学術講演

The development history and features of Hextend®, a high molecular weight hydroxyethylstarch in physiologically balanced electrolyte solution

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1. Introduction

BioTime, Inc., based in Emeryville, California, is engaged in the research and development of aqueous-based synthetic solutions that can be used as blood plasma volume expanders, blood replacement solutions during hypothermic (low temperature) surgery, and organ preservation solutions. Plasma volume expanders are used to treat blood loss in surgical or trauma patients until blood loss becomes so severe that a transfusion of packed red blood cells or other blood products is required.

BioTime's first product, Hextend®, is a physiologically balanced blood plasma volume expander with 6% hetastarch, for the treatment of hypovolemia. Hypovolemia is a condition caused by low blood volume, often from blood loss during surgery or from injury. Hextend® maintains circulatory system fluid volume and blood pressure and helps sustain vital organs during surgery.

Hextend®, approved for use in major surgery, is the only blood plasma volume expander that contains lactate, multiple electrolytes, glucose, and a medically approved form of starch called hetastarch, a high molecular weight hydroxyethyl starch. Hextend® is marketed in the United States and Canada by Hospira, Inc. of Lake Forest, IL and CJ Corp. located in Seoul, S. Korea.

In this article, we describe the product characteristics of Hextend® and analysis of in vitro studies on coagulation, compared to Hespan®. Hespan® has a similar molecular weight hetastarch as Hextend® but is formulated in 6% saline solution, compared to Hextend®, which is formulated with a number of important electrolytes. The composition and importance of these electrolytes are discussed. In addition, we discuss a number of clinical studies involving the use of Hextend®.

2. Product description

Hextend® is indicated for the treatment of hypovolemia. Hextend® was approved and marketed in the Untied States in 1999, Canada in 2002 and South Korea in 2004, and is being developed in Japan. Over 1.5 million units of Hextend® have been sold in the United States, with sales annually now exceeding those of hetastarch in saline solution. No serious adverse events related to the use of Hextend® have been reported.

The hetastarch involved in Hextend® shows a weight average molecular weight (M_w) of approximately 670k Daltons and the molar substitution (MS) of approximately 0.75. It is an equivalent hetastarch which is previously described as the M_w of 400k-480k Daltons and the MS of around 0.7 measured by different techniques.

Hextend®'s composition is compared to many of the other products used for plasma expansion. As can be seen, Hextend® more closely resembles the composition of plasma (Table 1). Hextend® has a lower composition of sodium and chloride ions. BioTime believes that the lower mEq/L of sodium and chloride concentrations contributes to several important attributes. These include: lower morbidity, less cholermic acidosis and better renal function.

Table 1　Composition of Plasma Volume Expanders

	Hextend®	Plasma	Hespander®	6% HES in saline	Lactated Ringer's
Dextrose (g/l)	1.0	1.0	10	—	—
Calcium (mEq/l)	5	5	2.7	—	3
Potassium (mEq/l)	3	4	4	—	4
Magnesium (mEq/l)	0.9	3	—	—	—
Sodium (mEq/l)	143	142	106	154	130
Chloride (mEq/l)	124	103	92	154	109
Hydroxyethylstarch (g/l)	60	—	60	60	—

Note: Hextend® and Lactated Ringer's also each contain 28 mEq/l of lactate(Hespander®:20Eq/l), which acts as a source of bicarbonate in patients with unimpaired lactate metabolism

Table 2　Competitively Advantaged Solution

	Saline	Lactated Ringer's	Albumin	Hetastarch in saline	Hextend®
Edema (swelling)	yes	yes	no	no	no
Plasma volume expansion efficacy	low	low	moderate	high	high
Derived from blood	no	no	yes	no	no
Electrolyte deficiency	yes	no	yes	yes	no
Acidosis	yes	no	yes	yes	no
Coagulopathy	yes	no	yes/no	yes	no
Approximate cost	low	low	high	moderate	moderate

Hextend® is compared to many of the other agents used in plasma volume expansion (Table 2). Hextend® provides effective plasma expansion, while having advantages with respect to edema, electrolyte deficiency and acidosis. Hextend is also not derived from blood, whereas albumin comes from the plasma fractionating process.

