock, leukocyte adhesion, blood flow, oxygen consumption

The early treatment of severe hemorrhagic hypotension offers few theoretical problems, simply a matter of blood loss control, general care and replacement of losses, specially losses of volume and $O_2$ carrying capacity. In practice, however the problem is more complex: in the overwhelming majority of cases, severe blood loss occurs out of hospital, often in more or less inaccessible scenarios. In most cases, hemorrhage control can

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only be ensured in a hospital setting and in some cases not even then, while volume replacement is torn between the conflicting concepts of crystalloid vs. colloid fluid. $O_2$ carrying capacity is in turn subject to debate concerning the minimal acceptable levels of hemoglobin coupled to the shadow of transmission of infectious diseases. In urban settings, large accidents may result in large blood loss, in a large number of patients. Rural settings may impose long travelling times, whereas military settings require consideration with respect to distance, terrain, and availability of personnel, and degree of hostility from enemy action. Thus, it may be safely stated that the extra-hospital setting in conjunction with very urgent therapeutic requirements imposes severe limitations to applicable procedures. Another important issue refers to the duration of this pre-hospital stage of care, which is also variabe, on account of distance to hospital, quality of ambulance/helicopter service, level of prevailing urban traffic, eventual need of extricating the patient from a severely distorted vehicle. It is therefore not surprising that transport time, counting from the start of bleeding to entry into hospital may range from a very few min. (e.g., when a person is injured in front of the hospital) to many hours (e.g. when a patient has to be extricated from a crashed vehicle and transported during rush hours through a large, traffic-congested city). Other fast or slow scenarios may be envisaged.

Arguments abound, concerning ideal fluid, ideal volume replacement, minimum $O_2$ carrying capacity, but one point draws agreement from all parties. The logistics of pre-hospital management of severe blood loss all but precludes the administration of ideal volumes of crystalloid or colloid solutions. In the most favorable scenarios, it is difficult to infuse much more than 800-1000 mL, during the pre-hospital stage of trauma patient management. This is clearly insufficient to replace lost circulating volume in the face of class III or class IV hemorrhage (blood loss greater than 30% of blood volume, ~ 1.5 L). These are, of course, the conditions which normally require most urgent treatment. Replacement of $O_2$ carrying capacity remains virtually impossible. These shortcomings led to the concept of the *scoop-and-run* strategy, on the grounds that, since it is impossible to provide even token volume replacement en route to hospital, no time should be wasted in securing an intravenous line on the site of the occurrence. More recently a new and potentially explosive concept has been proposed by the Houston Trauma Center[14]: volume replacement prior to full control of bleeding is dangerous, because it is may increase blood loss. This bold suggestion was made after comparison between two groups of patients: in one, treatment was withheld until hemorrhage had been controlled, while in the other standard of care ATLS procedures were instituted. This of course transcends the mere domain of therapeutic strategy and overflows into the field of ethics of patients management. It should be noted that the study on which this concept was based was seriously flawed: on one hand, it did show a significant advantage in favor of withholding treatment, but on the other it violated its own protocol in circa 20% of patient entries, all belonging to the withhold-treatment group, who received significant amounts of volume in spite of being attended on "withhold-treatment" days. In the absence of any rational expla-nation, the obvious assumption must be that in a number of these so called "mistakes", ethical considerations forced field workers, on the site of the occurrence, to violate the protocol in respect to hierarchically superior values of life protection.

## The concept of small volume hypertonic resuscitation

The effects of moderately hypertonic solutions were sporadically described in medical literature since the latter years of World War I[6, 103, 104, 118, 177, 179]. Effects were generally described as vasodilator, positive inotropic and transiently beneficial in hemorrhagic hypotension. The highly hypertonic (7.5%, 2 400 mOsm/L) NaCl solution (HS) first appeared in 1980, when it was shown that, given in a relatively small volume (4 mL/kg)[165], HS induced immediate and long lasting recovery of arterial pressure, cardiac output, vasodilation. It also induced moderate hyperosmolarity and hypernatremia, and restored base excess levels.

The addition of 6% dextran-70 to HS, first described in 1985[149], and exhaustively tested thereafter[62, 76, 94, 107, 117, 120, 131, 149, 150, 152, 162, 164, 168, 169, 173] significantly enhances the duration and intensity of volume expansion, with no loss of hemodynamic effects. This HSD solution: (NaCl at 7.5% + dextra-70 at 6%) accelerates volemic expansion, and converts the mere pressor effect of pure dextran to a nutritionally effective increase in blood pressure and cardiac output[164]. Toxicity evaluation showed that up to five times (20 mL/kg) the usually prescribed doses of HSD are free of toxic or collateral effects[40, 42, 43, 44, 153]. Consequently, this hyperosmotic-hyperoncotic crystalloid-colloid combination has become a standard small volume resuscitation solution. Two different colloids (dextran and hydroxyethylstarch) are used in preference to any others[76]. The total therapeutic dose for the average human adult is only 250 mL, a volume which is well within the logistic restrictions of pre-hospital care.

