Prehospital Fluid Replacement

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Introduction

Volume support is frequently required in critically ill patients exhibiting hypovolemia due to severe trauma, hemorrhage, or sepsis. Primary resuscitation from hemorrhagic shock calls for rapid infusion of crystalloids in combination with artificial colloids, whereas albumin or blood components are restricted to clinical use [1]. In the past years, a great body of experimental and clinical studies have been performed to explore the efficacy and safety of artificial colloids, i.e. gelatin, dextran and hydroxyethylstarch. New formulations of hydroxyethylstarch have been designed to optimize the volume effect, metabolism and thus half-life. In addition, a new concept called "small-volume resuscitation", consisting of bolus infusion of a small dose of hyperosmotic-hyperoncotic sodium chloride, has been introduced for primary fluid therapy, and is presently investigated in several controlled clinical trials. The following review summarizes the current status of fluid therapy for primary resuscitation of critically ill trauma patients.

Etiology

Hypovolemic shock is a clinical state determined as depletion of intravascular volume by which tissue perfusion is rendered inadequate with respect to delivery of oxygen and substrates to the cells [1]. Traumatic shock represents a subset of hypovolemic shock, where a critical reduction of blood volume is combined with the effects of tissue injury, eliciting the activation of inflammatory and coagulation systems. Despite the advances in primary trauma care, in the US as well as in Central Europe, trauma in conjunction with shock remains the leading cause of morbidity and mortality in teenagers and young adults [2, 3]. Since the description of multiple organ failure (MOF) accounting for a considerable percentage of late deaths after trauma and shock [4], the mortality rates of patients with established MOF or its close relative, the acute respiratory distress syndrome (ARDS), have not appreciably improved [5]. Still more than 75% of the patients dying with ARDS die from MOF and systemic hemodynamic instability rather than of hypoxia [6].

In the past years it has become an established fact that the primary factor rendering patients at risk of developing MOF after shock and trauma is the persistence of impaired microcirculation with tissue hypoxia and deterioration of cellular function [7, 8]. The two components which are primarily responsible for the decrease of

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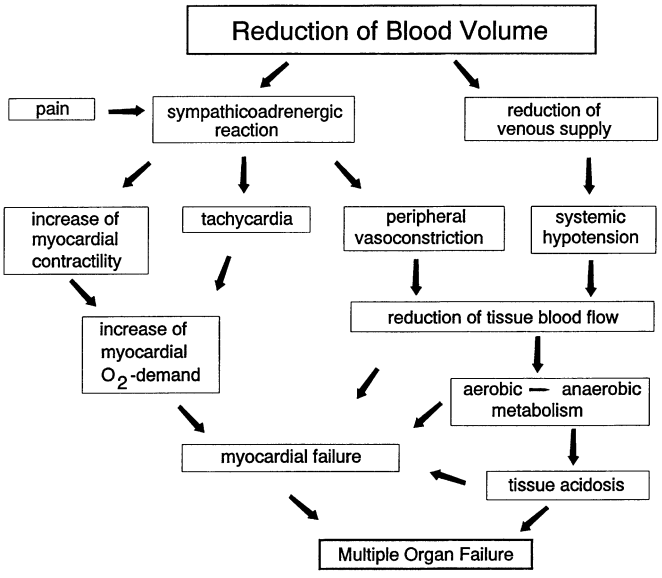

Fig. 1. Pathophysiology of trauma-induced hypovolemia, ultimately leading to multiple organ failure. (From [9] with permission)

nutritional blood flow following trauma and shock are hypovolemia and low perfusion (driving) pressure. The balance between total oxygen delivery (DO_2) and oxygen demand (clinically approximated as VO_2) is maintained as long as tissue oxygen extraction can be enhanced under conditions of reduced blood flow caused by blood loss. Beyond a critical point, however, tissue perfusion becomes inadequate to the local oxygen needs, resulting in anaerobic metabolism cellular acidosis, and reduction of specific organ functions bearing the risk of MOF (Fig. 1) [5, 7–9].

