Retrospective Review of Hextend Use in Trauma Patients Requiring Surgery

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Learning Objectives: 1) To determine the effect of intraoperative Hextend on various respiratory parameters, vitals signs, and outcome. 2) To describe the correlation between intraoperative Hextend use, crystalloid fluid use and severity of injury, American Society of Anesthesiologists physical status, and postoperative mechanical ventilation.

Abstract

In trauma patients who do not need blood products, the choice of resuscitative fluid is unclear. Factors influencing choice of fluid include effects on circulation, hemostasis, organ function, and metabolic state. Hextend is a colloidal plasma volume expander containing 6% hydroxyethyl starch in a physiologically balanced medium of electrolytes, glucose, and lactate. Hextend has been shown to be effective for the treatment of hypovolemia, and has a more favorable side effect profile compared with 6% hetastarch in saline. The purpose of this study was to investigate the intraoperative use of Hextend in trauma patients requiring surgery within 24 hours of admission to a Level 1 trauma center. The anesthesia and trauma surgery database of 512 consecutive trauma patients (age >16 years) was reviewed. Patients were retrospectively divided into two groups: Group A received Hextend as part of their resuscitation and Group B did not. Fluids were infused as necessary to maintain normovolemia. Transfusion of blood products was done as required. The majority of patients in both groups were male undergoing emergency orthopaedic, general, and neurosurgical procedures with general anesthesia and tracheal intubation following blunt trauma. Two patients died in each group. A greater percent of Hextend versus crystalloid patients required mechanical ventilation postoperatively, although the duration of mechanical ventilation was similar between groups. Compared with the crystalloid group, patients receiving Hextend had significantly higher American Society of Anesthesiologists (ASA) physical status, injury severity, longer and more complex surgery, greater blood loss, and larger fluid volumes infused. There were no differences in postoperative vital signs, alveolar-arterial oxygen gradient, and oxygen index between groups. In the crystalloid group, there was a significant correlation between blood loss, ASA physical status, injury severity, blood transfusion, and postoperative mechanical ventilation. In the Hextend group, there was a significant correlation between ASA physical status, injury severity, and postoperative mechanical ventilation. Hextend administration was not associated with worsened alveolar-arterial oxygen gradient, oxygen index, vital signs, or outcome, although its use was a marker for increased severity of injury, blood loss, and requirement for postoperative mechanical ventilation.

The choice of crystalloid or colloid solutions for intraoperative resuscitation of trauma patients requiring surgery is unresolved. Factors influencing choice of asanguinous fluids include effects on coagulation, metabolic state, alterations in macro and microcirculation, volume distribution, and organ function (e.g., kidney function and splanchnic perfusion).[1,2]

Resuscitation with crystalloid fluids alone may reduce colloid oncotic pressure and promote tissue edema through interstitial expansion with plasma water.[3] Colloid oncotic pressure of the plasma is the osmotic pressure exerted by the macromolecules or colloid molecules, which serves to retain plasma water within the intravascular compartment. Colloid oncotic pressure, together with the fluid filtration coefficient, capillary hydrostatic pressure, interstitial hydrostatic pressure, and reflection coefficient, determines fluid flux at vascular membranes.[2]

It has been suggested that decreased colloid oncotic pressure from infusion of crystalloid solutions would result in adverse pulmonary outcomes because of interstitial pulmonary edema.[4,5]

Hextend is a colloidal plasma volume expander containing 6% hydroxyethyl starch (HES) in a physiologically balanced medium of electrolytes, glucose, and lactate (Hextend: mean molecular HES weight approximately 670 kD; range, 450-800, degree of HES molar substitution 0.75; Abbott Laboratories, North Chicago, IL).

The purpose of this retrospective study was to investigate the intraoperative use of Hextend in trauma patients requiring surgery within 24 hours of admission to a Level 1 trauma center. The hypothesis was that, compared with Hextend, resuscitation with crystalloid fluids would increase the incidence of postoperative respiratory failure requiring mechanical ventilation.

