Strategies for Small Volume Resuscitation

Hyperosmotic-Hyperoncotic Solutions, Hemoglobin Based Oxygen Carriers and Closed-Loop Resuscitation

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ABSTRACT

Introduction: *Logistic constraints on combat casualty care preclude traditional resuscitation strategies which can require volumes and weights 3 fold or greater than hemorrhaged volume. We present a review of quantitative analyses of clinical and animal data on small volume strategies using 1) hypertonic-hyperosmotic solutions (HHS); 2) hemoglobin based oxygen carriers (HBOCs) and 3) closed-loop infusion regimens.*

Methods and Results: *Literature searches and recent queries to industry and academic researchers have allowed us to evaluate the record of 81 human HHS studies (12 trauma trials), 19 human HBOCs studies (3 trauma trials) and two clinical studies of closed-loop resuscitation.*

There are several hundreds animal studies and at least 82 clinical trials and reports evaluating small volume 7.2%-7.5% hypertonic saline (HS) most often combined with colloids, e.g., dextran (HSD) or hetastarch (HSS). HSD and HSS data has been published for 1,108 and 392 patients, respectively. Human studies have documented volume sparing and hemodynamic improvements. Meta-analyses suggest improved survival for hypotensive trauma patients treated with HSD with significant reductions in mortality found for patients with blood pressure < 70 mmHg, head trauma, and penetrating injury requiring surgery. HSD and HSS have received regulatory approval in 14 and 3 countries, respectively, with 81,000+ units sold. The primary reported use was head injury and trauma resuscitation. Complications and reported adverse events are surprisingly rare and not significantly different from other solutions.

HBOCs are potent volume expanders in addition to oxygen carriers with volume expansion greater than standard colloids. Several investigators have evaluated small volume hyperoncotic HBOCs or HS-HBOC formulations for hypotensive and normotensive resuscitation in animals. A consistent finding in resuscitation with HBOCs is depressed cardiac output. There is some evidence that HBOCs more efficiently unload oxygen from plasma hemoglobin as well as facilitate RBC unloading. We analyzed one volunteer study, 15 intraoperative trials, and 3 trauma studies using HBOCs. Perioperative studies generally suggest ability to deliver oxygen, but one trauma trial using HBOCs (HemAssist™) for treatment of trauma resulted in a dramatic increase in mortality, while an intraoperative trauma study using Polyheme™ demonstrated reductions in blood use and lower mortality compared to historic controls of patients refusing blood. Transfusion reductions with HBOC use have been modest. Two HBOCs (Hemopure and Polyheme) are now in new or planned large-scale multicenter prehospital trials of trauma treatment.

A new implementation of small volume resuscitation is closed-loop resuscitation (CLR), which employs microprocessors to titrate just enough fluid to reach a physiologic "target". Animal studies suggest less risk of rebleeding in uncontrolled hemorrhage and a reduction in fluid needs with CLR. The first clinical application of CLR was treatment of burn shock and the US Army.

Conclusions: *Independently sponsored civilian trauma trials and clinical evaluations in operational combat conditions of different small volume strategies are warranted.*

1.0 INTRODUCTION

Most of the modern clinical perspective of trauma care is from reports of urban trauma centers where prompt arrival of paramedics lends itself to rapid transport of patients to trauma centers for definitive care. [1, 2] Prehospital care for rural trauma, mass casualty and combat casualty are different than urban trauma for several reasons. 1) Patient transport times can be lengthy and the initiation of transport may be greatly delayed

[3, 4]. 2) Logistic constraints can result in a limited amount of volume being available for initial care of mass casualties and combat casualties. 3) Further, a high ratio of victims to care givers can occur such that focused care is unavailable for most patients. A better and more efficient means to treat trauma patients in these scenarios is needed. Small volume resuscitation can be considered a concept to improve the efficiency of fluid therapy such that there is physiological equivalence in a smaller volume. This can be approached by changing the composition of the fluids by changing the infusion regimens. For the military application small volume resuscitation does not have to be superior to standard of care therapy, rather it could simply be equivalent or the best possible choice after considering logistical constraints. On the other hand, all of the clinical work on these approaches has been for civilian care and thus in general researchers have attempted to determine if small volume resuscitation is better than conventional care. We will review three approaches that may allow resuscitation to be limited in volume by increasing the physiological efficiency. We present some background and physiology based on animal studies but the focus will be on the clinical trial data. These three approaches are: 1) the use of concentrated hyperosmotic-hyperoncotic small volume formulations; 2) the use of synthetic hemoglobin based oxygen carriers; and 3) the use of automated systems that titrate fluid therapy to endpoints.

2.0 HYPEROSMOTIC-HYPERONCOTIC SOLUTIONS

2.1 Historic development of hypertonic saline

There has been substantial interest and extensive preclinical and clinical experience in evaluating the use of hypertonic saline solutions for volume support. These effects have universally been show to reduce volume needs [5-10]. Hypertonic solutions mobilize an amount of cellular water proportional to osmotic load and tends to reduce overall volume needs in perioperative patients [11, 12]. Because cells become edematous during shock and surgical stresses [13-15], hypertonic resuscitation of shock will often normalize cell volume rather than reduce it below normal [16, 17]. Mildly hyperosmotic saline solutions (1.5-2.0%) are well described in studies of intraoperative volume replacement [7, 8] and for the resuscitation of major burns [5, 6]. In general, these mildly hypertonic solutions are reported to reduce fluid volume requirements; however, to date such formulations have not received widespread usage.

In the last 20 years, extensive research efforts have focused on a more concentrated hyperosmotic 7.2-7.5% NaCl solutions alone or mixed with a hyperoncotic colloid for small-volume resuscitation. The calculated osmolality of such solutions is 2464-2567 mOsm, but the measured osmolality is slightly less and they have been collectively referred to as 2400 mOsm formulations, since the first reported study by Velasco et al [18]. Because hyperosmotic crystalloid solutions provided profound, but often only transient hemodynamic improvement, consideration was given to mixing a hyperoncotic colloid with the hyperosmotic NaCl [19]. The rationale was that while the hyperosmotic sodium chloride would expand the vascular space by mobilizing extravascular water, adding a hyperoncotic colloid might selectively retain more of this water in the vascular space. Several independent groups confirmed the better hemodynamics, survival and higher cardiac outputs with HSD compared to HS alone in different models using hemorrhaged pigs, dogs and sheep [20-26]. These beneficial effects were attributed to a slightly better initial and, particularly, a more sustained plasma volume expansion.

Of particular note, Maningas et al, and Wade et al showed that treatment of severe hemorrhage in conscious pigs using small volumes of HSD caused a 100% survival, while similar volumes of HS alone, dextran alone or normal saline resulted in significantly less survival [26, 27] with survival benefit confirmed by others [20]. Hypertonic saline mixed with hetastarch (HSS) produced similar cardiovascular responses [28-31]. The confirmation of the sustained effectiveness of HSD suggested an ideal small-volume formulation for the

military [32, 33]. The Maningas studies are historically important because they were the stimulus that launched the clinical trauma trials of HSD.

2.2 Physiological Mechanisms

Intravenous infusion of a small-volume hyperosmotic-hyperoncotic solution in hemorrhaged animals rapidly initiate major physiological responses affecting vascular volume, heart and peripheral blood vessels that work synergistically together to increase cardiac output. These mechanisms along with their clinical correlations are schematically illustrated in Figure 1. Associated physiological and clinical responses include reduced peripheral vascular resistance, reduced pulmonary vascular resistance, diuresis/natriuresis, restoration of membrane potentials, correction of cellular edema, and lower subsequent volume requirements [16, 17, 34-36].

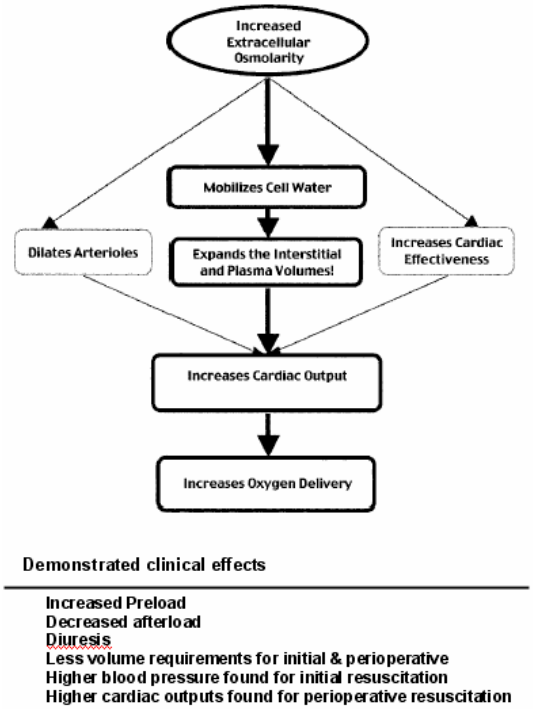

Figure 1.