Experimental data on the effects of HS/HSD show an early recovery of cardiac output, arterial pressure, base excess and oxygen availability[2, 3, 35, 56, 59, 60, 74, 112, 125, 134, 139, 148, 165], a widespread pre-capillary vasodilator response[31, 80, 81, 82, 107,130, 144], moderate hyperosmolarity and hypernatremia[74, 134, 143], reversal of high glucose and lactate blood levels[86], improved renal function[144, 151], unaltered pulmo-

nary gas exchange[138] and transient circulating volume expansion[73, 74, 143, 165, 167]. In the original study[165], when compared to an equal volume of isotonic saline, used as placebo, hypertonic NaCl was found to increase survival, from virtually zero to nearly 100%. Other studies, performed in dogs or in different animal species produced survival data which are somewhat less encouraging[155, 156].

HS/HSD interferes with endocrine secretions, when administered to animals in hemorrhagic hypotension: it decreases circulating levels of vasopressin, renin, and angiotensin[171], probably on account of the correction of hypotension and hypovolemia. Particularly interesting is the reduction of vasopressin circulating levels[170, 171], since this hormone is normally secreted in response to hyperosmolarity. In this situation, however the removal of the more powerful secretory drive induced by blood loss overrides the osmotic drive. HS does not interfere with atrial natriuretic factor[1].

HS appears to interfere significantly with the immune response, both in vivo and in vitro. It has been shown to reduce adherence of leukocytes to capillary endothelium[7], and to enhance proliferation of T-cells (obtained from peripheral blood of normal human volunteers), at NaCl concentrations normally encountered following hypertonic resuscitation[28]. It was also shown that the addition of prostaglandin E2 (PGE2) to isotonic culture media inhibits human peripheral blood T-cell proliferation by circa 30%, but has virtually no inhibiting effect in hypertonic media[28]. In a murine model of hemorrhagic shock, it has been shown[26, 27] that T-cell proliferation remained inhibited up to 24 hr after shock and lactated ringer's resuscitation, and that this immunosuppressive response is associated with high levels of Interleukin-4 (IL-4) and prostaglandin E2 (PGE2). In contrast, similarly shocked animals treated with HS exhibited normal T-cell proliferation and IL-4 and PGE2 levels comparable to those of unshocked controls. In a two-hit model of aggression, hemorrhagic shock followed 24 hr later by a septic aggression induced by cecal ligation and puncture, HS (which had been used to resuscitate from the initial hemorrhagic shock) significantly enhanced survival, in comparison to Lactated Ringer's (LR) treated animals. The latter group also exhibited significant pulmonary lesions identified as early ARDS[25]. In recently performed experiments[4] LR treated animals exhibited significant elevation of neutrophils in broncho-alveolar lavage, and high myeloperoxidase levels, when compared to HS treated mice, leading to the conclusion that HS prevents the pulmonary lesion normally encountered following hemorrhagic shock.

Suggested mechanisms of action included, from the early days, transient plasma volume expansion[73, 74, 143, 164, 167] a positive inotropic effect on cardiac contractility[22, 68, 69, 70, 71, 106], precapillary vasodilation through a direct action on vascular smooth muscle[31, 80, 81, 82, 130, 165], and venoconstriction, through a neural reflex, the afferent leg of which would lie in pulmonary vagal afferents, with an efferent limb via sympathetic venomotor fibers[87, 88, 89, 181]. The latter hypothesis has so far remained unconfirmed[3, 132, 163, 166]. A central action for hypertonic saline (HS)[166] has been suggested, but this also remains unconfirmed. Expansion of circulating volume is certainly part of the mechanism and the extra volume comes from the intracellular compartment fluid, which normally expands during hemorrhagic shock because of cell swelling. Cell types found to be the major volume contributors are endothelial and red blood cells, on account of their immediate contact with the hypertonic circulating fluid. This represents, of course, an additional bonus, because at capillary level, endothelial and erythrocyte swelling induce a very significant restriction to free flow of red cells[99, 100, 101, 102]. It has also been shown that HS restores resting action potential of excitatory cells, which are depolarized through hemorrhage[97, 111]. Although more research is certainly required in the field of the interactions of hypertonicity with the immune mechanisms, this may be the first convincing insight into the possible mechanism of the long lasting effects of hypertonic solutions after a single bolus injection.