Methods

We retrospectively reviewed the anesthesia and trauma surgery database of 512 consecutive trauma patients undergoing surgery within 24 hours of admission at MetroHealth Medical Center from June 2003 until August 2004. Inclusion criteria were age ≥16 years and requiring an operation within 24 hours of admission to the hospital. Patients were retrospectively divided into two groups: Group A (n = 188) received Hextend as part of their resuscitation and Group B (n = 324) did not. All operations were scheduled and performed as indicated by the surgical team. Anesthetic technique and drugs were at the discretion of the attending anesthesiologist and not dictated by protocol. Fluids available for use in our operating rooms were lactated Ringer's solution, 0.9% saline, and Hextend. There were no guidelines in place for Hextend use. Fluids were

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Presented at the MetroHealth Research Festival and Ohio Society of Anesthesiologists Annual Meeting, September, 2005.

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None of the authors have any conflicts of interest to report.

Implication statement: Hextend administration was not associated with worsened alveolar-arterial oxygen gradient, oxygen index, vital signs, or outcome, although its use was a marker for increased severity of injury, blood loss, and requirement for postoperative mechanical ventilation.

infused as necessary to maintain normovolemia. Transfusion of red blood cells was done intraoperatively to maintain a hematocrit of 20% or greater. Fresh-frozen plasma and platelet concentrates were transfused according to standard coagulation indices or for the subjective assessment of excessive diffuse oozing.

Variables studied included demographics, vital signs on admission to the postoperative anesthetic care unit or intensive care unit, injury severity, anesthesia and surgery times, fluid balance, blood gas analysis, requirement for postoperative mechanical ventilation, and 30-day mortality. Calculated data were alveolar-arterial oxygen gradient [$P_AO_2 = (F_iO_2 \cdot (760 - 47)) - (P_ACO_2 / 0.8)$, A-a gradient = $P_AO_2 - P_AO_2$] [A-a gradient = (713 · inspired oxygen concentration) – (arterial $pCO_2/0.8$) – arterial PO_2], and oxygen index (= arterial PO_2/inspired oxygen concentration). Complexity of surgery was classified as major, moderate, minor, and superficial as follows.

Major: Body cavities or major vessels are exposed to ambient temperature. Examples: major abdominal, thoracic, vascular, thoracic spine surgery, pelvic fracture, hip and femur surgery.

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Minor surgery: Closed reduction of fractures, facial injuries, ophthalmology injuries.

Superficial: Lacerations, debridement.

All statistical analyses were performed using Statistix 8.0 (Analytical Software, Tallahassee, FL). Data were compared between groups using chi square and unpaired Student's *t* test. Pearson's correlations were computed for duration of mechanical ventilation and other variables using a correlation matrix. Multilinear regression was then used to determine the "best" set of independent variables to predict requirement for postoperative mechanical ventilation. A P value < 0.05 was considered significant.

Results

The groups were similar with respect to age, weight, and height (Table 1). The majority of patients (>70%) in both groups were male undergoing emergency orthopaedic, general, and neurosurgical procedures following blunt trauma (Table 2). Tracheal intubation and general anesthesia were employed in 97% of the patients. After completion of surgery, 223 patients in the crystalloid group were admitted to the postanesthesia care unit and 99 to the intensive care unit. Corresponding numbers for the Hextend group were 70 and 116 patients. Two patients died in each group. Data from these two patients are included up until their time of death.

Compared with the crystalloid group, patients receiving Hextend had significantly ($P < 0.001$) higher American Society of Anesthesiologists (ASA) physical status, injury severity, longer and more complex surgery, greater blood loss, and larger fluid volumes infused (Tables 1 and 3). There were no differences in postoperative vital signs, A-a gradient, and oxygen index between groups (Table 4). A greater percent of Hextend versus crystalloid patients required mechanical ventilation postoperatively (52 vs. 24%; $P < 0.001$), although the duration of mechanical ventilation was similar between groups (Table 4, Figure 1).