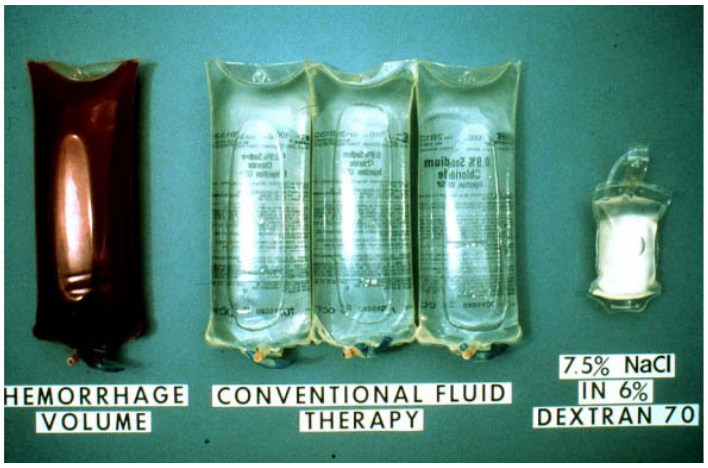

Figure 2.

Such powerful and rapid physiological effects could be deleterious, particularly if not used with an understanding of their effects. Figure 2 illustrates the physiological equivalence of HSD with lactated Ringer's and this simple picture is perhaps the single best guide to understanding the acute benefit as well as the potential dangers of hypertonic resuscitation. Most of the initial cardiovascular changes can be explained by the very rapid volume expansion, which occurs as soon as the fluids are infused [37]. Very aggressive resuscitation with rapid increases in blood pressure were believed to be an advantage when HSD was first studied in the mid 1980's [35]. Subsequent animal studies showed that early application of aggressive resuscitation deleteriously affected outcomes in animal models of uncontrolled hemorrhage as rapid bolus infusions of HSD caused rapid increases in blood pressure, internal bleeding and higher mortality [38-43]. Such increased bleeding is not due to the nature of the volume expander, but rather the rate at which the fluid is administered and the volume expansion and hemodynamics elicited. Since HSD has the hemodynamic impact of close to 3 liters of crystalloid, it should perhaps be infused as 3 liters of lactated Ringer's would be infused for trauma resuscitation. Limited resuscitation to intermediate levels of blood pressure and with slower infusions has been shown to lower mortality in anesthetized swine and rat models of uncontrolled hemorrhage [40-42] when compared with resuscitation designed to normalize blood pressure. Most notable is the enhanced survival benefit demonstrated by Stern et al when HSD was infused slowly versus rapidly [44]. Small volume resuscitation with slower infusion may improve clinical outcomes, while simultaneously accommodating special needs of the military by reducing the cube and weight of fluid needed in the field. There is also evidence that slower infusions may increase relative volume sparing. Greater volume sparing has been reported for both HSD and HSS in clinical intraoperative trials than in acute hemorrhagic shock trials where HSD has been bolused [12]. When HSD or LR was infused slower and titrated to physiological effect the ratio of isotonic to hypertonic volume needs were increased to 15-19 or greater than the 10 to one difference often referenced [45, 46].

It should be noted that rapid bolus infusion in anesthetized animals and humans can cause vasodilation and can transiently reduce blood pressure before increasing it [47-49]. This hypotension is due to an effect on the peripheral circulation, rather than the heart, as blood flow, both coronary blood flow and cardiac output are increased during the hypotension [48]. Another situation when infusions can be too rapid to be safe is with deep anesthesia and a preexisting compromised circulation [50, 51]. It has been suggested that in the operating room the use of hyperosmotic solutions should be titrated to physiological effect with respect to both dose and infusion rate [52]. Such data and rationale suggest that a slower infusion may be safer than a more rapid infusion in all conditions.

Recently, studies have provided conflicting conclusions about the effects of hypertonic saline and HSD infusion on cardiac function showing that infusion of hypertonic saline solution into the circulation or directly into coronary vessels causes increased contractility [53, 54], little effect on contractility [55-58], or decreased contractility [59, 60]. Some of the negative reports may be the result of studying very high doses or very fast infusion rates. Rapid infusions or inappropriately high doses cannot only cause fluid overload, but also arrhythmias [50, 61, 62]. Such doses or infusion rates can transiently cause very high concentrations of extracellular sodium or osmotic pressures and this is further rationale for slower infusions.

2.3 Rate of Infusion

More efficient volume expansion should not be a contraindication for trauma care, particularly for the combat casualty care, but rather optimal use of hypertonic fluids may require different infusion guidelines as to infusion rate. If the physician or medic appreciates the volume equivalency illustrated and estimated in Figure 2 and considers administering 250 mL of HSD in a regimen similar to 3 liters of LR the likelihood of misuse may be reduced. On the other hand, most of the clinical trauma trials of HSD were performed in the early 1990's when aggressive resuscitation was the standard of care. When HSD was infused rapidly per prehospital resuscitation protocols of the day, there was a survival benefit in these civilian trauma patients most representative of combat injuries and penetrating trauma requiring surgery [1, 63].

2.4 Peripheral Circulatory Effects

The effects of infusing hyperosmotic-hyperoncotic solutions on the peripheral vasculature and the microcirculation are generally to induce changes that augment flow. These are a reduction in peripheral vascular resistance, which is primarily due to arteriolar vasodilation [64]. Capillary perfusion may be further augmented by the ability of HSD to reverse specific cellular effects of ischemia and ischemia-reperfusion. HSD infusion shrinks endothelial cells that are swollen by hemorrhagic shock [16].

2.5 Immune Modulation of Hypertonicity

In the last 10 years there has been a growing body of evidence on the immune modulation of hypertonic resuscitation. *In vitro* and *in vivo* effects of hypertonicity on white cells suggest that a hyperosmolarity above 330 mOsm can down-regulate the initial inflammatory activation of neutrophils and upregulate immunological protection provided by lymphocytes [65-67]. Most recently, the down regulation of inflammatory cytokines and neutrophil activity along with proliferation of lymphocytes counts have been demonstrated in trauma patients treated with HSD [68]. Such data have resulted in one NIH sponsored injury trials of blunt trauma focusing on immune function as well as clinical outcome [69].

The strong and elegant science behind hypertonic immune modulation has suggested to some that HS and HSD be considered primarily as an anti-inflammatory drug and not a volume expander. From this consideration, HS alone is likely to be as efficacious as HSD. This may be a shortsighted viewpoint in that it negates the proven physiologic value to restoring vascular volume, perfusion and oxygen delivery in trauma patients. Physicians and medics administer fluids to trauma patients with an immediate need for augmentation of volume expansion and tissue oxygen delivery. The extensive animal work on HS versus HSD and the outcomes from clinical trials support the rationale for providing better volume expansion and associated hemodynamics of HSD compared to HS.

Table 1: All HS.