3. Clinical usage

Hextend® is being used in many of the large and well respected hospitals in the United States. Table 3 lists the hospitals using Hextend®. At the University of California, San Francisco, the switch from albumin to Hextend® has been done. Gan TJ et al conducted the phase III study of Hextend® at Duke University[1]. The Cleveland Clinic is also important, since a lot of high blood loss cardiovascular surgeries are performed there each year. Hextend® appears to be excellently suited for use in high blood loss surgeries. BioTime in June, 2001 participated in discussions with the military about use of Hextend® in combat fluid resuscitation (Figure 1). Hextend® has been used by the military for use in

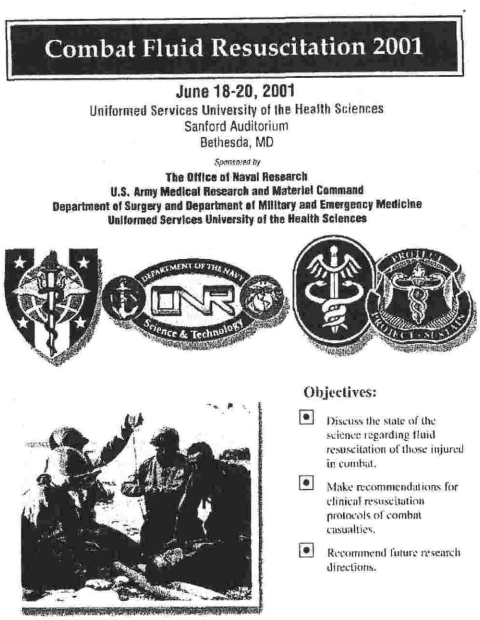
resuscitation on the battle field in Iraq and Afghanistan. Military and civilian experts in emergency and critical care medicine organized to form "Strategies TO Reduce Military and Civilian Transfusions" (STORMACT). The group's recommendation was to use Hextend® in treating blood loss. STORMACT recommended Hextend® based on evidence that Hextend® reduces bleeding, kidney dysfunction and acidosis compared to use of saline based products.

Table 3　U.S. Hospitals Using Hextend®

- University of California, San Francisco
- New York-Presbyterian
- University of Colorado
- Sloan Kettering Memorial
- MD Anderson
- University of Alabama Birmingham
- Massachusetts General
- Mayo Clinics
- Cleveland Clinics
- Sutter Hospitals
- Duke University
- University of Texas, Houston

etc.

Figure 1 Combat Fluid Resuscitation 2001



The current military recommendation for the use of Hextend® on the battlefield is for combat medics to administer a 500 ml bolus of Hextend® if the casualty is found in shock and to give a second 500 ml bolus at 3 minutes if the casualty is still in shock. Hextend® is also being used by special forces deployed in many parts of the world.

There are three types of products used for plasma replacement in the United States. These are the crystalloids, 6% hetastarch in saline and albumin. The crystalloids provide short term plasma volume effect. Ringer's lactate contains various electrolytes and lactate buffer. Ringer's has lower sodium and chloride ion concentrations compared to albumin and normal saline. Albumin is derived from blood. Albumin is generally higher priced and risk of contamination is potentially higher. Pentastarch in saline is also available, but is not indicated for plasma volume expansion.

Since the introduction of Hespan® (hetastarch in saline), physicians have restricted the product's use to 500 ml to 1 liter due to concerns about the suppressive effects on coagulation and excess bleeding. The high chloride content of Hespan® also was thought to impair renal function. Hextend®, with its unique formulation, overcomes the problems associated with Hespan®.

The Food and Drug Administration (FDA) Blood Products Advisory Committee in June 2002 held a meeting to address the excessive bleeding associated with hetastarch products[2,3]. Much of the evidence associated with preoperative bleeding of 6% hetastarch in saline comes from retrospective studies. A warning in the labeling for hydroxyethylstarch (HES) in saline was added to the package insert. A similar warning was not required for Hextend®. The package insert for Hespan® was required to add the following warning. Hespan® is not recommend for use as a cardiac bypass pump prime, while the patient is on cardiopulmonary

bypass, or in the immediate period after the pump has been disconnected, because of the risk of increasing coagulation abnormalities and bleeding in patients whose coagulations status is already impaired.