In the crystalloid group, there was a significant ($P < 0.001$) correlation between blood loss, ASA physical status, injury severity, blood transfusion, and postoperative mechanical ventilation (Table 5). In the Hextend group, there was a significant correlation between ASA physical status, injury severity, and postoperative mechanical ventilation (Table 5; $P < 0.001$).

Best subset regression model showed that in the Hextend group, 15% of the variability in mechanical ventilation days could be

Table 1. Patient Data*

	Crystalloid Group (n = 324)	**Hextend Group (n = 188)**
Age (yr)	40 ± 1	38 ± 1
Male	230 (71)	144 (77)
Female	94 (29)	44 (23)
Height (cm)	174 ± 1	173 ± 1
Weight (kg)	82 ± 1	87 ± 2
Mechanism of Injury†		
Blunt	67 (21)	55 (29)
Penetrating	257 (79)	133 (71)
ASA Physical Status‡		
I	20 (6)	4 (2)
II	171 (53)	64 (34)
III	76 (23)	62 (33)
IV	42 {13)	47 (25)
V	16 (5)	11 (6)
Injury Severity Score‡		
Median	10	17
25th–75th quartile	917	9–22

*Data are means ± SEM or number of patients (%).
†$P < 0.05$ between groups.
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Table 2. Surgery Data*

	Crystalloid Group (n = 324)	**Hextend Group (n = 188)**
Service		
Orthopaedics	206 (64)	110 (59)
Trauma, general	63 (19)	49 (26)
Neurosurgery	34 (11)	14 (7)
Plastics	12 (4)	2 (1)
Cardiothoracic	2 (1)	3 (2)
Vascular	7 (2)	10 (5)
Urology	4 (1)	0
Ophthalmology	10 (3)	0
Otolaryngology	10 (3)	2 (1)
Oral maxillofacial	1 (0.3)	0
Complexity of operation†		
Major	148 (46)	145 (77)
Moderate	147 (45)	39 (21)
Minor	24 (7)	3 (1.6)
Superficial	6 (2)	1 (0.5)
Emergent or urgent surgery	239 (74)	144 (77)

*Data are number of patients (%). There could be more than one surgical service per patient.
†$P < 0.001$ between groups.

Table 3. Intraoperative Data*

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Anesthesia time (min)†	184 ± 5	279 ± 11
Surgery time (min)†	123 ± 4	208 ± 10
Crystalloid (mL)†	2218 ± 86	4465 ± 231
Hextend (mL)	0	844 ± 38
Blood products†		
RBC (units)	3 ± 0.3, n = 50 (15%)	5 ± 0.6, n = 88 (47%)
FFP (units)	2 ± 3.7, n = 14 (4%)	3 ± 5, n = 25 (13%)
Platelets (units)	3 ± 2.5, n = 6 (2%)	6 ± 3.3, n = 11 (6%)
Cell saver (mL)	725, n = 2 (0.6%)	707, n = 10 (5%)
EBL (mL)†	311 ± 34	1439 ± 216

*Data are means ± SEM or number of patients (%). RBC, packed red blood cells; FFP, fresh-frozen plasma; EBL, estimated blood loss.
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Table 4. Postoperative Data