Redirection of Organ Blood Flow

Hypovolemia triggers a sympatho-adrenergic response resulting in peripheral vasoconstriction, a rise in heart rate, and a decline in systolic pressure when blood loss exceeds about 20% of blood volume. Blood flow to the skin and peripheral tissues is reduced in an effort to preserve perfusion of vital organs such as the brain, heart, liver and kidneys. Due to the high α-adrenergic innervation of the splanchnic vascular bed, blood flow to the intestine and to the gut mucosa in particular are curtailed, and early failure of intestinal barrier function further contributes to the process of protracted shock states [10]. Following a 29% hemorrhage, Zinner et al. [11], by means of the radioactive microspheres technique, demonstrated in cynomulgus monkeys a decrease in regional blood flow to all organs, except the myocardium, adrenal glands and hepatic artery. When after the 4-h shock period resuscitation was performed by reinfusion of shed blood and saline solution, splanchnic organs and kidneys remained underperfused in spite of adequate systemic arterial pressure. This pattern

stresses the sensitivity of the intestine and gut mucosa to hypoxia and ischemia/reperfusion (I/R), respectively, the latter being significant for the systemic alterations aggravating the course of the disease days or weeks after the primary insult by precipitating MOF and ultimately death.

Early in the course of hypovolemia and shock, the lumen of the capillaries becomes narrowed due to the swelling of hypoxic endothelial cells and the adhesion of activated polymorphonuclear leukocytes (PMN) to the endothelium of postcapillary venules. This phenomenon causes exclusion of microvessels from perfusion and leads to a highly heterogeneous perfusion pattern with the microcirculatory network [1, 8]. Occlusion of microvessels either by swollen endothelial cells or capillary plugging through uncontrolled activation of coagulation may completely abolish nutritional flow. In addition, the interaction of PMN with the venular endothelium impedes outflow from the capillaries and is followed by the release of vasoactive mediators and toxic oxygen species, promoting redistribution of tissue perfusion, macromolecular leakage, interstitital edema, and further impediment of nutritional flow and delivery of oxygen to the tissues [7, 8].

The normal microvascular perfusion is characterized by temporal and local variations of capillary flow, which in general is determined by local driving pressure, the dimensions of the capillary network and the rheologic properties of the blood. All these factors are compromized in patients after trauma and hemorrhagic shock. Rapid restoration of intravascular volume may lead to restitution of cardiac preload, however, the changes of microvascular permeability through the activation of cascade systems and activated leukocytes (whole body inflammatory response) may lead to pathologic shifts of fluid and plasmatic macromolecules resulting in tissue edema formation or third space fluid losses.

In the polytraumatized patient, an episode of hypotension with decreasing nutritional blood flow early on may produce focal, hence clinically undetectable, or, if more severe, global ischemia with reperfusion injury. Any subsequent insult will amplify the tissue response as manifested by increased cytokine production of macrophages, neutrophil oxidant release and microcirculatory disturbance [12].

Current hypotheses for the development of MOF after trauma and shock include

1) activation of macrophages and release of bioactive lipids, radicals and peptide mediators (interleukins, interferons, tumor necrosis factor);
2 persistence of focal ischemia and microvascular endothelial injury; and
3) translocation of gut-derived bacteria and/or endotoxins serving as trigger to initiate the whole body inflammatory response.

General Concepts of Shock Therapy

Prehospital, perioperative and intensive care-related efforts aimed at the reduction of trauma deaths focus on improvement of rapid resuscitation from hypovolemia and systemic hypotension, and early optimization of DO_2 to the tissues [13]. Primary therapy therefore must include control of hemorrhage, replacement of blood and fluid losses, while ensuring optimal pulmonary oxygenation [1]. In order to compensate for massive blood loss and to resolve shock, rapid infusion of even large amounts of fluids is often mandatory. Sympathicomimetic drugs are seldomly need-

ed, but may serve as transient means to ensure sufficient cardiac output and systemic (global driving) pressure. There is no indication for routine application of sodium bicarbonate in hypovolemic shock. In a prospective, blinded, controlled study in critically ill patients, who had metabolic acidosis and increased blood lactate, correction of acidemia using sodium bicarbonate did not improve central hemodynamics or the cardiovascular response to catecholamines [14]. It did, however, increase $PaCO_2$ and decrease plasma ionized calcium. Possible detrimental effects of bicarbonate may be summarized as follows: venous hypercapnia, decrease in intracellular pH, cerebrospinal fluid acidosis, tissue hypoxia, circulatory congestion and hypernatremia [15].

At the side of the accident, i.e. in the pre-clinical setting, blood (packed red blood cells) and blood components (fresh frozen plasma, thrombocyte concentrate, etc.) are not available. Current concerns about increasingly scare supplies, escalating costs, and the potential for transmitting severe, sometimes even fatal disease (non-A/non-B hepatitis, HIV-virus) have led to reconsider transfusion practice also within the hospital [16]. Moreover, from the physiological standpoint, the primary goal of hypovolemic shock therapy is to restore circulating volume and maintain optimum oxygen carrying capacity with a relatively low viscosity of the blood; this can best be achieved with a hematocrit of about 30% [17].

