REVIEW

OPERATING ROOM USE OF HYPERTONIC SOLUTIONS: A CLINICAL REVIEW

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Hyperosmotic-hyperoncotic solutions have been widely used during prehospital care of trauma patients and have shown positive hemodynamic effects. Recently, there has been a growing interest in intra-operative use of hypertonic solutions. We reviewed 30 clinical studies on the use of hypertonic saline solutions during surgeries, with the majority being cardiac surgeries. Reduced positive fluid balance, increased cardiac index, and decreased systemic vascular resistance were the main beneficial effects of using hypertonic solutions in this population. Well-designed clinical trials are highly needed, particularly in aortic aneurysm repair surgeries, where hypertonic solutions have shown many beneficial effects. Examining the immunomodulatory effects of hypertonic solutions should also be a priority in future studies.

KEYWORDS: Hypertonic solution; Saline solution; Surgery; Perioperative; Randomized control trial.

INTRODUCTION

Most of the clinical experiences to date on the use of hypertonic saline have come from trauma patients in the prehospital setting or en route to the emergency room.[1-3] The effects of hyperosmotic-hyperoncotic solutions (HHS) in rapidly restoring hemodynanic stability, boosting cardiac function, and possibly improving outcome, along with a demonstrated safety in trauma population, provide the basis for the growing interest in their perioperative use over the last two decades. The majority of studies were carried out in elderly cardiac surgery patients who were at an increased risk for intraoperative cardiac complications. The main goals of using HHS during the perioperative period are to prevent hypovolemia and to assure adequate tissue oxygenation while avoiding fluid overload. In this review, we included 30 studies[4-33] of human subjects treated with 7.2-7.5% NaCl

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alone (Hypertonic Saline - HS), NaCl with dextran (HSD) or NaCl with hetastarch (HSS). In 15 cases, the fluids were administered during cardiac surgeries (table 1). Seven cases involved patients undergoing aortic aneurysm repair (table 2), two cases involved providing tested hypertonic saline in neurosurgical patients (table 3), two cases involved patients undergoing abdominal hysterectomy (table 4), and four cases involved patients who underwent minor operations (table 5). Seven studies[34-40] tested the hypertonic saline using tonicity levels other than those examined previously (ranging from 1.8% to 5.85% NaCl) and were among the first reported clinical trials on the perioperative use of HS.[34] Two studies[41,42] had no control groups, and these studies were thus excluded from this review.

CARDIAC SURGERY

With the exception of two studies (involving patients undergoing cardiac valve surgery) from the group of cardiac surgeries,[22,31] all clinical experiences were derived from coronary artery bypass grafting (CABG) patients. Amongst all patients undergoing cardiac surgery, the most relevant finding was the substantial decrease in positive fluid balance. By titrating volume infusion against pulmonary capillary

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wedge pressure (PCWP), Oliveira et al.[16] while studying the effect of HSD in the hemodynamic status of cardiac patients, demonstrated an enormous positive fluid balance in the control group compared to the HSD group. HSD was being tested in regards to it's effect in the hemodynamic status and volume of fluid administrated. The Ringer's solution group required almost 4000 ml more positive fluid balance than the control group to arrive at the same hemodynamic status. A near zero balance was seen in the HSD group 48 hours after surgery. The Tollofsrud study[20] also reported a relevant 1200 ml cumulative spare volume in HHS patients using a 4 ml/kg of body weight fixed dose. Even when the HHS-treated group was compared to the control group, which used colloid solutions, administering hypertonic solution was deemed to be advantageous.[6,7] Furthermore, preoperative hemodilution with HHS in patients with normal left ventricular ejection fraction who underwent CABG was recently reported to decrease the need for perioperative fluid independent of the type of mixed colloid used.[30] Recently, in a study involving 50 patients undergoing cardiac valve surgery, Bueno and colleagues31 administered 4 ml/kg of HHS before cardiopulmonary bypass with a fluid balance of near zero during the first 48 hours as compared to a large positive balance in the Ringer's group. Finally, three studies by Jarvela and colleagues[25,26,28] stated that administering a single dose of 4 ml/kg of 7.5% NaCl over 30 minutes to CABG patients during the postoperative rewarming phase resulted in intense diuretic effects and decreased fluid retention. Excess body fluids that had accumulated during cardiopulmonary bypass and cardiac surgery were excreted because of the increased diuresis in these studies. In one study,[28] weight gain in the NS - 0.9% Saline control group was significantly greater than that in the HS group during the first postoperative day (1.9 ± 1.4 kg, median, 2.1 kg and 0.8 ± 1.5 kg, median, 0.8 kg, respectively; p=0.005). This result corroborated observations of decreased fluid retention.