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Systolic BP (mm Hg)	143 ± 1	145 ± 2
Diastolic BP (mm Hg)	70 ± 1	75 ± 1
Heart rate	99 ± 1	103 ± 1
Respiratory rate	17 ± .3	16 ± .3
Oxygen saturation (%)	97 ± .2	98 ± .2
Temperature (˚C)	36.6 ± .05	36.6 ± .08
Mechanical ventilation required†	78 (24)	98 (52)
Duration of ventilation (days)		
Median	2.5	3
25th–75th quartile	1-10	3-10
Range	1-37	1-66
Arterial blood gas analysis‡		
Inspired O_2 (%)	50 ± 2	60 ± 2
pH	7.33 ± .01	7.33 ± .01
pCO_2 (mm Hg)	38 ± .9	38 ± .6
pO_2 (mm Hg)	169 ± 10	171 ± 8
Hemoglobin (g/dL)	11.5 ± .3	10.4 ± .2
Hematocrit (%)	34.2 ± .8	30.9 ± .6
Alveolar—arterial O_2 gradient (mm Hg)	189 ± 13	216 ± 16
Oxygen index	305 ± 13	303 ± 14

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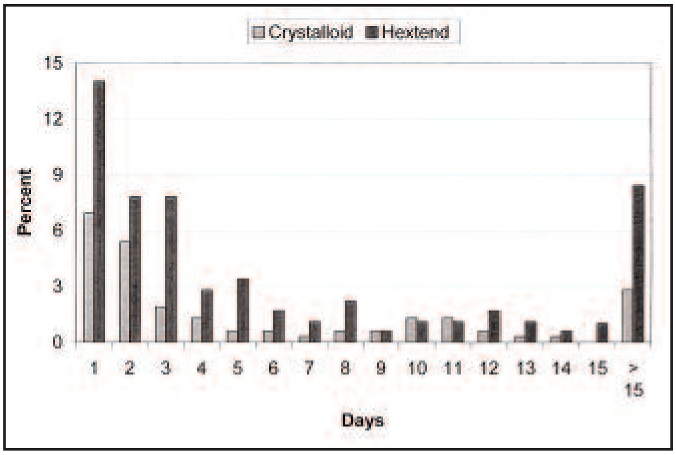

Figure 1. Frequency histogram of duration of postoperative mechanical ventilation in patients receiving crystalloid fluids alone (n = 324) or Hextend (n = 188). Mechanical ventilation was required more often in the Hextend compared with the crystalloid alone group ($P < 0.001$), although duration of ventilation was similar between groups.

predicted by injury severity (Figure 2, Table 6). By adding age to the model, the ability to accurately predict duration of ventilation improved to 17% (Figure 3). In the crystalloid group, 25% of the total variability in duration of ventilation was explained by ASA physical status (Figure 4, Table 6). By adding injury severity to the model, the ability to accurately predict duration of ventilation improved to 31% (Figure 5).

Discussion

Fluid management is a challenging task in trauma patients undergoing urgent and emergent surgery. The major goal is to stop the bleeding and replete intravascular volume to optimize blood pressure and tissue oxygen delivery. Choice, volume, and timing of intraoperative fluid resuscitation is based on correlates of hypoperfusion such as tachycardia, hypotension, low urinary output, low central venous pressure, and acid-base variables such as pH, base deficit, and lactate.[6-9]

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Urology	4 (1)	0
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Duration of ventilation (days)		
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Arterial blood gas analysis‡		
Inspired O_2 (%)	50 ± 2	60 ± 2
pH	7.33 ± .01	7.33 ± .01
pCO_2 (mm Hg)	38 ± .9	38 ± .6
pO_2 (mm Hg)	169 ± 10	171 ± 8
Hemoglobin (g/dL)	11.5 ± .3	10.4 ± .2
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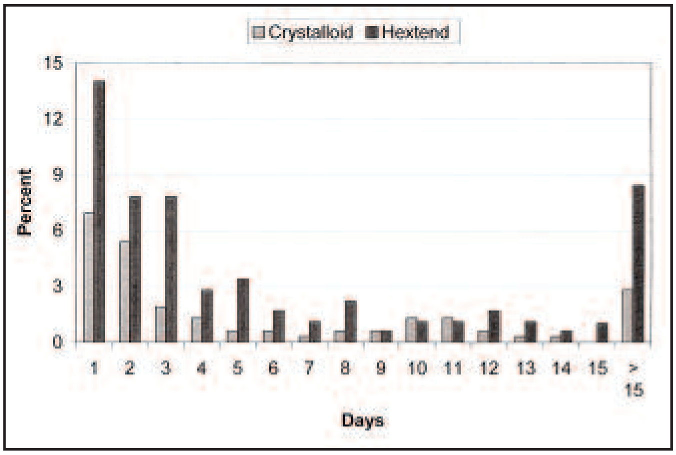