Acute Normovolemic Hemodilution is a procedure wherein hours or minutes prior to surgery, 1 to 3 liters of blood are collected while an equivalent volume of Hextend® is infused. Collected blood is used for re-infusion. With the use of Hextend®, cell savers, collection of blood, the need to use donated transfused blood can be significantly reduced.

4. *In vitro* studies of coagulation

Thromboelastogram (TEG) is a technique used to measure the time and strength of blood coagulation at different amounts of dilutions. Hextend® was compared to several other HES products. At 80% dilution, Hextend® is the only product whereby blood still clots (Table 4). At 60% dilution, Hextend® demonstrates the shortest time to clot. Albumin at 60% dilution does not clot. At all dilutions, Hextend® demonstrates the shortest r-time compared to the other products.

When looking at a graphic presentation of the r-times as determined for TEG analysis, Hextend® and PentaLyte® demonstrated the shortest r-time compared to other HES products and albumin at 60% dilution. Albumin does not clot at 60% dilution (Figure 2). When calcium is added to albumin, Haesteril® and Voluven®, the r-times are restored (Figure 3). Studies were done at 60% dilution. Calcium is believed to play a role in the coagulation cascade. Hextend® contains calcium which may explain the shortened r-times.

Figure 2　Colloid TEG Comparisons, r-times @60% dilution

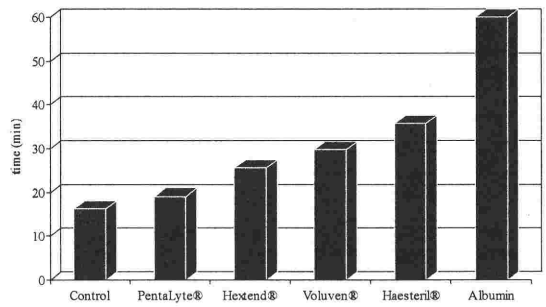
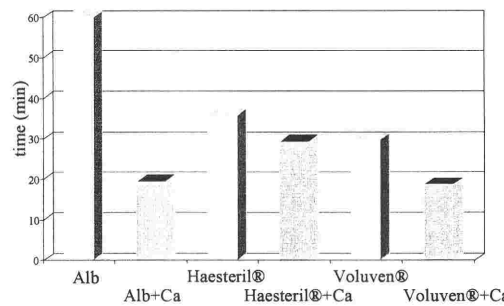


Figure 3　Calcium supplementation restores r-time



Deusch et al[4] measured *in vitro* the effects of HES solutions on platelets. Citrated whole blood was hemodiluted *in vitro* (20%) with Hextend®, the solvent for Hextend®, or Hespan®. Hextend®

Table 4　r-time[#] (min) of TEG analysis

Dilution	20%	40%	60%	80%
Hextend® (HMW HES/LE[*])	13.8±2.4	17.8±4.2	25.7±7.3[##]	33.9±17.6[##]
Sabax Hetastarch 6%® (HMW HES/NS[**])	21.4±13.3	26.8±10.1[##]	48.2±16.2	60.0[##]
Haes-Steril® (200kDa HES/NS[**])	16.3±3.5	16.4±7.5	35.8±18.4	60.0[##]
Voluven® (130kDa HES/NS[**])	16.7±2.7	15.4±2.6	29.8±13.4	60.0[##]
4.5% Albumin	15.8±3.7	20.3±4.7	60.0[##]	60.0[##]
Normal Saline	13.5±2.2	15.8±2.0	25.9±4.3[##]	60.0[##]

[#]: The time from when the sample is put on the thromboelastograph (TEG) until the first significant levels of detectable clot formation.

[##]: $p<0.05$ to the control (plasma:17.0±3.7min), [*]: Lactated electrolyte, [**]: Normal saline

was found to stimulate platelet function, while Hespan® inhibited platelet function. The solvent also stimulated platelet function. The addition of calcium (2.5nmol/l) to Hespan® reduced the inhibition caused by Hespan®. Deusch et al[4] further concludes that the stimulation of platelets by Hextend® may account for less blood loss and blood product usage when Hextend® is used instead of Hespan®.

5. Clinical studies

Three significant clinical studies, the phase III study, the elderly study and the cardiac studies, with the use of Hextend® are described.