Human Trials/Experiences with 7.5% NaCl

	Author	Sol.	Dose	Site	Patients	HS	HSD	HSS	Iso	Reference
1	**DeFelippe, 80**	HS	4 mL/kg	ICU	refractory shock	12				The Lancet 1980;Nov 8:1002-1004.
2	**Holcroft, 87**	HSD	250 mL	PH	trauma		10		10	Ann Surg 206:279-289
3	**Younes, 87**	HS	4 mL/kg	OR	aneurysm	18			13	Rev Ass Med Brasil 8;34:150-155
4	**Auler, 87**	HS	4 mL/kg	OR	aneurysm	5			5	Surgery 101:594-601.
5	**Younes,89,92**	HS/HSD	250 mL	ER	trauma	35	35		35	Surgical Forum 39:70-72;
6	**Holcroft,89**	HS/HSD	250 mL	ER	trauma		16		16	Braz J Med Biol Res 22:291–294
7	**Auler, 89**	HS/HSD	4 mL/kg	ICU	post cardiac bypass	15	15			Brazilian Journal 1989.
8	**Holcroft, 89**	HSD	250 mL	PH	trauma		29		31	Perspectives-Shock Res, Alan R. Liss: NY.p. 331-8
9	**Maningas, 89**	HSD	250 mL	PH	trauma		23		25	Am J Surg 1157:528-533.
10	**Vassar, 90**	HS	250 mL	ER	trauma	32	23		51	Arch Surg 125:1309-1316
11	**Boldt, 90a, 90b**	HSS	4.5 mL/kg	OR	cardiac surgery			30		Anaesthesia 45:928-934
12	**Kuss, 90**	HSS	4 mL/kg	ICU	sepsis			20		Prcdgs. - 4th Int Sym Hypertonic Resus. 1990:34
13	**Kroll, 90,92**	HSS	4 mL/kg	PH	trauma			16		Prcdgs. - 4th Int Conf Hypertonic Resus 1990:45
14	**Ramires, 90,92**	HS	2-4 mL/kg	ICU	right heart failure	6				Circulatory Shock 37:220-225.
15	**Hannemann, 90**	HSS	4 mL/kg	ICU	sepsis/resp. failure			41		Critical Care Med 18:S205
16	**Chavez-Negrete, 91**	HSD	250 mL	ER	hypovol. GI bleed.		26		23	Eur Surg Res 23:123-129.
17	**Meier-Hellman, 90**	HSS	2-5 mL/kg	ICU	head injury			5		Prcdgs. - 4th Int Sym Hypertonic Resus. 1990:27
18	**Boldt, 91**	HSS	210 mL	OR	cardiac surgery			15		Ann Thorac Surg 51:610-615
19	**Boldt, 91**	HSS	3.1 mL/kg	OR	cardiac surgery			15		Br J Anaesth 67:595-602
20	**Boldt, 91**	HSS	3.8 mL/kg	OR	cardiac surgery			15		J Cardiothorac Vasc Anesth 5:23-28
21	**Vassar, 91**	HSD	250 mL	PH	trauma		83		83	Arch Surg 126:1065-1072.

	Author	Sol.	Dose	Site	Patients	HS	HSD	HSS	Iso	Reference
22	**Mattox, 91**	HSD	250 mL	PH	trauma		211		211	Ann Surg 213:482-491.
23	**Vassar, 93**	HS/HSD	250 mL	PH	trauma	85	89		84	Arch Surg 128:1003-1013
24	**Chavez-Negrete,92(abs)**	HSD	250 mL	ICU	acute MI		11			Prcdgs. - 5th Internat Conf Hypertonic Resus
25	**Majluf,92 (abs)**	HSD	250 mL	ER	hypovolemic shock		25			Prcdgs. - 5th Internat Conf Hypertonic Resus
26	**Schaffartzik, 92 (abs)**	HSS	4 mL/kg	ICU	septic shock			21		Prcdgs. - 5th Internat Conf Hypertonic Resus
27	**Fabian, 93 (abs)**	HS	1.5 mL/kg	ICU	head injury	11				Unpub abstr, see Surgery 122:609-16
28	**Keller, 93 (abs)**	HSS	5 mL/kg	OR	oral surgery			20		Prcdgs. - 1993 Gulf Atlantic Anes, Res. Conf
29	**Vassar, 93**	HS/HSD	250 mL	PH	trauma	50	50		45	J Trauma 34:622-633;
30	**Gong, 93**	HS/HSD	30 mL	Clin	dialysis	10	10			J Am Soc Nephrol 13:1808-1812
31	**Prien, 93**	HSS	250 mL	OR	cardiac surgery			18	19	Zentralblatt fur Chirurgie 118:257-266
32	**Rocha e Silva, 94**	HSD	250 mL	ER	trauma		100		100	Shock 1994;1 (Suppl):2 (no. 7).
33	**Rudin, 94 (abs)**	HSD	4 mL/kg	OR	ortho-surgery		7		7	Prcdgs. 6th Internat Conf Hypertonic Resus
34	**Ellinger, 95**	HSS	168 ± 46 mL	OR	cardiac surgery			20	20	Shock 3:167-172.
35	**Frey, 94,**	HSD	250 mL	ICU	sepsis		21		22	Personal communication 1994.
36	**Albrecht, 95**	HSS	214 ± 64	OR	aneurysmectomy			11	12	Shock 3:152-156.
37	**Stehtzer, 94**	HSS	4 mL/kg	ICU	sepsis			23		Prcdgs. 6th Internat Conf Hypertonic Resus
38	**Goertz, 95**	HSS	4 mL/kg	OR	minor surgery			13	13	Anes 82: 1389-95, 96
39	**Sztark, 95**	HS	4mL/kg	OR	organ donors	10			6	Transplantation Prcdgs. 27:2473
40	**Oliveira, 95**	HSD	235 mL	OR	cardiac surgery		10		10	Shock 3:391-394.
41	**Jovanovici, 95**	HSD	4-5 mL/kg	OR	polytruama		20		20	Intensive Care Medicine, 21(Suppl 1):S156
42	**Bonazzi, 95**	HS	3.5 mL/kg	OR	aneurysm repair	10				Intensive Care Medicine, 21(Suppl 1):S223
43	**Walz, 95**	HS	0.5-1.0mL/kg	ICU	elevated ICP	10				Intensive Care Medicine, 21(Suppl 1)
44	**Tølløfsrud, 96**	HSD	4 mL/kg	Clin	healthy volunteers		9			Shock 6(Suppl): 30
45	**Dahlqvist, 96**	HS	4 mL/kg	ICU	critically ill	15				Shock 6(Suppl): 30-31

	Author	Sol.	Dose	Site	Patients	HS	HSD	HSS	Iso	Reference
46	**Strecker, 96**	HS	250 mL	OR	resected pheochrom.	1				Shock 6(Suppl): 31
47	**Kroll, 96**	HSS	250 mL	Clin	healthy volunteers			4		Shock 6(Suppl): 31
48	**Kroll, 96**	HSS	250 mL	OR	anesthetized pts			9	9	Shock 6(Suppl): 31-32
49	**Kroll, 96**	HSS	250 mL	Clin	healthy volunteers	4		4	4	Shock 6(Suppl): 31-32
50	**Izmail, 96**	HSS	250 mL	OR	anesthetized pts			9	9	Shock 6: 31-32, 1996
51	**Rask, 96**	HS	5 mL/kg	ICU	sepsis	2				Ugeskrift for Laeger 158:607-09
52	**Hanneman, 96**	HSS	2-4 mL/kg	ICU	septic shock			21		Shock 5:130-4
53	**Younes, 97**	HSD	250 mL	ER	trauma		101		111	Shock. 7:79-83
54	**Christ, 97**	HSD/HSS	250 mL	OR	aneurysm repair		9	3	16	Acta Anaesthesiologica, Scandinavica 41:62-70
55	**Gemma, 97**	HS	100 mL	OR	neurosurgery	25				J Neurosurg Anesthil 9:329-334
56	**Swensen, 97**	HS	3 mL/kg	Clin	healthy volunteers	8			8	Anesthesiology 87:204-12, 1997
57	**Hartl, 97**	HSS		ICU	elevated ICP, trauma					Acta Neuro-Chir (Wien) 50(S): 126-129
58	**Horn, 97**	HSS	2-12 mL/kg	ICU	elevated ICP			8		Zentralblatt fur Neurochirurgie, supp 97, p 15-16
59	**Schwartz, 98**	HSS	100 mL	ICU	stroke elevated ICP			9		Stroke 29:1550-1555
60	**Tølløfsrud, 98**	HSD	4 mL/kg	Clin	healthy volunteers		9			Acta Anaesthesiol Scand. 42:145-53
61	**Tølløfsrud, 98**	HSD	4 mL/kg	OR	cardiac surgery		10		10	Acta Anaesthesiol Scand. 42:154-61.
62	**Wiklund, 98**	HSD/HS	4 mL/lg	Clin	healthy volunteers	5	5		5	unpublished, part of regulatory package
63	**Sireix, 99**	HSS	250 mL	OR	mitral valve repair			HSS		Crit Care Med 27: 2159-2165
64	**Christ, 99**	HSS	250 mL	OR	aortic surgery	15			15	Int J Microcirc Clin Exp 17: 374-384
65	**Murphy 99**	HSD	4 mL/kg	ICU	burn		8		11	Arch Surg. 134:1091-7
66	**Durasnel, 99**	HS	100 mL	OR	spinal surgery	24			24	Ann. Fra, d'Anesthésie et de Réanimation 18:631-635
67	**Krenn, 00**	HSS	4 mL/kg	ICU	liver dysfunction			9		Transplantation-Proc., 32, 821-823, 2000
68	**Wall, 00**	HSD	250 mL	ICU	shock, elevated ICU		32			effectively treated raised ICP or low BP
69	**Jarvela, 01**	HS	4 mL/kg	OR	post cardiac surg	20			20	Intensive Care Med. 2002 Nov;28(11):1574-81