Figure 1. Frequency histogram of duration of postoperative mechanical ventilation in patients receiving crystalloid fluids alone (n = 324) or Hextend (n = 188). Mechanical ventilation was required more often in the Hextend compared with the crystalloid alone group ($P < 0.001$), although duration of ventilation was similar between groups.

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Discussion

Fluid management is a challenging task in trauma patients undergoing urgent and emergent surgery. The major goal is to stop the bleeding and replete intravascular volume to optimize blood pressure and tissue oxygen delivery. Choice, volume, and timing of intraoperative fluid resuscitation is based on correlates of hypoperfusion such as tachycardia, hypotension, low urinary output, low central venous pressure, and acid-base variables such as pH, base deficit, and lactate.[6-9]

Table 5. Pearson Correlations Between Duration of Mechanical Ventilation and Variable*

Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA physical status		
Correlation	0.51	0.22
P value	0.0000	0.0055
Injury Severity Score		
Correlation	0.46	0.41
P value	0.0000	0.0000
Estimated blood loss		
Correlation	0.18	0.05
P value	0.0018	NS (0.5)
Age		
Correlation	0.13	0.13
P value	0.025	NS (0.1)
Red blood cell transfusion		
Correlation	0.24	0.12
P value	0.0001	NS (0.1)
Fresh-frozen plasma transfusion		
Correlation	0.26	0.07
P value	0.0000	NS (0.4)

*ASA, American Society of Anesthesiologists; NS, not significant.

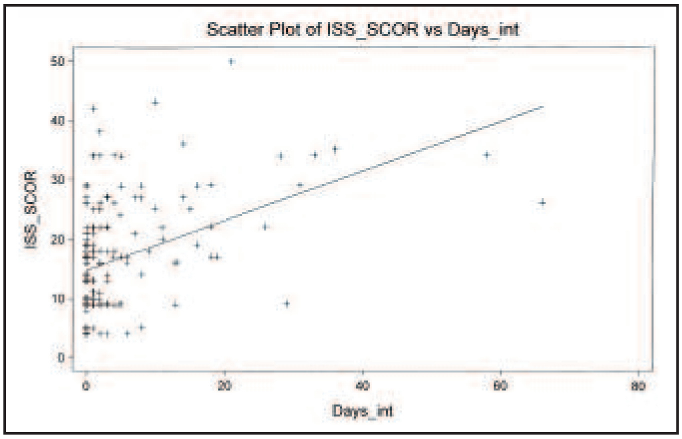

Figure 2. Scatter plot of Injury Severity Score (ISS_Scor) and duration of postoperative mechanical ventilation days (Days_int) in the Hextend group (r = 0.40).

Table 6. Results of the Multivariate Linear Regression for Duration of Mechanical Ventilation

Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA* physical status		
Coefficient	1.58	0.68
Standard error	0.23	0.37
P value	0.0000	0.07
Injury Severity Score		
Coefficient	0.14	0.15
Standard error	0.03	0.04
P value	0.0000	0.0003

* American Society of Anesthesiologists.

Quantifying the degree of postoperative respiratory failure requiring mechanical ventilation after trauma surgery is difficult. In the present study, use of crystalloid fluids was not associated with increased requirement for postoperative mechanical ventilation or worsened indices of oxygenation. However, increased blood loss and transfusion requirements in the crystalloid group were associated with increased duration of ventilation. Intraoperative use of Hextend was a marker for increased severity of injury, blood loss, duration and complexity of surgery, and requirement for postoperative mechanical ventilation. Patients in the Hextend group received approximately 2.4 times more asanguinous fluids, and were transfused more often compared with the crystalloid group.