BioTime's phase III study of Hextend® was conducted at Duke University and Mount Sinai Medical Center in New York under the direction of TJ Gan and others[1]. This study was used for the approval of Hextend® in the United States. Hextend® was compared to 6% hetastarch in saline. One hundred twenty patients were enrolled requiring major surgery. There were no volume restrictions and no albumin was allowed. Outcomes included safety, volume of fluids, estimated blood loss, heart rate, blood pressure, urine flow, etc. The goal of the study was to demonstrate that Hextend® was an equally effective plasma volume expander to 6% hetastarch in saline and safe for use. Compared to controls, the Hextend® patients showed significantly less blood loss in the transfused subset, better preservation of clotting function, less nausea and less need for calcium[1,5]. Hextend® also demonstrated less clinically related adverse events[1].

The phase III study found that 12 patients had clotting events with 6% hetastarch in saline compared to 2 patients treated with Hextend® (Figure 4). In the intra-operatively transfused subset of patients, statistically less blood loss occurred with Hextend® compared to 6%hetastarch in saline. Approximately 1500 ml of blood loss occurred with Hextend®, compared to approximately 2500 ml with 6% hetastarch in

Figure 4　Adverse events possibly related to the study drug that involve clotting

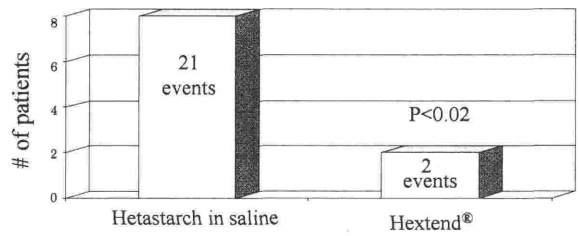


Figure 5　Estimated blood loss

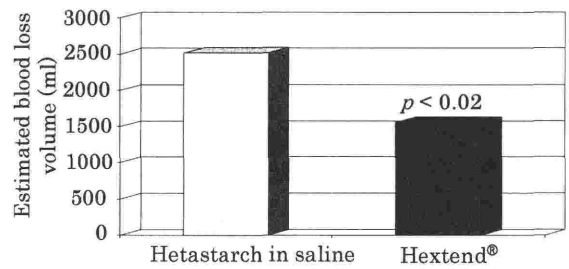


Figure 6　Estimated blood loss and RBCs, FFP and platelets transfused (intra-operatively)

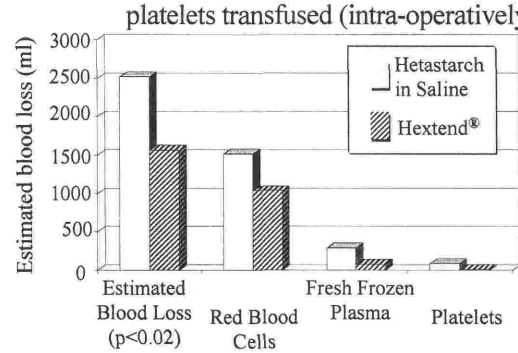


Figure 7　Patients transfused intra-operatively receiving calcium

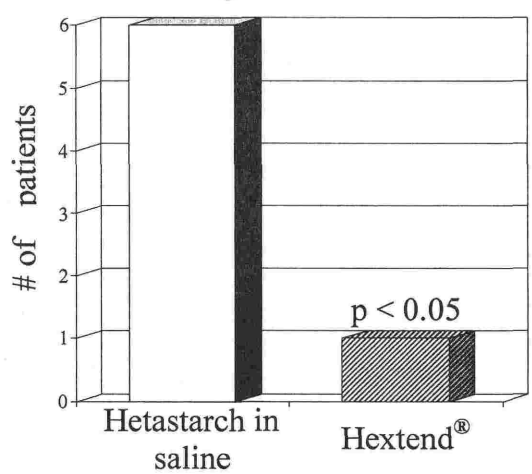
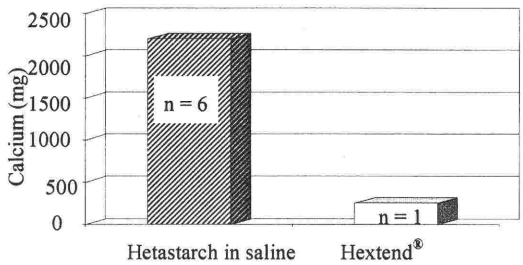