Cardiac index (CI) was another hemodynamic endpoint that was favourably altered by hypertonic saline in the majority of the studies and was independent of whether the solution infusion was titrated. Studies that titrated the same infusion as controls showed a substantial increase in left ventricular filling pressure.[7,16,20] In two studies[8,31] that used a fixed dose, the beneficial effect of increasing the CI lasted well into the 48h after surgery. However, by administering a single 250 ml postoperative dose of HHS and HSD, Sirieix et al.[22] verified a transient increase in CI that returned to baseline values within 3 hours despite significant increases in left ventricular preload and left ventricular ejection fraction in their patients. Also, the hemodynamic effects of HS lasted only about 1 hour in the Jarvela study.[25] However, the preoperative hemodilution with HSD and HSS in the Molter study[30] significantly augmented

CI. Another important effect of administrating hypertonic solutions throughout these studies was the reduction in systemic vascular resistance. Three studies[8,22,31] reported a reduction in pulmonary vascular resistance after infusion of HSS or HSD. Regarding mean arterial pressure (MAP), most authors observed either a transient increase or no significant difference in MAP compared to controls when hypertonic solutions were infused. Nevertheless, two studies required further attention. In the Prien study,[11] a transient drop in MAP was documented after infusion of a fixed dose of 250 ml HSS over 15 minutes. The 20% decrease in MAP from baseline was seen in the first 5 minutes of the infusion and was followed by hypervolemic left ventricular failure in the majority of these patients. By applying the same rate of infusion, Sirieix and colleagues[22] managed the severe hypotension that developed after hypertonic solution administration in three of 16 patients. However, they observed significant augmentation of MAP following hypertonic solution infusion in the majority of their patients compared to those given a control solution. These patients also reported significant increase in central venous pressure (CVP) following infusion of a hypertonic solution.

In general, the pulmonary function was positively affected throughout the studies. There was a statistically significant drop in PaO_2 in the control groups, while PaO_2 remained more constant in HSS treated patients.[8] Bueno et al.[31] reported that patients who underwent cardiopulmonary bypass maintained a significantly higher PaO_2/FiO_2 ratio after HSD infusion compared to those given Ringer's solution. Molter et al.[30] described a relevant higher O_2 delivery index in the hypertonic solution treated group. Furthermore, two additional studies demonstrated earlier extubation times after hypertonic saline administration.[19,31]

Hypernatremia was a common finding after using HHS in cardiac surgery. However, no neurological symptoms were associated with the increased sodium load, even when serum sodium reached concentrations of over 160 mmol/L.[31]

AORTIC ANEURYSM SURGERY

Since the first reported study in 1987 on the use of hypertonic saline (7.2-7.5% NaCl) in patients who underwent surgical repair of abdominal aortic aneurysm, a total of 91 such patients have been treated with hypertonic solutions to date. Most of the studies gave HS mixed with hydroxyetilhyl starch and had HES as the control solution (table 2). The most striking result was the reduced need for fluid intake in patients receiving HHS. First, Auler et al.[4] assessed HS in three abdominal aortic aneurysm AAA patients and found a decreased need for perioperative fluid despite a slightly greater blood loss in this group in relation

