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Review

Potential Use of Hypertonic Saline Solution (7-7.5% NaCl) Resuscitation in Hypovolemic and Endotoxic Shock

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ABSTRACT

The concept of small-volume resuscitation using hypertonic saline solution encompasses the rapid infusion of a small dose (4-5 ml per kg body weight) of 7-7.5% NaCl solution. Originally, Small Volume Resuscitation was aimed for initial therapy of severe hypovolemia and shock. The present review discusses the hemodyanamic and other effects of hypertonic saline solution in experimental hypovolemic and endotoxic shock. We comment on the mechanism of action of hypertonic saline, calling upon data in haemorrhagic and septic shock. In this review, the potential use of hypertonic saline solution resuscitation in hypovolemic and endotoxic shock is considered.

Key Words: Hypovolemic; Endotoxic; Hypertonic saline; Resuscitation; Shock.

INTRODUCTION

In several diseases, fluid therapy can be a life-saving procedure. Isotonic fluids have been widely used to rectify hypovolemia, acidosis and electrolyte imbalances. The administration of large volumes, however, has the disadvantage of requiring a long injection time; thus limiting the efficacy of the treatment, especially in large animals. Since administration of a hypertonic leads to recruitment of extravascular fluids into the vascular compartment, hypertonic solution seem likely to produce a more rapid response and marked haemodyanamic effects than isotonic solutions.

Gasthuys (1994) has reviewed the clinical uses of HTSS during or after anaesthesia in horses with colic. Cambier *et al.* (1997) reviewed the pharmacology of HTSS in healthy animals, in hypokalaemic metabolic alkalosis and affect of HTSS in oxygen transport by hemoglobin. The present review deals with pharmacological effects of HTSS in experimentally induced hypovolemic and endotoxic shock.

Hypovolemic shock. Briefly, the main physiopathological mechanisms involved in hypovolemic shock are decrease in the total blood volume, arterial pressure, cardiac output, and oxygen delivery. Compensatory mechanism includes tachycardia, systemic and pulmonary vasoconstriction, and increased myocardial contractility. Prolonged intense vasoconstriction predisposes to ischemia, hypoxia, and cellular acidosis (Fenner, 1991). Hypertonic saline has been used experimentally to limit the deleterious effects of blood loss. The following observation has been made.

Plasma volume expansion. After severe haemorrhage, infusion of a hypertonic solution (7% NaCl) was found to increase the cardiac output, causing a transient return to the pre-haemorrhage value within 3-15 minutes after initiation of resuscitation with 4 ml/kg in dogs (Velasco *et al*., 1980; Lopes *et al*., 1981; Rocha e Silva *et al*., 1987) or with 3-4 ml/kg in unanaesthetized sheep (Nakayama *et al*., 1984; Smith *et al*., 1985).

The expansion in plasma volume observed after infusion of a HTSS (7% NaCl) in dogs (4 ml/kg) (Rocha e Silva *et al*., 1987), horses (3.8-4.5 ml/kg) (Schmall *et al*., 1990a), and unanaesthetized sheep (3-4 ml/kg) (Nakayama *et al*., 1984; Smith *et al*., 1985) may certainly contribute to increased cardiac output. As measured by the dye dilution technique in unanaesthetized sheep, the plasma volume expansion after a blood loss of 1.6 L and infusion of 160 ml of hypertonic saline (7% NaCl) was 360 ml (Nakayama *et al*., 1984). Some water must, therefore, move from within cells into the extracellular space as a result of the osmotic action of the hypertonic saline (Rowe *et al*., 1972; Mazzoni *et al*., 1988; Schmall *et al*., 1990b; De Carvalho *et al*., 1999). This explains why it takes a smaller volume of hypertonic saline than isotonic saline to produce similar effects (Kein *et al*., 1991).

Cardiovascular effects of hypertonic saline. The increase in cardiac output correlated significantly with the expansion of plasma volume in sheep, but extrapolation to zero volume expansion suggested that hypertonic saline solutions exert some of their effects independently of volume expansion (Walsh & Kramer, 1991). Some studies of post-shock resuscitation by an infusion of hypertonic saline provided evidence that a cardiovascular reflex initiated by stimulation of pulmonary osmoreceptors and it plays a major role in improving the cardiac output in dogs, cats and rats (Lopes *et al*., 1981; Rocha e Silva *et al*., 1987; Younes *et al*., 2003).

This reflex would induce venoconstriction (Lopes *et al*., 1986) and selective muscular and cutaneous precapillary constriction (Rocha e Silva *et al*., 1986), which would redistribute the blood flow, allowing an increase in cardiac output. However, several recent studies have failed to confirm these findings in cats (Muir & Sally, 1989), dogs (Schertel *et al*., 1990), and sheep (Hands *et al*., 1988).