It is unlikely that use of Hextend contributed to the increased requirement for mechanical ventilation because multiple regression showed that major predictors for postoperative mechanical ventilation in the Hextend group were increased injury severity and ASA physical status. A previous study[10] comparing 4% albumin to normal saline for fluid resuscitation in the intensive care unit demonstrated equivalent requirements for mechanical ventilation in both groups (4.3 to 4.5 days), although there was increased mortality in head-injured patients randomized to the albumin (59 of 241 patients, 25%) as compared with the saline group (38 of 251 patients, 15%). In the present study, duration of ventilation was considerably shorter (2.5 to 3 days) and mortality was very low (0.6% to 1%) in both groups.

Other factors that may have contributed to mechanical ventilation postoperatively include diminished functional reserve capacity, hemodynamic alterations, atelectasis, decreased lung compliance, increased work of breathing, acute lung injury, and increased extravascular lung water. Acute lung injury and increased extravascular lung water would be expected to worsen A-a gradient and oxygen index, as evidenced in the present study. Despite these abnormalities, there were no differences between groups in oxygenation, acid-base, and other postoperative variables. Elderly patients may be at increased risk for requiring mechanical ventilation after trauma surgery because of alterations in control of respiration, lung structure, mechanics, and pulmonary blood flow. In the present study, age was only slightly predictive for duration of ventilation in the two groups.

The low mortality rate in both groups in the present study supports the effectiveness of both fluid management strategies in maintaining tissue homeostasis. There was no evidence that intraoperative use of colloids increased mortality as has been suggested by a meta-analysis of 24 studies involving 1,419 patients.[11] Of note, there were several patients in both groups who were unexpected survivors as evidenced by ASA physical status 5 and being alive at 30 days. All deaths occurred in ASA 5 patients, as expected.

Table 5. Pearson Correlations Between Duration of Mechanical Ventilation and Variable*

Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA physical status		
Correlation	0.51	0.22
P value	0.0000	0.0055
Injury Severity Score		
Correlation	0.46	0.41
P value	0.0000	0.0000
Estimated blood loss		
Correlation	0.18	0.05
P value	0.0018	NS (0.5)
Age		
Correlation	0.13	0.13
P value	0.025	NS (0.1)
Red blood cell transfusion		
Correlation	0.24	0.12
P value	0.0001	NS (0.1)
Fresh-frozen plasma transfusion		
Correlation	0.26	0.07
P value	0.0000	NS (0.4)

*ASA, American Society of Anesthesiologists; NS, not significant.

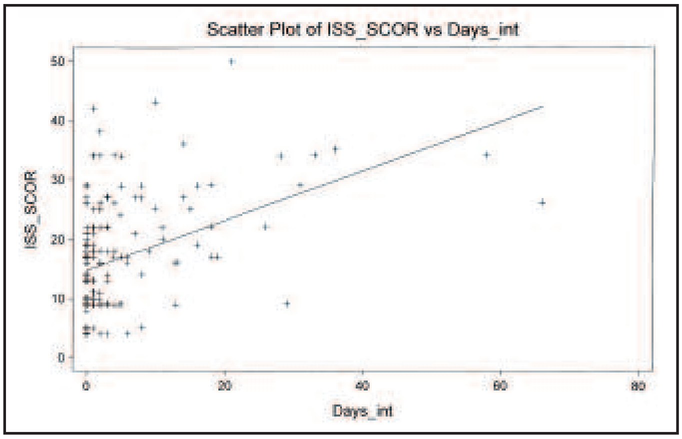

Figure 2. Scatter plot of Injury Severity Score (ISS_Scor) and duration of postoperative mechanical ventilation days (Days_int) in the Hextend group (r = 0.40).