New Concepts of Primary Volume Therapy

In general, rapid infusion of crystalloids together with artificial colloids is mandatory for primary resuscitation from severe hemorrhage and shock to compensate for the drastically reduced preload [1]. Consensus has been reached for the restricted use of albumin and blood components. Even large-volume fluid therapy may however fail to restore nutritional blood flow and cellular homeostasis, particularly in the splanchnic organs, and thus promote progression of shock into MOF. The primary reason for perfusion failure appears to be the fact that the volume necessary to compensate for massive blood losses can hardly ever been adequately replaced during the prehospital period [18]. The application of large volumes of IV fluids within a short time interval, on the other hand, bears the risk of provoking tissue edema particularly in the gut mucosa and the lungs, which in turn will aggravate the shock-specific microcirculatory defect.

New formulations of hydroxyethyl starch have been designed in the past years, to optimize volume effect, metabolism and thus half-life [19]. The impact of prehospital conventional volume therapy on the survival rate in almost 7000 patients was analyzed by Kaweski et al. [18]. During the time period until arrival in a trauma center, which averaged 36 min, either no volume therapy was started (scoop and run), or an IV line was inserted and 620–1550 mL of crystalloid solution were given during transport. However, even in the group of most severely injured patients (systolic blood pressure <90 mmHg, Injury Severity Score (ISS) >50) not more than 1250 ± 150 mL of crystalloids were applied. The survival rate in this latter group amounted 10%, and was not significantly different from patients with the same ISS without preclinical volume therapy. This study illustrates the dilemma concerning the practicability of preclinical fluid resuscitation, during which time the applica-

tion of crystalloids or colloids, in adequate amounts to compensate for massive blood loss, may be limited due to difficulties in gaining intravenous access with large-bore venous cannulas. In accordance, the average amount of fluid that is really administered during prehospital transport was reported to amount 500–1500 mL only [20].

Wang et al. [21] have shown that fluid resuscitation from experimental hemorrhage in rats by means of even 4 times the maximum bleedout volume of Ringer's lactate increased central venous pressure to more than twice the normal value, but failed to restore microvascular blood flow as determined by laser Doppler flowmetry. The authors concluded that, despite a large infusion volume of crystalloids and increased filling pressures, further pharmacological support may be needed in order to resolve the inadequacy of microvascular perfusion and capillary function.

The therapeutic outcome from traumatic-hemorrhagic shock depends upon the extent and duration of volume deficiency, as Baker and coworkers stated already over 15 years ago [22]. Recent insights into pathophysiology of shock and trauma indicate that no longer normalization of macrocirculation alone, but restoration of normal microcirculation must be the primary goal for prevention of organ dysfunction and MOF [1, 7, 8]. Modern strategies of primary volume therapy in patients with severe trauma and shock therefore focus on the following aspects

1) practicability, i.e. volume substitution in an amount realistic to the pre-clinical emergency setting;
2) efficacy, i.e. cardiocirculatory effect on macrohemodynamics (cardiac output, blood pressure) and microhemodynamics (nutritional blood flow); and
3) safety and potential adverse effects, e.g. risk of anaphylactic/anaphylactoid reactions.

Importance of the Time Factor

The experiences during evacuation of soldiers in the Vietnam and Korean wars have yielded that rapid transportation away from the front line significantly improved prognosis. This formed the basis for the concept of "scoop and run" also in the civilian setting, since, in the severe trauma scenario, transport time to hospital might be less than IV establishment time [20]. In contrast, recent data from a feasibility study in trauma patients reveal a 98.3% rate of successful establishment of IV lines, 96.7% of which were performed in less than 4 min [23]. Therefore it seems that efforts to replace the "golden 1 hour" by the "platinum 10 min" after trauma and shock – as suggested through the International Resuscitation Research Conference 1994 (IRRC '94) [24] – today must include both, i.e. rapid evacuation together with effective initial therapy. Although for hypotensive patients with penetrating torso injuries, delay of aggressive fluid resuscitation until operative intervention has been suggested to improve outcome [25], in general, for restitution of DO_2 to the tissues, early intubation (i.e. improving pulmonary oxygenation) [26] together with restoration of circulating blood volume (i.e. enhancing preload and thus cardiac output) still is regarded mandatory. The new concept of small-volume resuscitation consists of bolus infusion of a small dose of hyperosmotic NaCl/colloid solution. In the preclinical situation, it is attractive with regard to the small infusion volume needed to elicit an in-

stantaneous cardiovascular effect in states of severe and protracted hypovolemia, without the risk of fluid overload. Hyperosmotic saline solutions in concentrations ranging from 1.5 to 30% have been studied for their use in resuscitation from trauma, shock and perioperative hypovolemia for many years [27]. The novelty of this concept lies in its mode of action at the microcirculatory level and prompt circulatory effect, even when given in a dose as small as 4 mL/kg. With regard to the above mentioned goals of modern shock therapy, it appears as most promising new drug development.