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Table 1 - Perioperative studies on the use of hypertonic saline (7.2-7.5% NaCl) alone or in association with either dextran (HSD) or hydroxielthyl starch (HSS) compared to hydroxiethyl starch (HES), Ringer's solution (RL), normal saline (NS), NS-HSD or polygeline during cardiac surgery

Study by year	Solution Dose	Control Solution	n (solution)	n (control)
Boldt et al.[6] 1990	HSS 4.5ml/Kg	HES	10	20
Boldt et al.[7] 1991	HSS 2.7ml/Kg	HES	15	30
Boldt et al.[8] 1991	HSS 3.1ml/Kg	HES	15	15
Boldt et al.[9] 1991	HSS 3.8ml/Kg	HES	15	30
Auler et al.[10] 1992	HS 4ml/kg	NS	10	11
Prien et al.[11] 1993	HSS 3.5ml/kg	HES	18	19
Oliveira et al.[16] 1995	HSD 235ml	RL	10	10
Mazhar et al.[19] 1998	HS 5ml/kg	Polygeline	10	10
Tollofsrud et al.[20] 1998	HSD 4ml/kg	RL	10	10
Sirieix et al.[22] 1999	HSD/HSS 250ml	HES	16	8
Jarvela et al.[25] 2001	HS 4ml/kg	NS	20	20
Jarvela et al.[26] 2001 16 32	HS 4ml/kg	NS/HES	16	32
Jarvela et al.[28] 2002	HS 4ml/kg	NS	36	36
Molter et al.[30] 2003	HSD/HSS 150ml	NS/NS-HES/NS-HSD	16	27
Bueno et al.[31] 2004 RL 25 25	HSD 4ml/kg	RL	25	25
Total			242	303

Table 2 - Perioperative studies on the use of hypertonic saline (7.2-7.5% NaCl) alone or in association with either dextran (HSD) or hydroxielthyl starch (HSS) compared to hydroxiethyl starch (HES), Ringer's solution (RL)/6% Dextran70, or normal saline (NS) in aortic aneurysm surgery

Study by Year	Solution Dose	Control Solution	n (solution)	n (control)
Auler et al.[4] 1987	HS 4 ml/kg	NS	5	5
Younes et al.[5] 1988	HS 4 ml/kg	NS	18	13
Javanovic et al.[12] 1995	HSD 4-5 ml/kg	RL/6%Dextran70	9	19
Albrecht et al.[13] 1995	HSS 214 ml	HES	11	12
Ellinger et al.[14] 1995	HSS 2.4 ml/kg	HES	20	20
Christ et al.[17] 1997	HSD/HSS 3.3 ml/kg	HES	12	10
Ragaller et al.[23] 2000	HSS 162 ml	HES	16	16
Totals			91	95

to the NS group. More remarkable results were seen in two other studies. By preoperatively titrating a bolus of 50 ml of HSS to the endpoint of the highest CI at lowest PCWP in high risk patients, Ellinger and colleagues[14] demonstrated an average four-fold decrease in the need for fluid in these patients as compared to those in the control group, who were given HES. In the Christ study,[17] a fixed dose of 250 ml HHS was applied during aortic clamping for over 20 minutes and resulted in a significantly reduced fluid balance compared to the HES-treated control group (2471 ± 949 ml versus 3387 ± 1248 ml). Additional Ringer's solution was administrated in both groups to achieve defined PCWP. Recently, another study that titrated dose against the best PCWP/CI ratio infused the HSS solution after aortic clamping and reported less fluid retention compared to those given an HES solution (mean 162 ± 111 ml versus mean 265 ± 108 ml).[23] Other important effects of HHS on hemodynamic variables were also reported. In the Ellinger study,[14] the CI nearly doubled in patients treated with HSS in a titrated fashion compared to that in patients treated with HES.

Other studies have also demonstrated increased CIs.[4,17] In addition, a decrease in systemic vascular resistance index was reported immediately after the infusion of HS4 and after administration of HHS during aortic cross-clamping.[17] Auler

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et al.[4] also stated that pulmonary vascular resistance soon decreased after HS administration.