HS reduces intracranial hypertension, (induced by balloon inflation or localized brain injury), with a resulting increase in cerebral blood flow[8, 9, 32, 37, 38, 45, 46, 52, 53, 57, 58, 61, 90, 105, 122, 123, 142, 146, 174, 175, 176, 178,185, 186]. The effects of HS on experimental burn injuries are usually described as variable and transient, and tend to disappear by the end of the first 24 hours[48, 65, 66, 67, 116, 183]. Effects of HS on endotoxemia, or endotoxic shock have been described. In general they appear to be transient and partial[29, 30, 64, 68, 82, 124]. These scenarios should be re-evaluated in the light of recently described interferences of HS/HSD with immune responses. The use of HS for the treatment of shock in previously dehydrated animals has produced conflicting results[79, 92, 119, 172].

Hypertonic solutions are normally injected slowly, over 3-5 min by peripheral or central intravenous route, with no adverse effects to the histological structure of venous walls[55]. Intraosseous injections have been proved to be safe and efficacious[23, 41, 54, 75, 91, 114, 135, 136, 137, 140].

Simulations of clinical use of hypertonic solutions resulted in a certain amount of conflicting evidence. Kramer and his co-workers developed a protocol[72] in which unanesthetized sheep were bled to 50 mm Hg and kept at this pressure for 3 hr. This was followed by treatment with 200 mL HSD or lactated Ringer's solution (LR). After 30 more min of "no-treatment", all animals were resuscitated to their own pre-hemorrhage levels of cardiac output with isotonic fluid. During initial treatment, HSD restored cardiac output and arterial pressure to normal, and raised plasma $Na^+$ to 155 mEq/L. During isotonic resuscitation, only 500 mL of fluid was required to retain normal cardiac output for 2 hr. LR treated animals, in

contrast, exhibited no significant effects on pressure, output, or plasma $Na^+$, on initial treatment. Moreover, they required 2.5 L of isotonic fluid to recover to, and maintain a normal cardiac output for 2 hr. This is of course a typical model of controlled hemorrhage. However, it may be relevant to clinical situations, because similar findings, concerning rapid hemodynamic recovery and reduced fluid requirements are normally observed in human trauma patients. Bickell et al. developed a porcine model of uncontrolled bleeding[11, 12, 13], in which a standardized aortic lesion induced severe hypotension within 5 min. Given immediately after the initial fall of pressure, HSD intensified the shock condition and caused early death. In contrast, given 20-30 min after the initial hypotension, HSD restored stable hemodynamic conditions. This is also a clinically relevant model, in that it sounds a note of caution against ultra-early use of hypertonic solutions. Krausz and co-workers[49, 50, 51, 77, 126] described different protocols of uncontrolled arterial hemorrhagic shock in rats. In all of these, HS was given immediately after the initial fall of arterial blood pressure leading to severe hypotension and short survival times as the outcome. Animals treated with isotonic solutions did better with stable, albeit low levels of arterial pressure. Untreated animals had the best evolution, with highest levels of arterial pressure, longer and better overall survival. Authors attributed these results to renewed bleeding in HS treated rats, due to an intense initial pressor response, and to arterial vasodilation. These results reiterate the caution against ultra-early use of hypertonic solutions, but otherwise appear to have little clinical relevance, since no clinical data so far described (see below) show this pattern of evolution. Moreover, an independent duplication of one of these protocols (bleeding caused by total transection of the rat tail)[15] under 4 different anesthetic regimens (droperidol-ketamine, as used by Krausz et al., pentobarbitone, chloralorse and urethane) brought out an interesting fact: only under droperidol-ketamine, which incidentally is a very powerful arterial vasodilator, could the results described by Krausz et al. be partially reproduced: untreated and HS treated rats bled abundantly and died in similar proportions. In contrast, under all other anesthetic procedures, very little occurred. Yet another model of uncontrolled hemorrhage with severe blood loss (50% of total blood volume) into an artificially produced retroperitoneal hematoma has been recently described[133, 146]. Shock develops in less than 5 min and stabilizes at a blood pressure of 40 mm Hg, with cardiac output reduced to 25% of control. Treatment, 30 min after the start of bleeding, with 4 mL/Kg HSD, or with a volume of LR sufficient to restore mean arterial pressure to 90 mm Hg reverts the shock condition, with no indications of renewed bleeding as measured through the loss of marked red blood cells[147]. Therefore, and even though no attempt was made to control this bleeding, it appears to have tamponaded itself quite effectively. A number of clinical trauma situations in all likelihood follow this pattern. Other risks involved in the use of hypertonic solutions in uncontrolled hemorrhage are discussed in a number of reports[33, 34, 39].