	Author	Sol.	Dose	Site	Patients	HS	HSD	HSS	Iso	Reference
70	**Jarvela, 01**	HS	1.6 mL/kg	OR	pre spinal anesthesia	20			20	Acta Anaesthesiol Scand. 2001 Jul;45(6):776-81
71	**Olsson, 01**	HSD	250 mL	PH	trauma		47			Trauma care, 2001 11:85
72	**Drobin, 02**	HS, HSD	5-3 mL/kg	Clin	human volunteers	10	10		10	Anesthesiology. 96(6):1371-80
73	**Zs, 02**	HSS	4 mL/kg	ICU	sepsis			23		Br J Anaesth 89: 22-23, 2002
74	**Oliveira, 02**	HSD	250 mL	ICU	sepsis		13		16	Intensive Care Med. 2002 Nov;28(11):1574-81
75	**Rocha e Silva, 03**	HSD	0.5 - 4 mL/kg	OR	pedi cardiac surg		25			Shock 20:427-430
76	**Jarvela, 03**	HS	4 mL/kg	Clin	volunteers	8				Anaesthesia. 58(9):878-81
77	**Vialet, 03**	HS	2 mL/kg	ICU	head injury, coma	10			10	Critical Care Medicine. 31(6):1683-7
78	**Kollmar, 04**		100 mL	ICU	cerebral infarcts			10		13th Eur. Stroke Conf. Mannheim-Heidelberg
79	**Rizoli, 04**	HSD	250 mL	ICU	trauma		13		14	submitted for publication
80	**Cooper, 04**	HS	250 mL	PH	GCS<9, SBP<100	114			115	JAMA 291:1350-1357
81	**Bueno, 04**	HSD	4 mL/kg	OR	cardiac surg		25		25	Ann Thoracic Surgery 77(2):604-11
82	**Kolsen-Peterson, 04**	HS	4 mL/kg	OR	historectomy surg	20			42	Anesthesiology. 100(5):1108-18, 2004 May
Ongoing trials, marketing & pharmacovigilance data										
1	**Bulger, ongoing 2004**	HSD	250 mL	PH	Blunt trauma					U Washington news 6-16-03,
2	Tripartite (US, Canada & Great Britain) HSD trauma trial, to be started, 2004									personal communication
3	**Schimetta, 02**	HSS	250 mL		trauma, head injury			56,000		Wien Klin Wochenschr 114:89-95, 2002
4	**Buckley, 04**	HSD	250 mL		trauma	25,000				personal communication

Trial Totals = 610 1,130 392 1,355

All Hypertonic = 2,232

2.6 Clinical Record of Hyperosmotic/Hyperoncotic Solutions

The clinical use of ~2400 mOsm solutions had been studied for both perioperative use and most extensively in randomized blinded trials in which 250 mL of HSD was infused as first treatment for hypotensive trauma in the field or emergency room. Complete references are found in recent reviews [12, 37, 70-72] and are listed in Table 1 which lists all clinical reports and trials with ~2400 mOsm solutions that we are aware of. The reported number of patients treated with hypertonic saline continues to grow. The concentrated ~2400 mOsm hypertonic saline solutions have a remarkable record for safety and also suggest significant efficacy for the following indications: intra-operatively for volume expansion, to attenuate hypotension after aortic cross clamping and during renal dialysis, treat hypotension due to bleeding gastric ulcers, fluid maintenance of patients with burn injuries or sepsis, to reduce intracranial pressure and improve cerebral blood flow, and in the resuscitation of patients with hypotension and injuries due to trauma and hemorrhage (Table 2). Of all studies there is only one report of a negative outcome in which a HS-hetastarch formulation caused acute volume over load and cardiac instability in patients with cardiac failure [50]. Subsequent clinical studies examined hypertonic saline hetastarch in cardiac patients and found that poor outcomes are a result of not anticipating the large volume and potent volume expansion of hyperosmotic-hyperoncotic small volume formulations. The proper clinical perspective is that 250 mL of HSD or HS-hetastarch is equivalent to a ~3 liter infusion of isotonic crystalloid and hyperosmotic/hyperoncotic solutions should NOT be infused over a set time course where 3 liters of crystalloid is unwarranted. This message can perhaps be applied to certain young prehospital trauma patients with penetrating injury and ongoing bleeding as well as to older cardiac patients getting perioperative care. Hypertonic solutions for patients at risk for fluid overload or cardiac disease should be used cautiously and not in fixed doses, but rather titrated to effect [52]. Several studies report benefit from using HSD and HSS appropriately in patients during cardiac surgery [12, 73, 74], or after heart failure [75].

Table 2: 30 Day Mortality Outcomes of Hypertonic Resuscitation Trials for Trauma & Hemorrhage.

Hypertonic Saline (HS) alone, total n=948		
Reference	HS, n=454	SOC, n= 494
Younes, 92[76]	20.0%	22.9%
Vassar, 90[1]	53.1%	37.0%
Vassar, 93[77]	14.1%	16.7%
Vassar, 93[78]	40.0%	51.1%
Fabian, 94[79]	35.8%	37.3%
Fabian, 94[79]	35.2%	28.3%
Cooper,04[80]	44.7%	50.4%
all HS trials	35.4%	34.4%
	Δ HS vs SOC	-0.7%
Hypertonic Saline Dextran (HSD), total n=1284		
Reference	HSD, n=641	SOC, n=641
Younes, 92[76]	20.0%	22.9%
Maningas, 89[81]	13.0%	20.0%
Vassar, 90[82]	52.2%	54.2%
Vassar, 91[77]	36.1%	41.0%
Mattox, 91[1]	16.6%	19.9%
Chavez-N., 91[83]	3.8%	21.7%
Vassar, 93[78]	22.5%	16.7%
Vassar, 93[84]	44.0%	51.1%
Younes, 97[85]	26.7%	36.0%
all HSD trials	24.5%	28.7%
	Δ HSD vs SOC	-4.2%

2.7 HS and HSD Trauma Trials

Table 2 shows the 30 day mortality data of all trauma and hemorrhagic shock trials in which 7.5% NaCl (HS) alone or 7.5%NaCl-6% dextran (HSD) have been used to teat trauma. The trails were blinded and randomized with one exception [83] as to treatment with HS or HSD compared to an equal volume of the standard of care solutions (SOC; normal saline, Ringer's solution or Plasmalyte A). All solutions have been evaluated at 250 mL dose with additional fluids and medical care given as deemed clinically necessary. It should be made clear that these solutions were given in addition to all of the normal and subsequent care the patient required per trauma center protocol. No treatment was withheld.

Trauma trials with 7.5% HS without a colloid have overall shown less efficacy than trials with HSD as reviewed in a meta-analysis [86]. There were no statistically significant differences with the overall mortality being 0.7% less with the HS treatment, Table 2. A recent randomized study of the use of HS to treat traumatic head injury showed a 5.5% difference favoring HS, but this was not statistically significant [80].

On the other hand, the outcomes in the trauma trials with HSD more strongly support efficacy as shown in Table 2 and by an extensive individual patient data meta-analysis [63, 87, 88]. Most all of these trials documented an improvement in blood pressure, and several documented reduction in total volume needs.

Only one trial was statistically significant alone [85] and also suggested that the greatest survival benefit of HSD was in the patients with the lowest entry blood pressures. The view that HSD is more beneficial in severely injured has been borne out in several subgroup analyses of the more severely injured patients who often did show statistically significant increased survival in trauma patients with head injury [87], dehydration [89] and penetrating injury [1, 63]. Taken as a whole the HS and HSD studies suggest safety, volume sparing and improved outcome.