No hypotension developed in patients receiving HHS, regardless of whether the infusion was titrated;[14,17] the sodium load increased, but no related symptoms were reported.[17] One anaphylactoid reaction occurred and was attributed to HES use.[17] One patient died in the Ragaller study,[23] though it was unclear which group the patient belonged to. Three more patients developed serious complications in that study, but they were reported to be unrelated to fluid therapy.

NEUROSURGERY

Only two intraoperative studies involving neurosurgical patients were assessed for this review. While two other studies have been published, these two were excluded due to both a lack of controls[41] and the utilization of 3% NaCl solution rather than 7.2-7.5% NaCl solution.[39] Hemodynamic parameters did not change when HS was used as opposed to 20% mannitol in the two excluded studies. Gemma el al18 found no difference in brain bulk and cerebrospinal fluid (CSF) during elective procedures between infusion of a fixed dose of 2.5 ml/kg HS and administration of 2.5 ml/kg of mannitol. Erard and colleagues[29] reported that a single infusion of solutions of equal osmolarity, NaCl 7.5% or mannitol 20%, induced a similar osmolar variation over time in both hypertonic groups.

ABDOMINAL HYSTERECTOMY

Recently, Kolsen-Petersen and colleagues[32,33] published two studies on the use of HS in abdominal surgery. Based on previous studies in human blood cell cultures[43-45] and different animals models[43,46] that reported that hypertonicity is permissive for lymphocyte proliferation[43] and restrictive for neutrophil function,[45,46-50] the researchers observed the immunological effects of a fixed dose of HS on postoperative women who underwent abdominal hysterectomy. Their first randomized double-blind study[32] involved 62 women who received either 4 ml/kg of 7.5% or 32 ml/kg of 0.9% NaCl over 20 min. The study found that an infusion of HS saline did not alter the postoperative immune response after abdominal hysterectomy. In the subsequent clinical trial also by Kolsen-Peterson el al.,[33] modest changes from HS infusion were observed when compared to normal saline treated patients. These changes included a temporary increase in the number of B cells in the peripheral blood (p<0.01), an augmentation in the concentration of plasma elastase (p<0.05), and a decrease in the number of circulating neutrophils (p<0.001).

MINOR SURGERIES/HS FOR PRELOADING BEFORE SPINAL ANAESTHESIA

In a 1995 study demonstrating the inotropic effects of HS in anesthetised patients without cardiovascular disease, Goertz et al.[15] concluded that the apparent improvement of left ventricular systolic function in response to hypertonic saline/hetastarch was caused mainly by the combined effects of increased left ventricular preload and reduced left ventricular afterload. Three studies[21,24,27] focused on the use of HS for preloading before spinal anaesthesia. Two of these studies, conducted by Jarvela and colleagues,[24,27] found no significant differences regarding hemodynamic parameters and sodium load when the HS-infused group

Table 3 - Perioperative studies on the use of hypertonic saline (7.2 -7.5% NaCl) alone or in association with either dextran (HSD) or hydroxielthyl starch (HSS) compared to 20% mannitol or normal saline (NS) in neurosurgery

Study by Year	Solution dose	Control Solution	n (solution)	n (control)
Gemma et al.[18] 1997	HS 2.5 ml/kg	Mannitol	25	25
Erard et al.[29] 2003	HS 4.95 mOsmkg(-1)	Mannitol	10	20
Totals			35	45

Table 4 - Perioperative studies on the use of hypertonic saline (7.2 -7.5% NaCl) compared to normal saline (NS) in abdominal hysterectomy

Study by Year	Solution dose	Control	n (solution)	n (control)
Kolsen-Petersen et al.[32] 2004	HS 4 ml/kg	NS	21	41
Kolsen-Petersen et al.[33] 2004	HS 4 ml/kg	NS	10	10
Totals			31	51

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Table 5 - Perioperative studies on the use of hypertonic saline 7.2-7.5% NaCl) alone or in association with hydroxielthyl starch (HSS) compared to hydroxiethyl starch (HES) or normal saline (NS) in minor surgeries and before spinal anaesthesia