In addition to the expansion of plasma volume and pulmonary reflex, improved cardiac contractility, heart rate and vasodilatation might also contribute to the increased cardiac output. While the effects obtained in healthy animals are diverse, all authors' mention a positive inotropic effect from hypertonic saline (7.5% NaCl) used for post-haemorrhage resuscitation and negative inotropic in healthy dogs (Constable *et al*., 1994). In dogs (5 ml/kg) (Kein *et al*., 1991; Xiujun *et al*., 2002) and cats (4 ml/kg) (Muir & Sally, 1989), the maximal contractility, which exceeded the pre-haemorrhage value, was reached 5-30 min following resuscitation.

The heart rate data differ according to the species. In cats (7.5% NaCl, 4 ml/kg) (Muir & Sally, 1989) and dogs (NaCl7.5%, 5 ml/kg) (Kein *et al*., 1991), the heart rate which increased as a result of bleeding, was transiently normalized for 10-15 min after infusion but began to increase again thereafter. In dogs it returned to the post-haemorrhage value 60 minutes after resuscitation (Kramer *et al*., 1989; Brown *et al*., 1990) but it remained below this value in cats. In unanaesthetized sheep, tachycardia increased immediately following infusion (7% NaCl, 3-4 ml/kg); the mean heart rate was maximal 30 min post-resuscitation, reaching 120 beats per min (Nakayama *et al*., 1984). No heart rate changes were observed in horses following administration of hypertonic saline (NaCl 7%, 3.8-4.5 ml/kg) (Schmall *et al*., 1990).

In contrast to healthy animals, resuscitated animals displayed an increase in their mean arterial pressure directly after infusion of hypertonic saline solution. No transient hypotension was observed, probably due to the very low post-haemorrhage arterial pressure. Thus, the mean arterial pressure was maximal immediately after treatment with a7.5% solution in swine (11.5 ml/kg) (Maningas *et al*., 1986; Hellyer *et al*., 1994) and sheep (2-2.5 ml/kg) (Walsh & Kramer, 1991) or 10-15 min after treatment in horses (7% solution, 3.8-4.5 ml/kg) (Schmall *et al*., 1990a) and unanaesthetized sheep (7% solution, 3-4 ml/kg) (Nakayama *et al*., 1984). In dogs, the mean arterial pressure reached its maximum either immediately or 4 hour after infusion (4-5 ml/kg, 7.5% NaCl), in different studies (Velasco *et al*., 1980; lopes *et al*., 1981; Rocha e Silva *et al*., 1987; Kein *et al*., 1991).

Effects of hypertonic saline on urinary function. The output of urine is significantly reduced after haemorrhage. In sheep, the urinary output was restored to normal (Walsh & Kramer, 1991) after infusion of 7-7.5% NaCl (2-4 ml/kg) or to at least three times the baseline level (Nakayama *et al*., 1984; Us *et al*., 2001) during the first hour after resuscitation. This effect could be due to improved renal blood flow. Following resuscitation with 7.5% NaCl (4-5 ml/kg), the renal blood flow increased in dogs, a fact easily explained by the high cardiac output, but remained below baseline (Rocha e Silva *et al*., 1986; Kein *et al*., 1991). Release of arterial; natriuretic factor might also contribute to increasing the urine output (Richards *et al*., 1985).

Duration of effects induced by hypertonic solution. A major question is how long the desirable positive effects of hypertonic saline solutions can be sustained. In resuscitated dogs (7% NaCl; 4 ml/kg), the haemodyanamic effects throughout the entire experiment, i.e. for at least 6 hours (Velasco *et al*. 1980), but other authors have found these effects to be transient in dogs and other species, lasting only 15 min to 4 hrs (Nakayama *et al*., 1984; Maningas *et al*., 1986; Rocha e Silva *et al*., 1986; Muir & Sally, 1989; Schmall *et al*., 1990a; Kein *et al*., 1991b). Addition of a colloid (dextran70.6%) induced a greater initial plasma volume expansion and maintained the effects for a longer period, presumably because of its higher colloid osmotic pressure (Smith *et al*., 1985). Dextran solutions, however, may cause anaphylactic reactions (Renck *et al*., 1983) and abnormal blood coagulation (Holcroft *et al*., 1987), principally when large doses are used or upon prolonged infusion. While such side effects are rare, dextran solution remains infrequently used in veterinary medicine but if it is used along with hypertonic saline solution, it gives good results to resuscitate the hemorrhagic dogs (Chiara *et al*., 2003) and also improves cardiac output (Tobias *et al*., 1993).