Based on the randomized controlled trauma trials, Table 2, HSD appears to reduce mortality of hypotensive trauma. Over all the difference can be considered small, a 4.2% patient weighted mean change, or a 15% reduction of mortality. The largest subset of hypotensive trauma patients would survive without treatment and a smaller subset would die regardless of treatment. Only a small subset of perhaps 10-20% can benefit or be harmed by fluid therapy. Taken in light of this argument the benefit seems profound. However, treatment effects in randomized control trials can be greater or less than in standard clinical usage. Perhaps more important than a new round of controlled trials is to encourage post regulatory approval monitoring in those countries where HSD is approved for use. If civilian trauma centers can be matched as to general patient population, and a form of standardized outcome data collection can be generated, such data might be more valuable than a clinical trial because it could provide real world outcome effects. New trauma trials sponsored by the NIH and with military funding from the US, Canada and Great Britain has recently started or in final planning. Such trials may lead to US regulatory approval and/or use by US Armed forces. On the other hand, HSD has regulatory approval in most of the NATO countries and hypertonic saline hetastarch (HSS) in a growing number of them. Thus, many NATO military units could evaluate hypertonic resuscitation. Military surgeons and anesthesiologists in countries for which HSD or HSS is approved should be encouraged to become familiar with the extensive backgrounds of such products and use them electively in their homeland practices. Product placement with selective combat medical units along with a post regulatory monitoring program would provide the first real combat experience of small volume resuscitation and should be encouraged. The outcomes from case reports of units deployed with and without hypertonic formulations could be compared by an expert panel.

2.8 HSD versus HSS

Early studies comparing HSD versus HSS formulations suggested equivalent physiologic effects. HSD has had more extensive US exposure and use in trauma trials, while HSS has more European exposure and is most often used in intraoperative trials, particularly for cardiac surgery. In the small volume formulations the particular benefit or any side effect of the type of colloid is likely to be negligible. HSD had been show to be devoid of any apparent effect on coagulation or blood typing or inflammation in the trials to date. An extensive record of clinical safety has been established for HSS in Austria where it has been approved since 1991 and used in over 56,000 patients [90]. The primary indications for its use have been head injury, trauma, and intraoperative volume sparing.

2.9 Hypertonicity, Inflammation and Organ Failure

The renewed interest in HSD or HS alone has resulted from the pioneering studies of Junger and Hoyt who first established profound anti-inflammatory properties of a hypertonic bolus [91, 92]. Studies in cell culture and rodent models have suggested efficacy as survival is improved and organ failure (histology) greatly attenuated by hypertonic resuscitation [93, 94]. Thus, the concept of hypertonic therapy as a drug is intriguing. Indeed, incidents of organ failure (ARDS, renal failure, etc) were reduced in the USA multi-center trial 5/211 with HSD vs 20/211 with SOC as well as in incidents of MOF in the individual patient meta-analysis [88].

2.10 Combat Casualty Care

Despite all of the new hypertonic publications on inflammation and the older publications on the physiology of resuscitation the most straightforward rationale for its use of any fluid combat casualty care can be summarized in Figure 2. Even if HS alone is as effective at reducing inflammation as HSD the better volume expansion with HSD or HSS versus HS alone is sufficient rationale for choosing HSD or HSS over HS. Better volume expansion also equates with better cardiac output and blood pressure thus, periods of hypotension are less likely with head injury. The only rationale for choosing HS alone over HSS or HSD would be cost or untoward clinical results with HSD. However, taken as a whole the extensive clinical record of HSD and HS in trauma suggests, but does not prove, that HSD and probably HSS may be superior with respect to outcomes.

The early volume expansion properties of HSD are about 10-fold greater than that of standard crystalloids [95, 96]. Figure 2 provides the main rationale for use of HSD for combat casualty care volume sparing. More efficient volume expansion provides the rationale for its use in situations where hypovolemia impairs oxygen delivery. In situations where over resuscitation is a concern due to uncontrolled hemorrhage and or cardiac insufficiency the experimental record suggests that the solutions should be infused slowly and/or titrated to effect. If the medic appreciates the 10:1 volume equivalency and considers administering 250-mL dose in a regimen similar to how they would administer 2.5 liters the potential for misuse could be lessened. Three special patient populations to consider for combat casualty care are the safety and efficacy of hypertonic resuscitation with pre-existing dehydration, traumatic brain injury or penetrating injury.

2.11 Safety and Efficacy of 7.5% NaCl with Pre-existing Dehydration

A special problem of combat casualty care is that wounded combatants are almost always dehydrated. The anticipation is that at some level preexisting dehydration negates the safety and clinical effectiveness of hypertonic infusions. This concern motivated several studies that analyzed the safety and effectiveness of HSD in dehydrated animals and patients. Hemorrhaged and dehydrated rats infused with hypertonic saline after occlusion of the renal artery showed an increase in incidence of renal failure and a high mortality rate compared to groups treated with isotonic fluid [97]. However, these results were not confirmed in more realistic long-term studies of renal function in large-animal models with a 4 mL/kg dose of 7.5% NaCl dextran [98-101]. The beneficial volume expansion and cardiovascular effects of HSD were still apparent after water restriction over 2 to 4 days and increased preinfusion osmolalities of 325-340 mOsm/L in dehydrated sheep and swine [98, 99, 101] subjected to moderate to severe hemorrhage.

Of relevance to dehydration is the effectiveness of HSD's ability to increase survival in trauma patients with high preinfusion serum sodium [100]. Presumably, this patient population has pre-existing dehydration. Survival rates were low in this group when they were administered standard of care solutions, but survival was greatly and significantly improved in the HSD group. Counter intuitively, HSD has been used to effectively treat experimental dehydration in US Army sponsored studies [102, 103].

2.12 HSD and HS for Treatment of Head Injury

There is a strong physiological rationale for the use of hypertonic fluids to treat head injury particularly in the presence of hypotensive hypovolemia. Increased plasma hyperosmolality can translocate CSF and cellular water out of the brain and reduce the intracranial pressure associated with head injury. This edema lessening effect occurs in the regions of brain less traumatized, but a global reduction in ICP increased perfusion throughout the brain [104]. In animals with experimental mass lesions hypertonic resuscitation reduced ICP

and improved blood flow [105]. Again, at first this would suggest that HS would be expected to be as beneficial as HSD for these patients and this is likely true for the effects on ICP. But a key component of mortality in patents with traumatic brain injury is the prevention of hypotension. Chesnut et al showed that episodes of hypotension were significant predictors of outcome in head injured patients [106]. A single episode of systolic pressure below 90 mmHg doubled the mortality. The ability of HSD to restore and sustains volume expansion, cardiac output and blood pressure better than HS alone has been well demonstrated in animal trials and clinical trials and is the rationale for why HSD may be particularly effective in patients with head trauma. Wade et al performed a cohort analysis of individual patient data on patients with traumatic brain injury [87]. Treatment with HSD resulted in a survival until discharge of 37.9% (39 of 103) compared with 26.9% (32 of 119) with standard of care ($p = 0.080$). Using logistic regression, adjusting for trial and potential confounding variables, the treatment effect can be summarized by the odds ratio of 2.12 ($p = 0.048$) for survival until discharge. Practically, this means that patients who have traumatic brain injuries in the presence of hypotension and receive HSD are about twice as likely to survive as those who receive standard of care. A recent prehospital trial of HS alone for treatment of head injury showed a small, but statistically insignificant 5% difference in outcomes favoring HS [80]. It is likely that the clinical benefit of HSD shown in trauma trials results from both the direct affect on lowering ICP as well as the indirect affect of improving arterial pressure and cerebral perfusion.

2.13 Risk of Increased Bleeding in Penetrating Trauma

Increasing blood pressure will logically increase bleeding from injuries in which hemostasis is not established. Animal models of uncontrolled hemorrhage typically demonstrate worse outcomes with aggressive resuscitation. This has suggested the concepts of limited or hypotensive resuscitation. The risk of how HSD might induce bleeding and affect mortality can be addressed by evaluation of the clinical trauma trials. In general, nearly half the patients had penetrating injuries. These data have recently been reviewed [63]. In brief, HSD was more efficacious in penetrating trauma than in blunt trauma. Lower mortality was significant in the first USA multicenter trial for patients with penetrating injury that required surgery [1] and the conclusion was further supported by an individual patient data meta-analysis with data from the US multicenter study [63]. It would appear that the overall benefit of HSD on early hemodynamics and immune function outweighs any deleterious effect on bleeding. This also suggests that most penetrating trauma patients do not have lesions similar to those induced by a fixed size aortotomy or tail transection. Animal models of uncontrolled hemorrhage may have limited value for predicting responses of most trauma patients with penetrating injury.

3.0 HEMOGLOBIN BASED OXYGEN CARRIERS

3.1 Introduction

Immense scientific and commercial efforts continue towards the development of a safe and effective synthetic oxygen carrying solution that could be used in place of blood or packed red blood cells (RBCs). The greatest progress has been in the development of modified hemoglobin solutions, commonly called hemoglobin based oxygen carriers (HBOCs). The goal has been to produce a safe and effective HBOC with the functionality of packed RBCs and without the significant limitations of blood, i.e. immune suppression, loss of efficacy with storage and risk of viral contaminants. Such a product would have a huge market for preoperative and critical care medicine as a replacement for the current blood supply. Further, the hope is that an easily storable product could be used effectively for prehospital and battlefield trauma where current fluid resuscitation strategies are lacking in efficacy.