Study by Year	Solution dose	Control	n (solution)	n (control)
Goertz et al.[15] 1995	HSS 4 ml/kg	HES	13	13
Durasnel et al.[21] 1999	HS ±1.5 ml/kg	NS	24	24
Jarvela et al.[24] 2000	HS 1.6 ml/kg	NS	20	20
Jarvela et al.[27] 2001	HS 1.6 ml/kg	NS	20	20
Totals			77	77

was compared to the control group. However, in a separate study by Durasnel et al.,[21] infusion of 100 ml of HS for over 15 minutes prior to spinal anaesthesia effectively prevented the occurrence of hypotension when directly compared to patients infused with normal saline. Hypotension occurred in two of 24 patients in the HS group and eight of 24 in the NS group (p<0.05).

COMMENTS

The improved fluid balance seen in HHS-treated patients seems to be the result of various mechanisms. First, after the stress and shock of surgery, cells may become edematous.[51] As a result, HHS rapidly shifts fluid from the intracellular compartment to the intravascular space with consequent plasma expansion.[52] HSS increases renal blood flow and glomerular filtration rate, induces renal vasodilatation,[53] and decreases plasma aldosterone levels, all resulting in increased urine output.[54] An immediate increase in urine output following HHS administration was observed in several cardiac studies.[25,26,28,31] In the setting of CPB, extracorporeal circulation is particularly related to the release of cytokines, vasoactive mediators, hormones and autacoids that may cause endothelium damage, increased vascular permeability, tissue oedema, and vasoconstriction. Thus, fluid accumulation is an expected event during CPB due to increased extracellular fluid and intracellular oedema. In addition to the fluid shift from erythrocytes and endothelial cells, HHS may attenuate the inflammatory response, leading to less capillary leakage. In five studies,[6-8,16,31] the use of hypertonic solution before CPB may have led to a better inflammatory profile and accounted for the favourable fluid balance. Moreover, hypertonic infusions resulted in increased plasma protein[55] and decreased protein loss from the intravascular space, which may further have positives effects on fluid balance. However, analysis of serum protein was not the main concern in these studies.

While volume expansion and reduced afterload have been accepted as an explanation for the increased CI, the direct effects of hypertonic solutions on cardiac contractility remain controversial. Most recent results indicated that at least a slight effect may exist.[56-58] The remarkable increase in CI seen in the Ellinger study,[14] where HSS was titrated to the highest CI at lowest PCWP and suggested that hypertonic saline may improve cardiac performance. Only one study presented data conflicting with this hypothesis: transient hypervolomic left ventricular heart failure was induced by a 15-minute infusion of HHS in the Prien study.[11] This rapid HHS infusion rate could be accountable for the transient fluid overload seen in their patients. Moreover, severe hypotension occurred after a similar rate of administration in the Siriex study.[22] It is thus generally believed that the degree of hypotension is dependent upon the rate of infusion.[59] Therefore, a longer rate of infusion appears to be appropriate for intraoperative purposes.

Numerous reports of reductions in systemic vascular resistance index as well as a few reports of decreased pulmonary vascular resistance following HHS administration were all consistent with the existing established model.[60-62]

The most transient hemodynamic effects seen in the Javerla studies[25-27] could be explained by the strong diuretic effects observed immediately after infusion of HS.

The decrease in volume overload along with the improved microcirculation and the decreased interstitial oedema may be responsible for the more efficient pulmonary function observed in several studies.[8,20,31] Large volume resuscitation with crystalloids worsened lung oedema and prolonged the need for mechanical ventilation.[63-65] Christ et al.[17] has suggested that less fluid excess accompanied by decreased oedema formation is particularly beneficial for high risk patients.