Figure 8　Average calcium given to the patients receiving calcium intra-operatively



saline (Figure 5). Examining the patients that were transfused intra-operatively, the use of red blood cells, fresh frozen plasma and platelets was less in the Hextend® group compared to patients treated with 6% hetastarch in saline (Figure 6). Six patients receiving the 6% hetastarch in saline product required receipt of calcium whereas only one patient required calcium when Hextend® was used (Figure 7). These results were statistically significant. The amount of calcium required in the 6% hetastarch in saline group was much higher than the Hextend® group (Figure 8).

An elderly patients study was conducted in England under the direction of Wilkes NJ[6] at Middlesex Hospital and Royal Free Hospital in London England. Forty seven patients were enrolled for major surgery. Fluids used were for treatment of hypovolemia and there was no limitation on volume and albumin administration was allowed. Comparison groups were Hespan® plus normal saline (HES/NS) versus Hextend® plus lactated Ringer's (HES/LR). Outcomes analyzed included chloride, ionized calcium and total calcium, acid/base balance, potassium and estimated blood loss. Compared to the HES/NS, the HES/LR patients demonstrated better outcomes. Hextend® treated major surgical patients showed significantly better protection against acidosis and better maintenance of intra-gastric mucosal pH, blood calcium and chloride[6]. The change from baseline for Hextend® measuring both calcium and ionized calcium in plasma was statistically less compared to 6% hetastarch in saline (Figure 9). The incidence of hyperchloremic acidosis in the HES/LR group was statistically lower that the HES/NS group with p=0001 (Figure 10). Sixty six percent of the HES/NS patients demonstrated hyperchloremic acidosis. The study was stopped early due to concerns about patients being treated with HES/NS.

Three cardiac clinical studies were performed by Bennett-Guerrero E et.al[7], Petroni K, et.al[8], and Shander A[9].

The first study that will be discussed involves a study performed by Bennett-Guerrero E et.al at Columbia University in New York, involving 200 patients[7]. Groups in the study received lactated Ringers, Hextend®, Hespan® or albumin. Fluids were for treatment of hypovolemia and there were no volume limitations. One liter of study fluid was added to the bypass prime. Outcomes measured included r-times from TEG, blood products used, renal function, post op pain, edema DVT's and cost benefit Urine output measured in first 4 hours demonstrated greatest volume output for Hextend® versus other study groups (Figure 11). Patients treated with lactated Ringer's solution demonstrated the second highest urine