The complex challenge of developing an oxygen carrier and the relative availability and familiarity with plasma expanders has focused the development of RBC substitutes almost exclusively on their ability to load and unload oxygen. This is unfortunate because HBOCs have unique pharmacologic and physiologic properties in solution, which can impart unexpected effects on colloid osmotic pressure (COP), volume expansion as well as associated hemodynamic responses. Several recent reviews have focused on the oxygen carrier properties of RBC substitutes or on their clinical utility [107-109].

3.2 Utility of HBOCs

The clinical need and physical characteristic of HBOCs suggests two different roles: 1) correction of anemia and 2) resuscitation of hypovolemic blood loss. Formulations of free hemoglobin tetramers made-up to the concentration of blood (12-18-g/dl) or to packed-RBCs (20-25-g/dl) would be excessively hyperoncotic. Polymerization is a strategy used to increase Hb concentration, while minimizing increases in COP and the two HBOCs that have advanced the farthest in clinical trials are both glutaraldehyde polymerized hemoglobins made from human (Polyheme) and bovine blood (Hemopure) with COPs similar to healthy humans. While normal COP for humans is 28-mmHg, most surgical and anemic patients have some level of hemodilution and substantially lower COPs.

Hyperoncotic solutions can be effective for correction of hypovolemia as they are efficient volume expanders. However, packed RBCs are rarely administered to correct volume, but rather are used to correct anemia. Fresh whole blood is logically the ideal product for blood loss, but it is rarely used for resuscitation. Anemic patients are typically normovolemic or even hypervolemic, and thus, in order to deliver an effective load of Hb, a concentration higher than normal blood is needed. Packed red blood cells have a hemoglobin concentration of ~25 g/dl, normal whole blood is ~15 g/dl and all of the HBOCs under development are more dilute, 10-13 g/dl. Use of HBOCs to correct anemia has the potential to induce hypervolemia. Hypovolemia is often not well tolerated in patients with cardiac dysfunction attributable to heart disease or acute traumatic insult. To the extent that the HBOCs have a colloid osmotic pressure higher than patients plasma the *in vivo* concentration of hemoglobin after infusion can be further reduced.

The other potential role for a hyperoncotic HBOC is as a resuscitative fluid in patients with hemorrhagic shock in which hypovolemia and not anemia is the primary deficit. Standard of care treatment of hemorrhage and trauma is to administer asanguineous fluids, crystalloid or colloids. Resuscitation with asanguineous fluids can restore lost volume, increase cardiac output and oxygen delivery. However, the improvement in oxygen delivery is limited by the hemodilution. HBOCs would at first seem to be an ideal solution, as colloids they should be excellent volume expanders and they also can maintain or even correct hemodilution. For this review we will analyze clinical trial data and animal studies to assess the record and potential of HBOCs as a RBC substitute and as a resuscitative fluid. While traditional volume expanders cause some level of anemia, Hct levels as low as 25-30 are tolerated in most patients.

Table 3: Hemoglobin and Perfluorocarbon Based RBC Substitutes with Advanced Clinical Testing.

Company	HBOC name	Source	Clinical Testing
Northfield Labs	Polyheme	Human RBC	Phase II-III, intraop and prehospital trauma
Biopure	Hemopure	Bovine Hb	Phase II-III, orthopedic & general surgery
Hemosol	Hemolink	Human RBC	Phase II, cardiothoracic surgery-trials
Curacyte, Inc	PHP-Hb	Human RBC	Phase II, sepsis, cancer
Sangart	Hemospan	Human RBC	Phase I completed, Phase II, elective surgery
Failed Products			
Baxter	HemAssist†	Human RBC	Phase III, adverse outcomes ↑ mortality in trauma
Somatogen	Optro†	Recombinant Hb	Phase II, cardiac surgery excessive vasoconstriction, poor clinical results

† Development cancelled or trials stopped due to adverse outcomes.

Physical and chemical properties of RBC substitutes

HBOC	Chemistry	conc. g/dl	COP (mmHg)
Polyheme	Pyridoxylated tetramers and glutaraldehyde-polymerized human	10	~28
Hemopure	Glutaraldehyde- polymerized bovine	13	26
Hemolink	o-Raffinose-polymerized human	10	26
PHP-Hb	Pyridoxylated tetramers conjugated with polyoxyethylene	10	96
Hemospan	Tetramers conjugated with PEG	4.4	46
HemAssist	Diaspirin Cross-linked tetramer	10	34
Optro	Cross-linked by generic mutation	5	≈ 15

3.3 Products in development

Table 3 lists most of the HBOCs that are or have been in clinical trials as part of the US Food and Drug Administration's (FDA) regulatory process. Perhaps the most extensively studied and financed, HBOC was HemAssist™ or diaspirin cross-linked hemoglobin (DCLHb), which dramatically failed in trauma trials. Over one hundred animal studies and several trials in volunteers and elective surgery patients suggested that DCLHb had acceptable safety and efficacy. However, when used as early emergency room treatment of severely traumatized patients a significantly increased mortality was observed [110, 111]. Subsequent animal studies which mimicked severe trauma and hemorrhage also showed an increase in mortality with DCLHb vs packed RBCs, particularly when DCLHb was infused along with large volume crystalloid infusions [112-114]. The take home message may be that most animal models and even clinical trials do not have the sensitivity to fully evaluate safety or efficacy of HBOCs in severely injured patients. Prehospital or emergency room use of HBOC may be more challenging than intraoperative use where skilled anesthesiologists pharmacologically titrate infusion rate and administer drugs to prevent extreme hemodynamic alterations.

Table 4: Selected HBOC Trials.

Trial subjects	patients (n=)		Transfusions				Physiology			
			units/patient		% patients					
indication	HBOC	Cont.	HBOC	Cont.	HBOC	Cont.	BP	SVR	CI	DO2
Hemopure (Biopure)										
orthped. Surgery[115]	350	RBC (338)	1.4u	3.1u	30%	100%	⇑			
cardiac surgery[116]	49	RBC, (49)	1.7 u	2.2 u	66%	100%	⇑		⇓	
surgery patients[117]	42	LR, (26)	3.3 u	3.7u						
aortic repair[118]	48	RBC, (24)			73%	100%	⇑			
preop hemodilut. [119]	12	hespan (12)					⇑	⇑	⇓	⇓
preop hemodilut. [120]	6	hespan (6)					⇑	⇑	⇓	⇓
exercise volunteers[121]	6	RBC (6)			10%	47%			⇓	
Hemolink (Hemosol)										
autologous donation[122]	149	pstarch (150)	0.3u	0.7u	56%	76%				
cardiac surgery[123]	30	pstarch (30)			10%	47%	⇑			
cardiac surgery[124]					55%	82%	⇑			
Polyheme (Northfield)										
trauma surgery	171	historical								
trauma surgery[125]	21	RBC (23)	7.8u	11.3u						
Hemassist (Baxter)										
major surgery[126]	92	RBC (89)			87%	100%				
prehospital trauma[127]	58	RBC (63)	3.1L	4.7L						
major surgery[128]	12	RBC (12)	similar		67%	100%	⇑			
cardiac surgery[129]	104	RBC (105)			81%	100%				
aortic surgery[130]	34	RBC (105)					⇑	⇑	⇓	⇓
ER trauma[111]	52	RBC (46)								
stroke[131]	40	saline (45)					⇑			

3.4 Clinical Trials

Table 4 lists selected clinical trials of Polyheme, Hemopure, Hemolink and HemAssist (DCLHb). The Hb substrate used by the different pharmaceutical companies comes from outdated human and bovine blood.

Northfield Laboratories' Polyheme™ and Biopure's Hemopure™, and Hemosol's Hemolink have advanced to large scale FDA Phase 3 trials [132, 133]. However, research setbacks and disappointing trials have occurred more often than not. Diaspirin cross-linked hemoglobin (DCLHb) developed by the US Army and Baxter's Hemoglobin Therapeutics is the best-studied RBC substitute. DCLHbs development was cancelled after it exhibited a high mortality rate in trauma trials [110]. Somatogen cancelled development of Optro after cardiac surgery trials of its product produced adverse events. Hemosol's phase III trial of Hemolink has been halted to evaluate an imbalance in adverse events. Nothfield and Biopure continue with their phase III clinical research. Prehospital trauma trials have just started for Polyheme and are planned for Hemorpure. The FDA halted Biopure's US clinical trials in 2003 pending some key animal experiments to address specific questions. Because of the dramatic failures in safety issues the FDA is likely to be cautious and conservative before granting marketing approval to a RBC substitute. A commercially available blood substitute will likely not be available in the next two years.