Table 6. Results of the Multivariate Linear Regression for Duration of Mechanical Ventilation

Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA* physical status		
Coefficient	1.58	0.68
Standard error	0.23	0.37
P value	0.0000	0.07
Injury Severity Score		
Coefficient	0.14	0.15
Standard error	0.03	0.04
P value	0.0000	0.0003

* American Society of Anesthesiologists.

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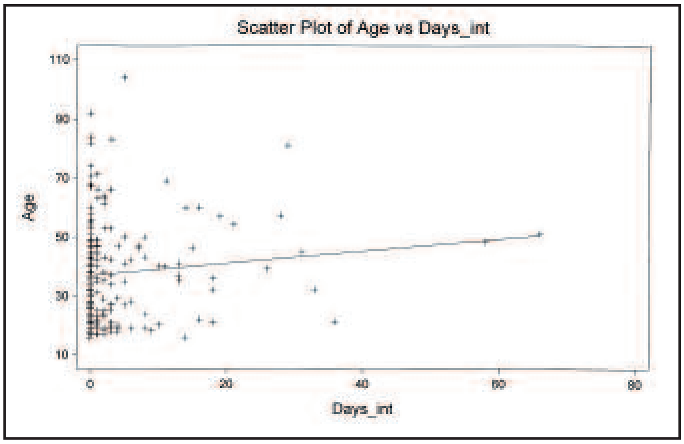

Figure 3. Scatter plot of age (years) and duration of postoperative mechanical ventilation days (Days_int) in the Hextend group.

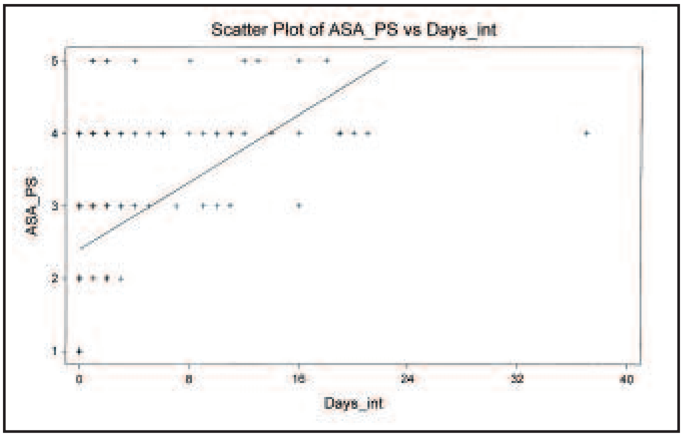

Figure 4. Scatter plot of American Society of Anesthesiologists Physical Status (ASA_PS) and duration of postoperative mechanical ventilation days (Days_int) in the crystalloid fluid alone group (*r* = 0.56).

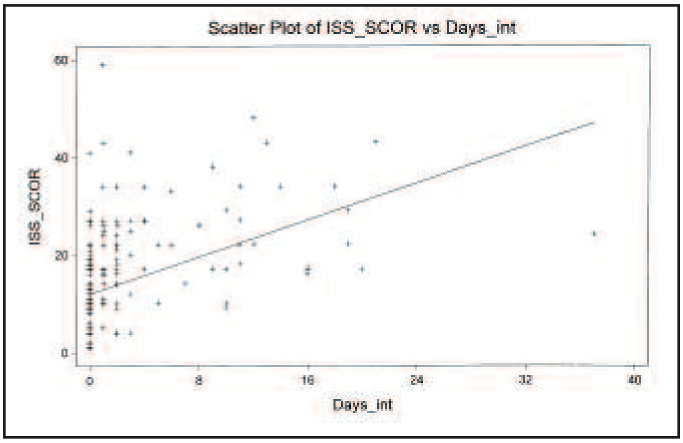

Figure 5. Scatter plot of Injury Severity Score (ISS_Scor) and duration of postoperative mechanical ventilation days (Days_int) in the crystalloid fluid alone group.