Three studies have shown that a titrated dose was the preferred method of administrating hypertonic solution in a perioperative setting. The Prien study11 reported a case of left ventricular fluid overload caused by a fixed dose of 3-4 ml/kg over 15 minutes. Ellinger et al.[14] titrated the infusion in patients undergoing aortic aneurysm surgery and found that a fixed dosage of 4 ml/kg was too high for at-risk cardiac patients with slight hypovolemia. Furthermore, severe hypotension developed after the infusion of a

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fixed 250 ml dose given over 15 minutes in patients who underwent cardiac valve repair in the Sirieix study.[22] Titrated infusion gained further support from animal studies. Pascual et al.[55] administered titrated doses of HSD in a swine model of intra-operative hemorrhagia and found greater volume expansion effect of the solution in hypovolemic conditions. Furthermore, Nguyen et al.[66] reported the advantages of titrated resuscitation in haemorrhaged adult sheep. Thus, the use of titrated HHS infusion in this population seems to be more appropriate.

However, it is clear that certain limitations exist in isolated studies of aortic aneurysm repair. First, these studies included a small number of patients with little synchronization. None of the studies involved more than 20 patients in the tested groups, which limited the power of the statistical analysis. There were also many different deficiencies in the study designs and methodologies. Auler et al.[4] performed a non-randomised study and included patients with thoracoabdominal and abdominal aneurysm in the experimental group. Furthermore, the studies were not blind. Albrecht and colleagues[13] examined patients before surgery and during the induction of anaesthesia. In the Ragaller study,[23] the staff was not blinded, which increased the possibility of bias once the parameters were defined. Furthermore, the studies assessed only a limited number of outcome measures. None of the clinical studies considered the immunomodulatory effects of hypertonic saline. Consistent with the 2002 Cochrane group review[67] on the use of intravenous fluids (non-blood fluids) for abdominal aortic surgery, we also found no overwhelming evidence to support or reject the preferential use of any particular type of fluid.

For neurosurgical patients, however, the current shortage of studies precluded drawing any conclusions. The lower utilization of HS in neurosurgery may be the result of a lack of studies as well as study parameters on the safety and beneficial effects of using HS.[18,29] Despite the similarity of the HS dose used by three studies for preloading before spinal anaesthesia,[21,24,27] only one group reported that infusion of the solution was capable of preventing hypotension.[21] These studies used low HS doses, while most clinical trials that reported positive effects from HS used higher doses.

The discrepancy between the modest findings reported by Kolsen-Petersen et al.[32,33] and the results from previous studies on the immunomodulatory properties of HS may be due to the small number of patients and the characteristics of the studied population. Kolsen-Petersen et al. studied healthy normovolemic women who underwent a standardized surgical procedure. The immunologic response to trauma depended heavily on the amount of tissue injury[68] and blood loss.[69] Ischemic reperfusion injury seen in abdominal aortic aneurysm repair is another important cause of inflammatory response.[70] However, as mentioned earlier, CPB during cardiac surgery was also associated with further inflammation. Based on these results, patients undergoing aortic aneurysm repair (particularly ruptured aortic aneurysm repair) appear to be the population that experiences the most beneficial effects from hypertonic solutions.

The use of colloids along with hypertonic saline prolongs volume expansion and may also positively influence cardiac function. However, colloids are also linked to a small but significant number of complications, particularly anaphylactic reactions and changes in coagulation function. An anaphylactic reaction in one patient was attributed to HES use in the Christ study.[17] In two other studies,[16,20] drainages from the chest were slightly greater in the HSD groups, but the difference was not statistically significant.

CONCLUSION

Our analysis of 30 published clinical studies on the perioperative use of hypertonic saline (7.2-7.5% NaCl) solutions has shown that administration of the hypertonic solution resulted in beneficial hemodynamic effects, particularly during cardiac surgery. The previously observed reductions in positive fluid balance, increases in CI and decreases in systemic vascular resistance further supported our recommendation of HS use during surgery. Furthermore, our study further indicated that dose administration should be titrated and that the rate of infusion should be slow. This review also demonstrated the urgent need for well-designed randomized clinical trials, particularly in the setting of aortic aneurysm repair, where HS has shown many beneficial effects. The immunomodulatory effects of HS should also be a priority in future studies.

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