3.5 Plasma Volume Expansion

Fischer et al compared plasma volume expansion (ΔPV) after a 30-min infusion of 20 mL/kg 6% DCLHb, iso-oncotic 7.8% human albumin versus 60 mL/kg of LR in conscious sheep under conditions of normovolemia and hemorrhagic hypovolemia [134]. The ΔPV for DCLHb calculated from Evans blue indicator dilution and Hct dilution was nearly 2x greater than for albumin. The relatively increased expansion of 10% DCLHb versus 7.8% human albumin is quite surprising as the albumin was made-up to be an iso-oncotic control to the DCLHb. The explanation for the enhanced volume expansion of DCLHb is unknown, but several mechanisms can be hypothesized. PV enhancement could be due to a reduction in capillary pressure due to arteriolar vasoconstriction. Alternatively, increased lymphatic pumping could return interstitial protein into the circulation and augment the plasma colloid osmotic pressure and expansion. Indeed, Fischer et al. did report an increased plasma protein concentration, increased total vascular plasma protein and increased COP in the DCLHb group despite the albumin and DCLHb being matched for volume infused and colloid osmotic pressure [134].

Oxyglobin is a FDA approved veterinary product made from bovine hemoglobin (Biopure) but has a higher colloid osmotic pressure (~40 mmHg) than the human product, Hemopure. Oxyglobin was also found to be a potent volume expander increasing blood volume more than hespan in hemorrhaged rabbits. There is little data in the literature that we are aware of on the volume expansion effects of Hemopure, Polyheme or Hemolink. No direct comparisons have been made with the products under clinical evaluation of volume expansion, Table 3.

3.6 Relationships between HBOC Volume Expansion and Cardiac Output

The goal of volume expansion is almost always to increase venous return and cardiac output (CO). Reports of HBOC infusion are shown to have no effect or cause only a modest increase or an actual decrease in CO [134, 135]. Cardiac output could be reduced by the increase in left and right heart afterload known to occur due to vasoconstriction. Binding or scavenging of nitric oxide (NO) by interstitial hemoglobin blocks the normal basal level of vascular dilation due to NO diffusion from the endothelial cell to smooth muscle. It is hypothesized that polymerized HBOCs cause less vasoconstriction than the tetramer HBOC due to reduced vascular leakage into the interstitium [136]. Figure 3 shows ΔCO plotted versus right arterial pressure for LR, albumin and DCLHb as calculated from data of Fischer et al. and Brauer et al [134, 137]. Data suggest an altered starling filling pressure cardiac output curve with DCLHb. A suggested hypothesis is that the HBOCs do not increase CO because of the greater O_2 delivery. However, this is not satisfying, because all other volume expanders increase O_2 delivery and O_2 therapy alone does not reduce CO. Vane et al. found some

deaths in animals treated with DCLHb after large volume LR treatment of hemorrhage in an anesthetized model of a major abdominal surgical procedure [138]. These authors concluded that the combination of vasoconstriction, hypervolemia and cardiac depression likely contributed to the poor outcomes. These data suggest that some level of cardiac dysfunction or impairment can occur with some HBOCs. Human volunteer and patient data comparing how infusion of HBOCs and traditional plasma expanders alter CO, right atrial pressure and blood volume are not available. However, depressed CO has been reported in several clinical trials of both tetramer HBOCs and polymerized HBOCs [116, 119-121, 130].

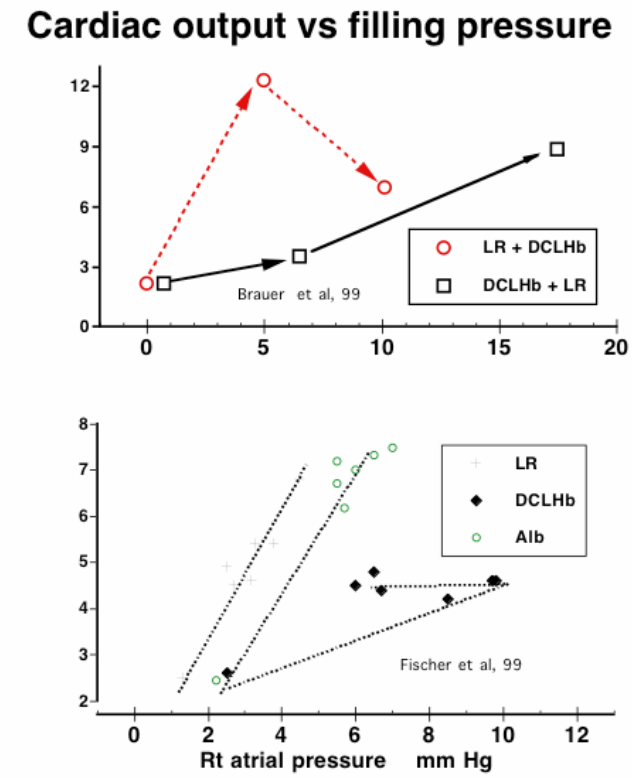

Figure 3.

3.7 HBOCs as RBC Substitutes

Animal models demonstrating effectiveness of HBOCs often focus on its ability to delivery oxygen in exchange transfusion or with infusion in normovolemia "top loading." There are few clinically relevant animal models in which the HBOCs have been compared with RBC transfusion. On the other hand, several clinical trials have evaluated this. In general, such trials suggest a moderate reduction in blood needs in the first 24-hrs that diminish, approaching insignificance over 7-days. Table 4 shows that HBOC typically reduced transfusion volume per patient by about 20-50% and they only eliminate transfusion in 15-30% of patients compared with control groups. The apparent reason for this modest sparing of transfusion requirements is the short half-life of the HBOCs, typically 10-20 hrs versus the long half-life of several days for RBCs. None of the present HBOCs are likely to provide a more than a partial solution to blood replacement. Nothfield sponsored a single group study showing that Polyheme was tolerated in 171 patients with clinical outcomes better than historical controls of patients who refused blood [139]. Interpretation of

results versus such a control group is difficult, particularly in light of an earlier two-armed Polyheme versus RBC trial where the HBOC only reduced RBC transfusion volume needs by 31%. It is most likely that HBOCs may provide a bridge or early treatment, but do not appear to replace transfusion. The disappointing intraoperative trial results is perhaps the main reason that the two leading HBOC companies now focus on prehospital resuscitation of trauma.

3.8 HBOCs as Resuscitative Fluids

HBOCs or oxygen carrying plasma expanders have the potential to be an effective resuscitation solution. Their long shelf life and lack of cross-typing requirements make them attractive as a prehospital fluid. Additionally, substantial oncotic pressure and volume expansion of the HBOCs makes them attractive for the treatment of hypovolemia. Asanguineous fluids expand vascular volume, increase cardiac output, but dilute RBCs and oxygen content. However, increased cardiac output may effectively increase oxygen delivery several fold from depressed levels associated with shock to normal or even supranormal levels. Augmentation of supranormal levels of CO with fluid resuscitation often occurs without full restoration of blood pressure presumably due to lowered viscosity and widespread vasodilation from local autoregulatory mechanisms. Unfortunately, many, if not all HBOCs appear to impair CO enough such that DO_2 is not increased above that reported for conventional volume expanders. Recent comparison of the use of Polyheme compared to Hextend in hemorrhaged anesthetized swine and conscious rats when both solutions were infused to maintain a systolic blood pressure to ≈ 70 mmHg for limited 'hypotensive' resuscitation showed no oxygenation or hemodynamic advantage (rat, pig) and an increased mortality (rat) [140, 141]. It may be that the oxygen carrying plasma expanders offer minimal advantage in limited resuscitation regimens due to the small dose of Hb administered.

Similar conclusions on ineffectiveness of HBOCs in small volumes can be reached studying the combination of hypertonic 7.5% saline plus HBOC (HSHb). Such mixtures were suggested as an improvement over a small increase in oxygen delivery attributable to replacing dextran with an HBOC and assuming cardiac output is increased equally. However, an analysis of experimental data suggests that HSD [142] is almost as effective as HSHb [143] assuming equivalent CO augmentation. Results would be worse for HS-Hb if plasma hemoglobin induced depression of CO.