In the past decade, the concept of primary resuscitation by means of hyperosmotic saline solution has been elaborated and various research groups have demonstrated that, even in the presence of a 50% blood loss, a volume as small as 4 mL/kg of 7.2–7.5 % sodium chloride is sufficient to restore cardiac output almost instantaneously, and at the same time to significantly increase systemic pressure [27]. Small-volume resuscitation today is defined as "bolus infusion of 4 mL/kg of hyperosmotic/hyperoncotic saline solution within 2–5 min through a peripheral vein (...) for primary resuscitation from severe hypovolemia associated with trauma and hemorrhage" [27].

Small-Volume Resuscitation

IV bolus application of hyperosmotic sodium chloride results in a rapid and pronounced increase of the plasma sodium concentration and thereby initiates a steep transmembraneous osmotic gradient. The most important mechanism of action of hyperosmotic saline is the instantaneous mobilization of endogenous fluid along the osmotic gradient with increase of intravascular volume (Fig. 2) [27, 28]. In addition, direct myocardial stimulation, central nervous system (CNS) stimulation, neurogenic reflex mechanisms, enhanced sympathetic discharge, hormone release, improvement of blood fluidity, re-establishment of spontaneous arteriolar vasomotion, and

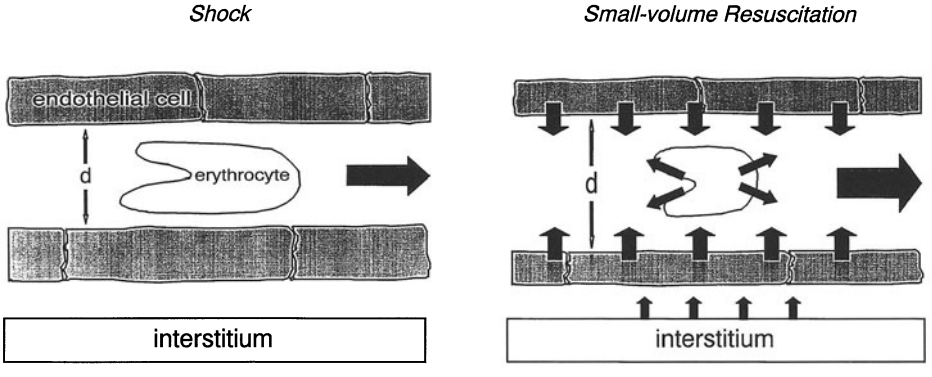

Fig. 2. With the establishment of an osmotic gradient, there is an immediate onset of fluid shift from the endothelium and the interstitium into the intravascular compartment, with increase of plasma volume, increase of vessel diameter due to endothelial de-swelling, and thus enhanced blood flow

peripheral arterial vasodilatation are discussed as mechanisms of action [27]. Latest data from experimental studies in dogs with burn injury [29] and in pigs resuscitated from hemorrhagic shock [30] have failed, however, to confirm a direct myocardial stimulating effect. The authors were unable to demonstrate significant changes in the end-systolic pressure-volume relationship and stroke work end-diastolic volume relationship [29], or end-systolic elastance and segmental preload recruitable stroke work [30] upon hyperosmotic saline bolus infusion. Both groups of investigators attribute the circulatory effect to rapid augmentation of ventricular preload and a reduction of afterload.

Vassar and Holcroft [31] on the basis of their clinical experience in the field of small-volume resuscitation estimate that administration of 250 mL 7.5% NaCl/6% dextran 70 to a 70-kg patient who has suffered a 2-L blood loss will result in plasma volume expansion of at least 700 mL. To achieve equivalent plasma volume expansion with lactated Ringer's solution, these authors estimate 2.8 L of solution to be necessary. Mazzoni et al. [28] have calculated that, after a 20% blood loss, 7.5% saline solution given over 10 sec in an amount equivalent to 1/7 of the actual blood loss allows to re-establish normal blood volume within 1 min. These authors ascribe the instantaneous circulatory effect to the rapid influx of fluid first of all from the microvascular endothelium and red blood cells [28, 32]. This fluid shift effect is most pronounced in those capillary districts with swollen endothelium: the more swollen the endothelium, the greater the effect of hyperosmotic solutions in reducing hydraulic resistance and improving tissue perfusion [28]. According to Mazzoni et al. [33], who investigated the volume changes of endothelial cell monolayers on exposure to anisotonic media, the increase in plasma osmolality to 460 mOsmol/kg – which is transiently obtained at the end of bolus infusion of 7.5% saline [28] – should result in shrinkage of endothelial volume by 20%.