Endotoxic shock. Endotoxins are toxic lipopolysaccharide constituents of Gram-negative bacteria. During endotoxic shock, an immediate decline in blood pressure accompanies a considerable redistribution of blood flow. Central volume is reduced, resulting in inadequate delivery of oxygen and nutrients to tissues (Fenner, 1991).

As mentioned above, endotoxic shock is characterized by a reduced effective circulating blood volume, due to pooling of blood in venous capacitance beds, and by a decreased plasma volume (Chein *et al*., 1966). In calves and other species, infusions of E. coli endotoxin caused the cardiac index, central plasma volume and mean systolic arterial pressure to fall, and the heart rate, pulmonary vascular resistance, systemic vascular resistance and mean pulmonary arterial pressure to rise. The packed cell volume increased (by 30-35% following administration of 20 microgram/kg endotoxin over 5 hrs.), whereas the total plasma protein level remained unchanged (Olson & Brown, 1985; Constable *et al*., 1991b).

Plasma volume expansion. As after haemorrhagic shock, an increase in plasma volume was observed in calves (Constable *et al*., 1991a) and dogs (Mullins & Hudgens, 1987) following infusion of hypertonic saline (respectively 4 ml/kg of 7% NaCl and 12 ml/kg of 3.2% NaCl). Endotoxin induced transient hyperglycemia, followed by a prolonged period of hypoglycemia. Since administration of

the hypertonic solution did not influence these changes (Constable *et al*., 1991b), the observed plasma volume expansion seems to be due to ion-induced hyperosmolality.

Expansion of the plasma volume certainly contributed to the cardiac index and cardiac output increases observed in pigs (7.2% NaCl, 4 ml/kg) (Kreimeier *et al*., 1991), calves (7% NaCl, 4 ml/kg) (Constable *et al*., 1991a), dogs 3.5-7.5% NaCl, 6-64.5 ml/kg) (Prough *et al*., 1985; Luypaert *et al*., 1986; Mullins & Hudgens, 1987) and standing horses (7% NaCl, 5 ml/kg) (Bertone *et al*., 1990) following infusion of hypertonic saline. In all these trials, the cardiac index and cardiac output recorded for 1-3 hrs after resuscitation equaled or exceeded the values recorded before endotoxemia (Bertone *et al*., 1990; Constable *et al*., 1991a).

Cardiovascular effects of hypertonic saline. The increased stroke volume and cardiac contractility (d*P*/d*t*) recorded in calves (Constable *et al*., 1991a) following infusion of 4 ml/kg of 7% NaCl also contributed to the increase in cardiac output. The effects on stroke volume and cardiac contractility were maximal 15 and 10 min respectively, after infusion. The cardiac contractility remained above baseline (i.e. values measured before challenge) for 1 hr after resuscitation, but the stroke volume decreased immediately after peaking (Constable *et al*., 1991a).

The systemic vascular resistance decreased after resuscitation with 7% NaCl, reaching a minimum 75 min after the initiation of resuscitation in standing horses (5 ml/kg) (Bertone *et al*., 1990) but only 10 min after initiation in calves (4 ml/kg) (Constable *et al*., 1991a). The systemic vascular resistance stayed below baseline for 2-3 hrs after resuscitation, but the high cardiac output observed after resuscitation allowed an increase in mean arterial pressure, which peaked 12-50 min after resuscitation, although it remained below baseline. This was observed in calves (7% NaCl, 4 ml/kg) (Constable *et al*., 1991a), pigs (7.2% NaCl, 4 ml/kg) (Kristensen & Modig, 1990; Kreimeier *et al*., 1991) and dogs (3.5-7.5% NaCl, 6-64.5 ml/kg) (Prough *et al*., 1985; Luypaert *et al*., 1986; Mullins & Hudgens, 1987). By contrast, pulmonary arterial pressure, which remained above baseline in dogs throughout the experiment (4 h), was somewhat reduced, reaching a maximum 30 min after infusion of 3.5% NaCl (64.5 ml/kg) (Luypaert *et al*., 1986). Pressure changes recorded in calves were due to a lower pulmonary vascular resistance, which was minimal 10 min after infusion (7% NaCl, 4 ml/kg) (Constable *et al*., 1991a).

In standing horses, Bertone and colleagues (1990) compared the effects of a hypertonic saline (7%) and isotonic (0.9%) solutions injected at the same rate (5 ml/kg). Hypertonic saline was found to promote more profound and longer-lasting cardiovascular normalization than isotonic saline. Data obtained in dogs suggest that the combination of hyperosmotic mechanisms induced by hypertonic solutions, with water transfer from the extravascular to the vascular compartment, is equivalent to the effect produced when large volume of isotonic solution is administered (Mullins & Hudgens, 1987). As in the treatment of haemorrhagic shock, dextran can prolong the haemodyanamic response in endotoxaemic calves. An interesting alternative to the use of dextran might be to add bovine serum protein to the hypertonic saline. The added protein might increase the plasma osmotic pressure sufficiently to sustain the expansion in plasma volume induced by the hypertonic saline (Constable *et al*., 1991a).