3.9 New Formulations

A novel approach to HBOC development has been the development of a counterintuitive formulation of polyethylene glycol-modified human hemoglobin (MalPEG-Hb). MalPEG-Hb is an anemic (4-g/dl), viscous, hyperoncotic formulation with a P50 of 5.5 mmHg. Data suggests that the free Hb in plasma unloads oxygen more efficiently compared to RBC Hb due to the removal of the microcirculatory spatial heterogenicity imposed by cellular Hb [144-146]. Enhanced O_2 unloading might increase arteriolar O_2 tension and induce arteriolar vasoconstriction [147-149]. This opposes the conventional well-researched view that Hb's affinity for nitric oxide (NO) is responsible for the vasoconstriction. [150] In theory the elevated O_2 affinity (low P50) of MalPEG-Hb delays the early release and prevents vasoconstriction. Further, vasodilation may be induced by MalPEG-Hb's high viscosity increasing blood-endothelial sheer forces and thus enhancing NO release. [151]

The vision is that MalPEG-Hb's other unique features might increase its effectiveness enough to compensate for its diluted concentration. Data of microcirculatory function in a skin window suggests enhanced O_2 delivery [152], but such enhancement may not take place in more critical tissue with higher O_2 demands and life sustaining function. Still the concept that a hemoglobin solution with high oncotic pressures and high viscosity has enhanced efficacy is intriguing and deserves evaluation in clinically relevant models.

3.10 HBOCs as Small Volume Formulations

A series of experiments sponsored by the US Air Force evaluated Hemopure as a small volume formulation for hypotensive resuscitation [153-155]. When infused to a hypotensive target pressure (60mmHg) the volume sparing of an HBOC can be profound due to induced vasoconstriction, as these investigators demonstrated. Outcomes measured in an anesthetized swine model were better or equal to small volume Hemopure compared with large volume lactated Ringer's or HSD [155]. However, acute doses of LR and HSD studied were exceedingly high (19+ liters of LR and 1500 mL of HSD). Thus, control animals were over resuscitated and 1500 mL of HSD is 6x the recommended dose and probably toxic. Hemopure caused a notable reduction in cardiac output and venous oxygenation. One interpretation is that enhanced HBOC oxygen unloading and reduced venous oxygenation are evidence of enhanced tissue delivery of oxygen. However, the traditional view is that cardiac output and oxygen delivery (DO_2) were insufficient and lower tissue oxygenation occurs in at least some tissues. Recently, Polyheme was provided to the US Army for independent animal testing using hypotensive resuscitation models in three laboratories. Polyheme did not increase DO2 more than Hextend in hemorrhaged swine [156], nor did it improve mortality versus Hextend in swine and rats [157, 158]. It may be that small volume or limited resuscitation with HBOCs is ineffective due to the limited dose. Resuscitation to hypotensive targets can reduce HBOC volume needs compared to Hextend due to HBOC vasoconstrictor activity, but there was no apparent advantage in survival or physiology when compared with Hextend formulations. Most HBOCs appear to cause some level of vasoconstriction and depression of cardiac output. Polyheme and Hemospan (MalPEG-Hb) may be the least vasoconstrictive agents. Until recently there was almost no preclinical data on Polyheme in the literature. Recently, the US Army sponsored studies in swine models demonstrating that Polyheme also causes systemic vasoconstriction and depressed CO [156, 157].

3.11 HBOC Conclusion and Recommendations

Hemoglobin based oxygen carriers are potent plasma expanders with a modest vascular half-life. Both properties may be a limitation for use as a blood substitute, but may have utility and advantages as an acute resuscitative fluid. The limited amount of independent experience with the HBOC solutions currently under development makes conclusions difficult.

Infusion regimens for HBOCs will likely be different than for packed RBCs or asanguineous fluids due to the unique physical properties and physiological effects of HBOCs. At present it is not clear if such solutions will offer an improvement in standard of care. Safe and effective oxygen carrying plasma expander remains an attractive goal. It is likely that effective Hb molecular structure, optimal concentrations, and carrier solutions will be developed. Such development and clinical utility will take substantial preclinical and clinical study to define the safety and efficacy and the optimal therapeutic regimens of such formulations.

4.0 TITRATED CLOSED-LOOP RESUSCITATION

One approach to reducing volume needs may be to provide automated computer controlled fluid resuscitation, which can be tailored to individual patient needs and frees up clinical personnel. Severe hemorrhagic hypotension must be quickly addressed and corrected to prevent cardiac arrest, ischemic injury and organ dysfunction. On the other hand, the ideal system would eliminate wasteful and excessively rapid resuscitation that could be deleterious. The rationale is that rapid increases in blood pressure can lead to additional bleeding. A method to accurately guide and control fluid resuscitation of hemorrhage could improve outcomes by reducing incidences of both excessive and inadequate resuscitation.

Endpoint resuscitation occurs when fluid therapy is titrated proportional to the measured values of a specific physiological variable or endpoint. The use of endpoint resuscitation has largely been restricted to the intensive care unit and operating room environments where continuous monitoring and staffing allow careful titration of therapy to a target variable level or range. With the development of new portable monitoring technologies and computer-controlled infusion pumps, automated “closed-loop" titrated endpoint resuscitation may be feasible for prehospital and emergency room use. Fred Pearce of Walter Reed has historically been an advocate of early closed-loop control for combat casualty care. An effective "Resuscitation System" would need to fulfill several requirements. We have been using automated resuscitation systems both to facilitate our research, but also as a means to test the concept of closed-loop fluid therapy in hemorrhage and burns [159-162]. The first report of closed-control of fluid therapy we are aware of is that of Bowman and Westenskow who built and tested, in dogs and patients, a system that provided microprocessor-controlled fluid resuscitation of burn shock using urinary output as an endpoint [163]. Kramer et al. have designed and tested a similar system in sheep [162] and have begun evaluating a fluid balance monitor in burn-injured patients as a first step in doing closed-loop clinical trials. Burn injury is one scenario where excessive fluid therapy has become common [164] and a system of tightly controlling fluid therapy to achieve, but not exceeding urinary output targets may ultimately reduce morbidity of fluid overload. Such a fluid therapy system lends itself to initial care through enroute care and the first 24 – 28 hours. Burn resuscitation is a relatively slow process that occurs over many hours to days.

Hemorrhagic shock typically provides a more acute life threatening challenge than burn injury. In hemorrhage, fluid therapy is needed in a manner of minutes and stabilization must occur in a manner of a few hours or less. Urinary output is not a useful endpoint for acute resuscitation of hemorrhage. In order to perform initial closed-loop resuscitation of hemorrhage, measurement of rapidly responsive endpoints (arterial pressure, cardiac output or skeletal muscle oxygenation) have been evaluated [159-161].

Resuscitation System prototypes have used a LabView controller with preprogrammed algorithms that convert the value of an endpoint variable into a specific infusion rate. We suggest that such algorithms, which define infusion rate as a function of an endpoint variable, may not be optimized by a linear relationship. Thus, we designed non-linear decision table algorithms that infuse fluid quickly when the endpoint variable is low near an *a priori* defined ‘critical level’, but then greatly reduce infusion rate as the defined ‘stable level’ was approached [159]. Such a system can be designed to provide different algorithms for different clinical scenarios. For example, with penetrating injury hypotensive resuscitation might be optimal to reduce risk of rebleeding, while with head injury normotensive resuscitation would likely be needed since periods of hypotension increase morbidity and mortality with head trauma. Further, different endpoints and different targets might be used to provide initial care, e.g., blood pressure versus sustained care in which lactate and urinary output might be more useful indices.

A secondary goal of such an approach is to reduce fluid volumes required for combat casualty care. This approach did appear to reduce the extend of rebleeding when compared against aggressive fluid therapy such as has been show to increase bleeding and death in sheep and swine models of uncontrolled aortic bleeding.[161, 165]

However, much research and development remains to determine if such closed-loop resuscitation has real clinical applicability or if it will remain a laboratory tool.

5.0 CONCLUSSION

5.1 Different Strategies for Small Volume Resuscitation

Different strategies for small volume resuscitation include making volume expansion more efficient (hyperosmotic-hyperoncotic formulations) adding oxygen carrying capacity (HBOCs) or using titrated resuscitation regimens. Small volume resuscitation regimens could be particularly useful to address the logistic limitations of combat casualty care. At present the only approach that has a proven clinical record and product approval is hypertonic saline mixed with dextran or hetastarch. Military medial use and evaluation in NATO countries with product approval is encouraged.

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