Although crystalloid solutions such as lactated Ringer's solution and isotonic 0.9% sodium chloride are the preferred nonblood solutions for fluid resuscitation of patients with blunt and penetrating trauma, colloid solutions such as HES are more effective plasma expanders and increase colloid oncotic pressure, which serves to retain plasma water within the intravascular compartment and minimize interstitial edema within vital organs such as the lung, heart, and brain. Intraoperative use of colloid solutions has been associated with improved outcome and decreased hospital stay,[12,13] possibly because of decreased tissue edema, nausea, vomiting, and pain.

Administration of large volumes of HES such as Hespan (6% HES in 0.9% sodium chloride; mean molecular weight approximately 600 kD, degree of molar substitution 0.75; Baxter, Deerfield, IL) causes coagulopathy. Indeed, because of the adverse effects of Hespan on hemostasis, (e.g., impaired platelet aggregation, type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, decreased von Willebrand factor antigen, and factor VIII-related ristocetin cofactor),[14,15] this colloid was withdrawn from our hospital formulary and replaced with Hextend, which is associated with better thromboelastographic parameters of dynamic clot formation compared with Hespan.[7]

Patients receiving Hextend in the present study had increased blood loss and blood transfusion compared with the crystalloid group, likely due to increased injury severity and complexity of surgery. It is recognized that medium-molecular weight HES (130 kD, 200 kD) with lower molar substitution (0.4, 0.5) has less negative effects on coagulation compared with first-generation HES preparations.[16] Nonetheless, there is evidence that, unlike Hespan, Hextend does not inhibit platelet function, which may be related to its solvent containing calcium chloride dihydrate (2.5 mmol/L).[17] Further, Hextend may be the preferred solution for alternative resuscitation strategies such as hypotensive resuscitation in clinical settings that prevent the application of standard Advanced Trauma Life Support care.[18] There is evidence that Hextend may be beneficial after head injury. For example, Hextend as the sole resuscitation fluid after severe traumatic brain injury in pigs, reduced fluid requirement, eliminated the need for mannitol, improved neurologic outcome, and had no adverse effect on the coagulation profile relative to crystalloid fluids plus mannitol standard of care.[19] Compared with normal saline, volume resuscitation with Hextend was associated with less metabolic acidosis and longer survival in an animal model of septic shock.[20]

Storage and accumulation of Hextend in the body does occur. Hextend undergoes slow intravascular catabolism by alpha-amylase. The median serum half-life during 7 days was 38.2 hours.[21] The smaller molecules are rapidly eliminated by glomerular filtration. Hemodilution is observed for 24 to 48 hours after short-term infusion. A varying amount of Hextend is taken up by the reticuloendothelial system. Severe pruritus has been reported.[22] Life-threatening anaphylactic reactions may occur with different kinds of hetastarch preparations but appear to be rare.[23,24]

Limitations of this study include its retrospective nature and the confounding effects of different injuries, surgeries, and fluid management strategies. It is acknowledged that many different HES preparations are available with varying concentration, molecular weight, and molar substitution.[25] Therefore, the applicability of these data to other starch compounds and colloid solutions in trauma patients remains to be determined. A prospective study of Hextend versus crystalloid to minimize posttraumatic respiratory complications appears warranted.

In conclusion, compared with Hextend, resuscitation with crystalloid fluids was not associated with increased duration of mechanical ventilation, or worsened A-a gradient and oxygen index after surgery in trauma patients. Intraoperative use of Hextend was a marker for increased severity of injury, ASA status, blood loss, fluid requirements, surgery complexity, and requirement for postoperative mechanical ventilation. Increasing ASA status and injury severity were associated with increased duration of postoperative mechanical ventilation regardless of fluid group.

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