Furthermore, using ^{31}P-nuclear magnetic resonance (NMR) technique, the early cellular response to an increase of extracellular osmolality from 320 to 480 mOsm/kg by addition of NaCl has been analyzed, demonstrating that C6 glioma cells shrink by 33% of their original volume [34]. This occurs simultaneously with an increase of intracellular pH and adenosine triphosphate (ATP) concentration, when corrected for the decrease of cell volume. If pH is assumed to be a critical factor in the sense that cells are regulating pH at the expense of volume, then clinical management of the shock victim should consider manipulation of pH to limit capillary dysfunction, eventually through restoration of normal endothelial cell volume by bolus infusion of hyperosmotic saline solutions [35].

Results from animal studies have suggested that the rapid cardiovascular reponse to hyperosmotic solutions with increase of cardiac output and restoration of peripheral blood flow might, at least in part, be mediated by the instantaneous release of eicosanoids [36] with an enhanced 6-keto-$PGF_{1\alpha}$/thromboxane B_2 ratio [37]. This may also explain the characteristic, acute hypotensive response observed following rapid hyperosmotic saline infusion in dogs, which is not mediated by cardiac depression, but by a decrease in total peripheral resistance [38]. The potential role of other mediators is still under investigation. From studies of endothelial cells grown on beads, the link between capillary flow (shear-stress) and the production of nitric oxide (NO) has been emphasized [39], and the involvement of NO in this process therefore remains to be analyzed.

The established effects of primary resuscitation by means of hyperosmotic saline either alone or in combination with hyperoncotic dextran can be summarized on the basis of the experimental data as follows

1) immediate increase of systemic pressure and cardiac output, while vascular resistance is reduced;
2) instantaneous increase of nutritional blood flow and reduction of post-ischemic reperfusion injury;
3) resumption of organ function as seen by increase of urinary output; and
4) increased survival rate.

Effect of Hyperosmotic Saline on Post-Ischemic Leukocyte-Endothelial Interaction

Chemotactic accumulation of circulating leukocytes and their adhesion to the endothelial lining of post-capillary venules have long been recognized as key features of post-ischemic reperfusion injury [40, 41]. In the post-capillary venules, leukocytes interact with endothelial cells and promote capillary leakage and edema formation. The extent of leukocyte adherence seems to result from an increase in the quotient of adhesive forces and dispersal forces together with an upregulation of CD11/CD18 receptors, leading to a decrease in leukocyte rolling velocity (Fig. 3) [42]. In contrast, capillary leukostasis predominantly seems to be a pressure-related phenomenon that is not receptor-dependent and is reversible with early restoration of perfusion pressure [43].

Nolte and co-workers [44] published the first data on the leukocyte/endothelial interaction when hyperosmotic-hyperoncotic dextran solution wash given after I/R injury in the hamster dorsal skin fold model. The authors demonstrated that following 4 h of ischemia and reperfusion of striated muscle, the number of leukocytes adhering to the endothelium of post-capillary venules was significantly reduced for

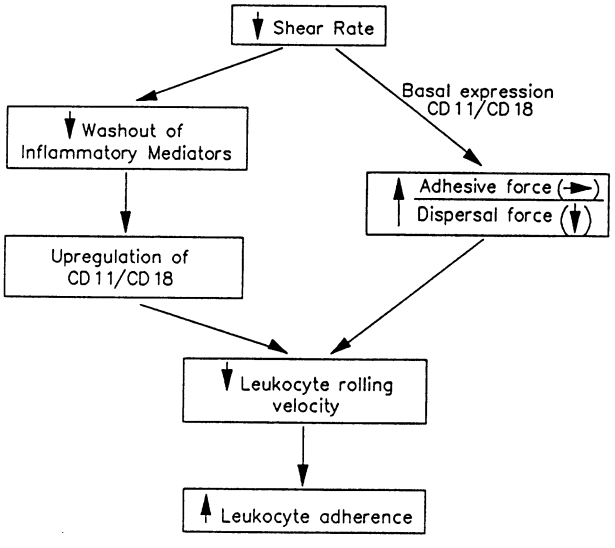

Fig. 3. Interaction of reduced shear rate in trauma and shock and upregulation of CD11/CD18-receptors of PMN resulting in enhanced leukocyte adherence to post-capillary venules. (From [42] with permission)

as long as 24 h after bolus infusion of 7.2% NaCl/10% dextran 60. In addition, hyperosmotic saline dextran effectively attenuated macromolecular leakage and reduced capillary endothelial swelling as verified by the increase of capillary lumenal diameters upon small-volume resuscitation. An important finding was that hyperosmotic saline alone proved significantly less efficient in protecting from post-ischemic leukocyte/endothelial interaction and its sequelae.