Figure 9　Delta calcium; Base to end of surgery

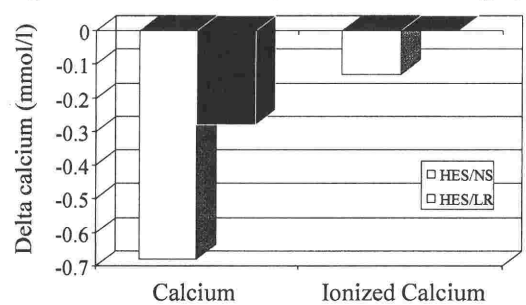


Figure 10　Incidence of hyperchloremic acidosis

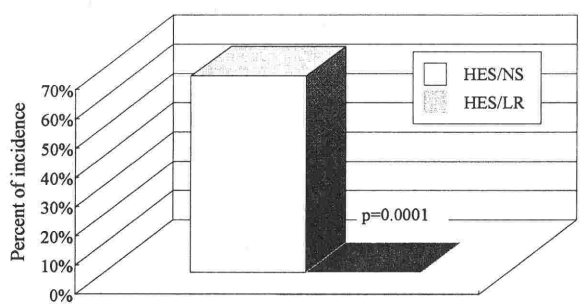


Figure 11　Postoperative urine output

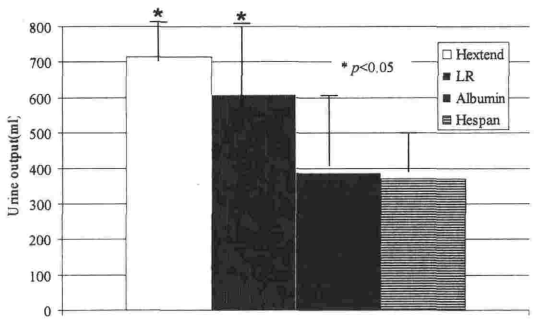


Figure 12　Postoperative Serum Creatinine

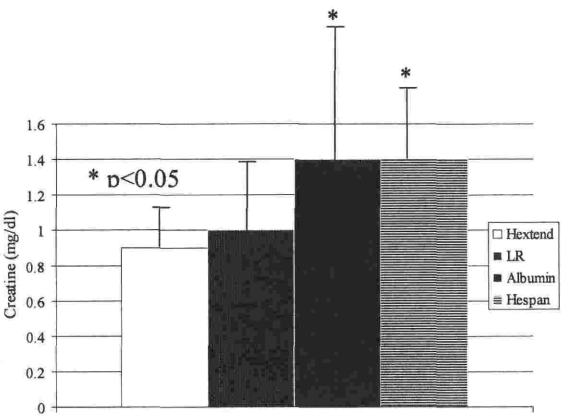
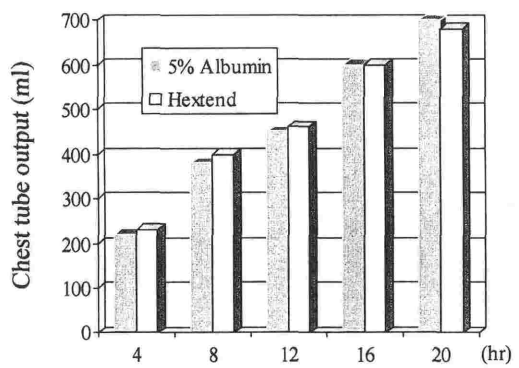


Figure 13　Chest tube output



output in liters, but was statistically less ($p<0.05$) than Hextend® (Figure 11). Hextend® treated patients demonstrated lower serum creatinine levels in mg/dl compared to patients receiving other fluids (Figure 12). Higher urine output and lower serum creatinine levels are indicators of more normal kidney function. With respect to other blood products required such as packed red blood cells, fresh frozen plasma, and platelets, Hextend® patients required less blood products than those using Hespan® (Table 5). Hextend and albumin were similar in the amount of blood products used (Table 5). In this study, patients treated with Hextend® demonstrated better renal function, shorter time to first meal and reduced length of hospital stay[7]. Patients also demonstrated less post-op pain, swelling, nausea and vomiting[7]. No serious related adverse events were found with the Hextend® use. The mean volume of the study fluids was high at 3500 ml. The maximum volume was 6 liters. Hextend® demonstrated major advantages on coagulation and kidney function compared to other plasma volume products.

The second fluid cardiac study was performed by Petroni K et al[8]. Twenty eight patients were randomized to Hextend or 5% albumin during surgery. No difference was found in chest tube output, pre and post op hematocrits, pre and post op TEG and blood product usage. Figure 13 demonstrates that chest tube output for patients receiving either Hextend® or albumin was comparable.

The third fluid cardiac study was done by Shander A of Englewood Hospital and Medical Center[9]. This is a study involving Hextend® use wherein the data are compared to retrospective data on Hespan® in cardiac surgery (Table 6). Hextend® was used in volumes of 500-2000ml/case. Coagulopathies were very rare. Only 4 patients out of 504 were required for re-exploration for bleeding. Very low transfusion rates occurred with only 9.9% of patients receiving packed red blood cells, 2.6% fresh frozen plasma and platelets and 0.9% cryoprecipitate. Table 6 discusses that the use of intraoperative blood products was far less in the Hextend® patients compared to retrospective data derived from Hespan® in similar patient groups. Postoperative blood products usage was also much less for Hextend® after 28 days compared to Hespan® when blood product usage was

measured at 24 hours. Chest tube bleeding was also less for Hextend® treated patients compared to the Hespan® group.