The respiratory effects of hypertonic saline. Endotoxin induces a severe hypoxemia in calves, which is accompanied by significant increases in the arterial-alveolar O_2 gradient, the physiological shunt fraction and the ratio of physiological dead space to tidal volume. Infusion of hypertonic saline solutions (7% NaCl, 4 ml/kg) failed to induce any significant improvement in these parameters (Constable *et al*., 1991b).

Immunomodulatory effects of hypertonic saline solution. Haemorrhage and sepsis often initiate a systemic inflammatory response that is accompanied by organ dysfunction, most commonly acute lung injury (Angle *et al*., 1998a). Neutrophil sequestration in a lung is a necessary prerequisite for development of lung injury in most models of haemorrhagic and septic shock (Angle *et al*., 1998a). Ischemia has been shown to lead to accumulation of neutrophils and other leukocytes in the microvascular bed of many organs (Welbourn *et al*., 1991; Holman & Maier, 1988; Botha *et al*., 1995). HTSS has been shown to reduce lung injury after haemorrhagic shock (Angle *et al*., 1998a; Rizzoli *et al*., 1998). These studies showed that HTSS produced following improvements in the lung: reduction in neutrophil accumulation, less neutrophils recovered on bronchioalveoler lavage and reduced albumin leak. The mechanism of neutrophil sequestration or adhesion depends on the particular inflammatory condition. The CD11b integrin is a vital component of neutrophil-endothelial interactions, and in this respect Rizoli and colleagues (1998) showed that HTSS prevented lipopolysaccharide stimulated expression and activation of CD11b. Coraborating those data, HTSS has been shown to decrease neutrophil L-selectin expression and to eliminate neutrophil priming by mesenteric lymph production (Angle *et al*., 1998b; Zallen *et al*., 2000); this suggests that HTSS reduced lung injury by preventing neutrophil adhesion to endothelium. Also, Oreopoulos and colleagues (2000) showed inhibition of ischemia/reperfusion induced hepatic expression of intercellular adhesion molecule-1 mRNA with HTSS as compared with normal saline.

The effect of hypertonic saline on urinary system. Endotoxin induces a major decrease in the glomerular filteration rate and in urine production (Constable *et al*., 1991a). These changes probably result from hypovolemia, systemic arterial hypotension and vasopressin release (Szczepanska-Sadowska *et al*., 1979). Contrary to its effect after haemorrhagic shock, 4 ml/kg of 7% NaCl administered to calves induced only a modest increase in urine output after endotoxic shock. These moderate responses compared

to that observed following haemorrhage remain unexplained. The renal damage caused by endotoxin could partly explain this phenomenon.

CONCLUSIONS

The pharmacological effects of hypertonic saline administration can be summarized briefly as follows. After administration of 7-7.5% NaCl at a mean rate of 4-5 ml/kg, a marked increase in cardiac output has been found in all species under various physiological and physiopathological conditions. Two factors combine variably to produce this effect. One is an increase in stroke volume, due to plasma volume expansion and perhaps also to a direct effect on cardiac contractility, although this is a still disputed. An increased stroke volume was observed in all experimental situations. The second factor contributing to a higher cardiac output is an increased heart rate, always observed in healthy animals but not in pathological situations: the opposite effect was indeed observed in endotoxaemic animals; while in haemorrhagic animals the heart rate decreased, increased or remained unchanged. The variability of this response did not seem related to the animal species.

A vasodilator effect is induced in all species and all physiopathological conditions. In healthy animals, this effect is explained by the release of vasoactive substances and a decrease in the release of vasopressin and norepinephrine.

The improved cardiac output and plasma volume explains the increased arterial pressure observed in all experimental models.

Hypertonic saline improves urinary function in cases of haemorrhagic shock and also in endotoxic shock, but to a lesser extent. This appears to reflect the high cardiac output resulting in an improved renal blood flow. The weaker response observed in cases of endotoxic shock may be attributed to the renal damage caused by the endotoxin.

At tissue level, hypertonic saline can induce endothelial cell shrinkage, potentially increasing the inner capillary diameter and reducing hydraulic resistance. Such effects should favor tissue perfusion. All these effects could be useful in several pathological situations, but it would be advantageous to prolong them in time. More concentrated solutions have been tested (10-14% NaCl), but they were associated with a marked toxicity, as indicated by convulsions (Smith *et al*., 1985) and a rapid decline in survival (Traverso *et al*., 1987).

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