The molecular mechanisms of leukocyte adhesion to endothelial cells have been further investigated *in vitro*. Incubation of isolated leukocytes in buffer solutions with increasing osmolarity seems to counteract the FMLP-induced upregulation of β_2-integrins in a dose-dependent manner. At the same time FMLP-induced shedding of L-selectin is reduced, suggesting that these changes are not due to a non-specific artifact, such as effects of the hyperosmotic medium on epitope-antibody recognition [45]. When compared to physiologic osmolarity (290 mM), FMLP-induced CD18 upregulation and L-selectin shedding were significantly reduced at osmolarities that are typically found in humans and animals after resuscitation with hyperosmotic solutions.

Role of the Colloid Component

The short duration of the circulatory effects – which are elicited by the sharp increase in plasma osmolality – have been attributed to the rapid equilibration of the hyperosmotic solute between extra- and intracellular compartments. As many authors were concerned about the transience of the cardiovascular response after small-volume resuscitation using hyperosmotic saline and in order to preserve the intravascular volume gain, 7.2–7.5% saline solution has been combined with a colloid containing a high water-binding capacity, i.e. 4.2–24% dextran 60/70 or 6–20% hydroxyethyl starch 200 000 and 450 000, respectively [27]. Thus one should obtain a synergistic effect 1) by increasing plasma osmolality and mobilization of endogenous body water, and 2) by providing high plasma oncotic pressure for conservation of the volume effect. Animal studies have revealed that, compared with hyperosmotic sodium chloride alone, the addition of a colloid indeed causes a sustained circulatory response and increased survival [27].

Moreover, the colloid also exhibits an additive acute circulatory effect. From our previous experiments employing radioactive microspheres in protracted traumatic-hemorrhagic hypotension (MAP 40 mmHg for 75 min) in beagles with a 50% blood loss, we could demonstrate that the nutritional blood flow in the kidneys and the gastrointestinal tract increased instantaneously and significantly more pronounced when 10% dextran 60 was given in addition to 7.2 NaCl [46]. Walsh and coworkers [47] have shown in hypovolemic sheep treated by small-volume resuscitation that the dextran component (either 0, 12 or 24% dextran 70 were used) exhibits an additive effect on plasma volume and cardiac output increase.

Following bolus infusion of 7.5% NaCl, rapid plasma volume expansion occurs, amounting to 8–12 mL/kg, as measured by Smith and coworkers [48] in studies on conscious sheep subjected to hemorrhagic shock. Since 1 g dextran binds ~20 mL water, 6% dextran 60/70 solution will bind ~5 mL/kg when given in a dose of 4 mL/kg. The conventional dextran 60/70 could therefore not have the oncotic pow-

er of keeping all the mobilized water within the intravascular compartment. Higher concentrated dextran solutions, particularly the 10% dextran 60/7.2% saline solution, thus seem more adequate in terms of pharmacologic properties. Even though the optimal concentration of the colloid has not yet been identified, several animal studies have demonstrated the superiority of a hyperoncotic substance as co-component of small-volume resuscitation in comparison with hyperosmotic saline alone, with respect to survival of pigs subjected to severe hemorrhage (6% dextran 70) [49], an enhanced plasma volume effect in normovolemic horses (24% dextran 70) [50], a dose-dependent increase in cardiac output and systemic pressure (0, 6, and 12% dextran 70) [51], and reduction of reperfusion injury (10% dextran 60) [44].

Prehospital Trials

The data from the first US multicenter trial on prehospital hyperosmotic saline/dextran infusion for post-traumatic hypotension were published in 1991 [52]. The 359 patients analyzed had a mean ISS of 19, and received either 250 mL of 7.5% saline in 6% dextran 70 or Ringer's lactate, followed by conventional therapy. There was no difference in overall survival within the first 24 h, however, in the subgroup of patients requiring surgery and those with penetrating injury, hyperosmotic saline/dextran infusion proved superior to Ringer's lactate ($p < 0.02$ and $p < 0.01$, respectively); in addition, there were fewer complications (ARDS, renal failure, coagulopathy) than in the standard treatment group.