Table 5　Blood products required, exploration for bleeding and DVT's

OR+24hr	HES/NS	Hextend®	Albumin	LR
PRBC(units)	4(2-6)	2(0-4)	2(0-4)	1(0-4)
FFP(units)	3(0-6)	0(0-4.5)	0(0-0)	0(0-0)
Plts(units)	6(0-9)	0(0-6)	0(0-6)	0(0-6)
Patients receiving Plts or FFP (%)	69	47	42	26
Re-exploration for bleeding (%)	10	2	2	0
DVT's	2	2	7	8

Table 6　Englewood clinical experience with Hextend® --retrospective meta-analysis of clinical experience with Hespan®--

Comparator		Englewood Medical Center (Hextend®)		Mayo (Hespan®)	
Number of patients		504		234	
CPB time(min)		122.6±37.11		111±32	
Intraoperative dose(mL/kg BW)		9.8±4.3		9.8±3.8	
Intraoperative blood products (%)	PRBC	2.2		29.5	
	FFP	0.6		11.1	
	Platelets	0.9		15.4	
	Cryo	0		Not specified	
Postoperative blood products (%)	PRBC	9.9	28day	47.4	24hr
	FFP	2.6		30.3	
	Platelets	2.2		26.9	
	Cryo	0.9		9.0	
Chest tube bleeding (mL/24hr)		452±271		1284±686	

6. Reduction of albumin usage

Shaughnessey T studied at the University of San Francisco what would be the dollar savings if albumin was replaced with Hextend® in surgical situations[10], where possible. Pre-intervention, the hospital used 9,000 units of albumin/yr. Post-intervention, albumin usage was 2,662units/yr. Hextend® was used as first line colloid. Patients in the post- Hextend® period had a shorter average length of stay in the ICU compared to the pre- Hextend® period (Table 7). Thirty percent of post- Hextend® patients were placed on CT Surgery Fast Track compared to ten percent in the pre- Hextend® period (Table 7). There was no change in preoperative outcome as result of the switch to Hextend®.

Table 7　UCSF colloid utilization perioperative morbidity 1999-2000

	Pre-Hextend®	Post-Hextend®
CT Surgery Fast Track	10%	30%
Spine Surgery ICU Admissions	9%	3%
Average Length of ICU Stay	7days	5days

Note: No change in perioperative outcome

7. Potential future applications

Hextend® or HetaCool®, a slightly modified formulation of Hextend®, which has been especially designed for use at low temperature, could be used in low temperature, bloodless surgery which is presently inoperable cardiovascular and neurologic patients, where the length of surgery would be so long as to compromise patient outcome. Due to its high molecular weight and ability to maintain perfusion to organs, Hextend® could reduce the development of ischemia and lower the risk for multi-organ damage and septic shock.

Nielson V compared Hextend® vs. lactated Ringer's Solution on rabbits where hepatic-induced injury was induced followed by reperfusion[11]. He found that Hextend® reduced plasma LDH and xanthine oxidase release, indicating evidence of reduced organ injury[11].

Dogs revived after hypothermic complete blood replacement with Hextend® can survive and recover with no gross discernable pathologic consequences in 50% of dogs[12]. Other complementary studies have been performed in other animals[13].

High molecular weight, high degree of substitution and slow metabolism of Hextend® may by important factors for good organ perfusion and potential use in the prevention of sepsis and septic shock. Compared with 0.9% saline, volume resuscitation with Hextend was associated with less metabolic acidosis and longer survival in an experimental rat model of septic shock[14]. Due to a number of factors such as limited permeability, anti-inflammatory activity and balanced formulation may be indicators of potential use of Hextend® in treatment or prevention of sepsis.

8. Closing words

In August of 2005, experts in fluid resuscitation met in London to discuss which products should be used and under what circumstances. Many diverse opinions were expressed and physicians tend to use those products that they are most familiar. They indicated that there is no one product available today that has the most desired profile or was ideal. There was some consensus of key points derived from the meeting. Most important points included the need to reduce or eliminate transfusions where ever possible, that balanced electrolyte solutions appear to be better than saline based products and an important goal should be to maintain normal renal function. Hextend® provided in balanced electrolyte solution is one of the most appropriate candidates to offer patient benefit.

Hextend® has been used in the U.S., Canada and Korea without any serious related adverse events reported since approval in the U.S. in 1999. Data is available that indicates that Hextend® reduces the incidence of renal dysfunction, nausea, vomiting, peripheral edema and pain.

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