Clinical studies on the use of hypertonic solutions in hypovolemic shock began with a sequential study[36] of 12 shocked patients pronounced to be in refractory hypovolemic shock by the ICU medical staff in charge (persistence of critical hypotension for at least 4 hr, with no response to 5 L of crystalloids and/or blood, and absence of response to vasoactive therapy. HS was administered in 50 mL aliquots, at 15 min intervals, to an end point of recovery of mean arterial pressure to 80 mm Hg, or to a maximum of 200 mL. Fluid/blood replacement followed, in adherences to the Institution's routine procedures. A significant pressor response with recovery of consciousness, and of urine flow was observed in 11 out of these 12 patients. Fluid requirements, over the next 24 hr were reduced by 90% with respect to initial volumes. Nine of these patients were ultimately discharged from hospital. This study suffers, of course, from the lack of an adequate control group, but it appeared to be justified, on account of the "in-extremis" condition of the patients. Dosing of HS was deliberately fractionated into 50 mL aliquots, to ensure interruption of treatment if required. In no case was this necessary.

Randomized double blind prospective studies on the effects of HS, or HSD, used as first treatment of shock have been performed, involving a total of approximately 1 500 patients[63, 98, 157, 158, 159, 160, 161, 180, 181, 182]. These studies have shown that HS and HSD are safe and free from collateral, toxic, or undesirable side effects. No clotting, renal, neural, cardiopulmonary, or septic complications were noted; signs of renewed bleeding were conspicuously absent. In terms of efficacy, a majority of these studies show an early significant rise in arterial blood pressure and a non significant trend towards higher levels of survival. The University of California studies[63, 145, 158, 159, 160, 161] showed a significant difference in outcome for cranial trauma, in favor of HSD; the USA multicenter trial[98] showed a significant difference in favor of HSD in the subpopulation arriving alive at the Hospital and requiring surgical intervention.The intra-hospital São Paulo trial, which detected a significant overall difference in survival indicated that a mean arterial presure below 50 mm Hg is a prognostic index for survival which distinguishes positively in favor of HSD. A metanalysis of the individual patient files entered into all published studies conforming to a uniform protocol, show a significant ($p < 0.005$) diference in survival, to favor HSD (Wade et al., in press). The use of HSD for primary care in shock and trauma is further discussed in a number of different papers[83, 84, 85, 95, 96]. The use of HS/HSD in current

veterinary practice, mainly associated with hypovolemic shock has also been repeatedly reported[10, 47, 93, 107, 108, 109, 110, 139, 184].

HSD or HSS (7.5% NaCl - 6% hydroxyethylstarch - 200 kDalton) administration to patients about to undergo cardiopulmonary bypass for cardiac surgery results in higher cardiac output before, and immediately following cardiopulmonary bypass, as well as zero fluid balance, in contrast to a positive balance in control, HSD/HSS untreated patients[16, 17, 18, 19, 20, 21, 115]. However, acutely adverse effects have been described[121] in patients with significant cardiac deficit. Reduction in gut tissue water, but no improvements in intestinal mucosal perfusion, under cardiac bypass have also been shown[154].

The effects of hypertonicity upon the aortic declamping hypotension have been described[5, 143, 145]. Given immediately after declamping, hypertonic solutions induce partial restoration of arterial pressure; given immediately before declamping, hypertonicity partially prevents decampling hypotension.

HS given to patients following right ventricular acute infarct induce a lasting restoration of arterial pressure and cardiac output[127, 141], and an early reduction of enzymes associated to myocardial lesion[24].

New concepts in the field refer to the experimental use of hypertonic solutions in which $Cl^-$ is partly replaced by acetate, in order to induce an isochloremic resuscitation[127, 128, 129]. These HA (2 500 mOsm/L sodium acetate) or HAD (2 500 mOsm/L sodium acetate, plus 6% dextran-70) solutions have been found to induce a low pressure high cardiac output type of response[78, 113, 127, 128], with no significant elevation of blood $Cl^-$ levels, and early corection of blood pH. They should not, however, be attempted in clinical situations, until more work has been done to determine their safety. The combination of HS with $\alpha$-$\alpha$-hemoglobin, as an oxygen carrying oncotic factor is also under current study, in experimental conditions (Figueiredo et al., in press).

In conclusion, hypertonic solutions appear to have multiple physiological effects in severe hypotensive shock or in hypotensive like situations, many of which require further research. It also appears to have potential clinical applications in the primary treatment of hypovolemic shock, in cardiac surgery with cardiopulmonary bypass and in myocardial infarct. The interaction of hypertonic solutions with pro-inflammatory mediators has barely been scratched, and may induce a critical review of many concepts.

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*Nothing great was ever achieved without enthusiasm.*

Nada grande se consiguió nunca sin entusiasmo.

Ralph Waldo Emerson (1803-1882)