So far, the application of hyperosmotic saline/dextran solutions has proven safe in patients, and in none of the controlled clinical trials adverse effects could be attributed to the colloid component, nor have anaphylactoid reactions been observed [27]. The necessity of the colloid component, although having been proven most effective in the experimental settings, was analyzed in a second multicenter trial, in which hypotensive trauma patients from 6 trauma systems served by helicopter transport were investigated [53]. The 4 treatment groups included lactated Ringer's solution, 7.5% sodium chloride, 7.5% sodium chloride combined with 6% dextran 70, and 7.5% sodium chloride combined with 12% dextran 70, each of the solutions given in a quantity of 250 mL and followed by conventional isotonic volume support. Only the 7.5% sodium chloride solution was associated with an increase in blood pressure and survival to hospital discharge compared with survival as predicted by the Major Trauma Outcome Study [54]. The impact of this study, however, is limited, since it was terminated prematurely and only 194 patients were included in the final analysis instead of the 600 planned, infusion of a considerable amount of isotonic solutions was administered and, in almost a third of the patients, medical anti-shock trousers (MAST) were inflated at a time when the infusion of the test solution had not yet been started. Although this management might more closely correspond to the preclinical scenario, this study therefore failed to give a definite answer on the role of the colloid component.

In an attempt to gain access to a more representative data base, in 1994 Wade et al. [55] introduced the results of a meta-analysis on hyperosmotic saline/dextran or hyperosmotic saline alone on survival following traumatic injury; 9 trials were included, yielding a total number of 1889 patients. Inclusion criteria was a systolic blood

pressure of below 100 mmHg. The results are depicted in Table 1. Although the necessity of the colloid component had been debated in the study of Vassar et al. [56], no signficant difference could be established between hyperosmotic (7.5%) saline alone vs. lactated Ringer's solution, whereas the hyperosmotic saline dextran solution (7.5% NaCl/6% dextran 70) yielded a 5.1% higher survival rate [55]. This data base has recently been further explored, and the scientific community awaits its publication.

Table 1. Efficacy of hyperosmotic saline/dextran (HSD) or hyperosmotic saline (HS) compared to lactated Ringer's solution (LR) on 30-day survival following traumatic injury. (From [55] with permission)

	HS vs. LR		HSD vs. LR	
Number of patients	340	379	588	582
Survivors	235	262	441	407
Percentage (%)	69	69	75	70[a]

[a] significant difference ($p < 0.05$)

Table 2. Field of potential indications for small-volume resuscitation

Type of derangement/shock	Indication	Impact
Trauma	pre-hospital setting	volume substitution, microcirculatory resuscitation
	emergency room	microcirculatory resuscitation
	intraoperatively	volume substitution
Head trauma	increased ICP	lowering ICP, improvement of CBF
Hypovolemic shock	anaphylaxis	volume refill
	intraoperatively	volume substitution (in case of sudden bleeding)
Septic shock	hyperdynamic state	microcirculatory resuscitation, increase of tissue oxygen uptake
Burn injury	microcirculatory failure	reduction of edema formation, microcirculatory resuscitation, attenuation of bacterial translocation
Intensive care	MOF, organ failure	improvement of organ blood flow and organ function, attenuation of bacterial translocation
Cardiogenic shock	myocardial infarction	volume expansion, positive inotropic effect
Cardiovascular surgery	aortic aneurysm	volume support, attenuation of reperfusion injury, decrease of volume requirements
	cardiac surgery	
Anesthesiological management	epidural anesthesia	in general: no indication
	physiological volume replacement	in general: no indication

ICP: intracranial pressure, CBF: cerebral blood flow, MOF: multiple organ failure

In view of data from diverse controlled clinical trials, the concept of small-volume resuscitation so far has been demonstrated to be feasible and effective with respect to conventional fluid therapy for primary resuscitation of trauma patients undergoing helicopter transport [57], in the emergency room [58, 59], in cardiac surgery [60, 61], in critically ill patients [62], and even for treatment of acute myocardial infarction [63]. In addition, the effect of 5% saline solution for fluid preloading before lumbar extradural anesthesia [64], as well as 7.2% NaCl/6% hydroxyethyl starch 200 000/0.5 applied for doubling pulmonary capillary wedge pressure (PCWP) after induction of anesthesia in patients undergoing cardiac surgery [60], have been investigated. In these trials, the hyperosmotic saline solution was judged to be beneficial, especially for those situations when rapid fluid preloading is desired without excess free water administration. A list of potential indications for small-volume resuscitation is given in Table 2.

Treatment of Trauma Combined with Head Injury

Data gathered by the US Traumatic Coma Data Bank Study indicate that mortality is doubled in case of severe head injury in the presence of hemorrhagic shock [65], highlighting the significance of prompt and effective shock therapy at the scene and during evacuation of the patient [66]. Criticism has arisen regarding the potential risk of hyperosmotic saline resuscitation in severe trauma combined with head injury. When used for resuscitation from experimental hemorrhagic shock with associated intracranial hypertension, however, 7.2% saline has been shown to reduce intracranial pressure (ICP) and increase regional cerebral blood flow [67, 68]. These findings have been confirmed in polytraumatized ICU patients with increased ICP, non-responding to conventional therapy, in whom already 5 min post-infusion of 4 mL/kg 7.5% NaCl/hydroxyethyl starch 200 000/0.6 [69], ICP had decreased significantly; this was paralleled by an increase of cerebral perfusion pressure (CPP) by 19–43%.

It has been demonstrated that the incidence of mortality and morbidity resulting from severe head trauma is strongly related to elevated ICP and hypotension [70]. Administration of small volumes (250 mL) of 7.5% NaCl/dextran 70 before hospitalization has been shown to increase blood pressure of severely injured patients more effectively than lactated Ringer's solution, with a tendency towards improving survival in patients with severe head injury [57]. In addition, the data from the latest multicenter trial [53] seem to suggest that hypotensive trauma patients with baseline Glasgow Coma Scale of 8 or less benefit most from hyperosmotic (7.5%) saline resuscitation. Current concepts of initial management of head injury include hyperosmotic saline containing solutions as fluids of choice [71].

Artificial Oxygen Carrying Solutions

Due to the potential risks and side effects associated with the therapy of homologous blood and blood components [16], another therapeutic attempt aims at an in-

crease of DO_2 by infusion of artificial oxygen carriers [72, 73]. These are modified stroma-free hemoglobin solutions and perfluorocarbon (PFC) and perfluorooctylbromide (PFOB) emulsions. Oxygen transport could be enhanced through these solutions *in vivo*; however, results from controlled clinical trials are not yet available. The main problems are the reversible binding and release of oxygen molecules (low P_{50}-value) and biological compatibility, contamination of the solutions with endotoxin, antigenicity, interaction with the NO system (NO-scavenging), and the risk of organ deterioration, particularly of liver and kidney function [72]. In the preclinical setting, a further problem is the storage of these solutions with regard to their short half-life and the need for cooling. A promising component seems to come up by lyophilized liposome encapsulated hemoglobin [74]; however, thrombocytopenia and induction of thromboxane release into plasma have been reported in animal studies. Taken together, at this time the use of artificial oxygen carrying solutions as adjunct to conventional fluid therapy of severe hypovolemia and trauma-induced shock, although promising in the experimental setting, still needs unravelling of potential unwanted side effects, followed by controlled clinical trials investigating their efficacy and safety.

Conclusion

Hypovolemic shock is a clinical state determined as depletion of intravascular volume by which tissue perfusion is rendered inadequate with respect to delivery of oxygen and substrates to the cells. It is the most common type of shock in emergency medicine as well as in major surgery. The prognosis of patients is significantly affected by the severity and the duration of shock and consecutive secondary organ dysfunction, and therefore by the speed of recognition and appropriateness of medical intervention. The primary objective of therapy is to restore nutritional blood flow and provide oxygen delivery adequate to tissue oxygen needs. Besides the rapid restoration of macrohemodynamics and prevention of early deaths, the new concept of small-volume resuscitation by IV bolus infusion of a small volume (4 mL/kg B.W.) of a 7.2–7.5% NaCl/colloid solution aims at the prevention of late complications, such as sepsis and multiple organ failure, on the basis of persisting microcirculatory disturbances. The novelty of this therapy lies in its operational mechanisms at the microcirculatory level; these include the mobilization of fluid preferentially from edematous endothelium (vasodilation) and the reduction of post-ischemic leukocyte adherence to the endothelium of post-capillary venules (reopening of shock-narrowed capillaries). Restoration of nutritional blood flow is thus efficiently promoted. Recently presented data from a cohort analysis of 8 preclinical studies show an increase in survival rate by about 5% when compared to standard of care. In addition, artificial oxygen carrying solutions have recently been investigated, which might be useful for primary resuscitation from severe hypovolemia through increasing oxygen transport capacity and thus global DO_2. Although this appears to represent a major therapeutic approach, re-establishment of nutritional blood flow remains the key factor for restoration of oxygen delivery to cells after severe trauma and shock.

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