EQUINE

Effect of hydroxyethyl starch infusion on colloid oncotic pressure in hypoproteinemic horses

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Objective—To determine the effect of hydroxyethyl starch (HES) on colloid oncotic pressure (π) during fluid resuscitation of hypoproteinemic horses and to evaluate the clinical usefulness of direct and indirect methods for determination of π before and after infusion of a synthetic colloid.

Design—Prospective clinical study.

Animals—11 hypoproteinemic horses.

Procedure—Horses received IV infusions of 8 to 10 ml of a 6% solution of HES/kg (3.6 to 4.5 ml/lb) of body weight during fluid resuscitation. Blood samples were obtained for determination of plasma measured colloid oncotic pressure (π_{meas}) and plasma total protein and albumin (A) concentrations. Plasma globulin concentration (G) was calculated as the difference between plasma total protein and albumin concentrations. Calculated values for colloid oncotic pressure (π_{A+G}) were determined by use of a predictive nomogram previously developed for horses.

Results—There was no significant difference between the means of π_{meas} and π_{A+G} at the beginning of HES infusion. After HES infusion, the mean of π_{meas} was increased significantly from baseline for 6 hours. Mean plasma total protein and albumin concentrations and π_{A+G} were decreased significantly from baseline for 24 hours. Differences between mean π_{meas} and π_{A+G} after HES infusion were significant for 24 hours.

Conclusions and Clinical Relevance—There was good agreement between plasma π_{meas} and π_{A+G} in blood samples obtained from hypoproteinemic horses immediately before infusion of HES. Use of a predictive nomogram did not, however, account for the oncotic effect of HES. Results of comparison of π_{meas} to π_{A+G} after HES infusion suggest that a significant oncotic effect was maintained for 24 hours in the study horses. (*J Am Vet Med Assoc* 2001;218: 1130–1135)

The Starling-Landis equation describes forces governing transcapillary fluid exchange and resultant distribution of body fluids (**Appendix**).[1,2] Understanding the relationship between these terms, it is clear that **capillary colloid oncotic pressure (π)** promotes retention of fluid within the microvasculature.[1-7] Proteins, predominantly albumin, are the only dissolved substances in plasma that do not readily diffuse through the capillary membrane, thereby generating π.[1-7]

In horses, conditions causing a loss of intravascular fluid and proteins can lead to a hypovolemic hypooncotic state. Fluid resuscitation with crystalloid solutions further dilutes plasma proteins, lowering π and resulting in an obligatory increase in interstitial fluid volume.[5-12] If the lymphatic capacity of tissues is exceeded, interstitial edema develops with potentially adverse effects on tissue oxygenation and organ function.[5-17] Important roles of π and the Starling-Landis equilibrium in maintaining capillary fluid dynamics in the lung, myocardium, intestine, and integument are established.[5-13,16-18] In contrast to crystalloids, resuscitation with colloid solutions containing large oncotically active molecules preserves π, thereby limiting transcapillary fluid movement and resulting in more effective plasma volume expansion.[5-13,16,19,20] Resuscitation of shock states requires smaller volumes and shorter infusion times to restore hemodynamic stability and improve tissue oxygen transport.[6,9,16,19,20] Natural colloids (plasma and albumin) or synthetic colloids (gelatins, dextrans, starches, and polymerized hemoglobins) are available for clinical use. The indications, advantages, and potential complications of the various colloid solutions have been extensively discussed.[3,4,6,21-23]

Hydroxyethyl starch (HES) is a synthetic colloid produced by hydrolysis and subsequent hydroxyethyl substitution of amylopectin, a branched polysaccharide polymer.[4,21,24,25] Preparations of HES are heterogeneous or polydispersed solutions characterized by the molecular weight distribution and degree of substitution of HES polymers they contain.[4,21,24,25] When compared with crystalloids under experimental conditions of hypoproteinemia, HES limits transvascular fluid filtration and interstitial edema formation by augmenting capillary π and increasing the capillary-to-interstitial oncotic gradient ($\pi_c - \pi_i$).[11,12] In clinical studies, the oncotic and volume expanding effects of HES are similar to albumin's,[16,19,26,27] with greater improvements in cardiorespiratory variables, compared with those obtained by crystalloid resuscitation.[9,16,20] The primary clinical concern regarding the use of HES relates to its effects on hemostatic mechanisms.[22,24,25] Oncotic, hemodilutional, and hemostatic effects of hetastarch, a high molecular weight HES, have been investigated in clinically normal ponies.[28]

The importance of monitoring π during fluid replacement therapy has been recognized.[7,14,15,29-32] A reduction in π to < 20 mm Hg during fluid therapy in humans is associated with a disproportionate increase in the interstitial fluid volume relative to plasma vol-

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ume expansion.[7,14,15] Capillary colloid oncotic pressure is determined by direct oncometric measurement and by indirect methods using predictive nomograms.[2,7,29-34] Equations describing the relationship of π to plasma or serum protein concentrations have limitations in accurately estimating π in critically ill humans.[29,31,32] A nomogram for estimating π from albumin and globulin concentrations has been developed for horses[34]; however, there is limited understanding of the clinical usefulness of predictive nomograms in hypoproteinemic horses.

The purpose of the study reported here was to determine the effect of HES on π during fluid resuscitation of hypoproteinemic horses and to evaluate the clinical usefulness of direct and indirect methods for determination of π before and after infusion of a synthetic colloid.

Materials and Methods

Animals—Eleven horses admitted to the Hagyard-Davidson-McGee medicine facility between December 1997 and July 1998 were included in the study. Inclusion criteria for study horses were either a plasma total protein concentration < 5.7 g/dl (reference range, 5.7 to 7.4 g/dl) or plasma albumin concentration < 2.9 g/dl (reference range, 2.9 to 3.6 g/dl).[35] Diagnoses included primary enteritis (8 horses), postoperative large colon volvulus (2), and postoperative small intestinal incarceration (1). All horses were Thoroughbreds. There were 5 adults, 4 yearlings, 1 weanling, and one 3-month-old suckling foal.

Fluid administration—Horses received IV infusions of 8 to 10 ml of a 6% solution of HES (in 0.9% sodium chloride)[a]/kg (3.6 to 4.5 ml/lb) of body weight during a 4-hour period by gravity infusion. In addition to HES, all horses received isotonic crystalloids (5 to 40 ml/kg/h [2.3 to 18.2 ml/lb/h]), and 6 horses received plasma (5 to 10 ml/kg [2.3 to 4.5ml/lb]) during the 48-hour study period. Fluid therapy was guided by assessment of PCV, plasma total protein, albumin, and electrolyte concentrations, acid-base balance, and clinical variables. Horses were observed for adverse reactions during administration of fluids.

Sample collection—Venous blood samples were collected and placed in evacuated tubes containing sodium heparin.[b] Samples were used for determination of plasma **measured colloid oncotic pressure (π_{meas})** and plasma total protein and albumin concentrations. Blood samples were obtained immediately before (baseline), at the end of HES infusion (time e), and 6, 12, 24, and 48 hours after HES infusion.

Laboratory methods—Heparinized venous blood samples were centrifuged, and plasma was collected and stored frozen at –20 C. The π_{meas} of thawed plasma samples was determined as described,[28,33] using a commercially available instrument[c] equipped with a hydrostatic pressure transducer and a semipermeable membrane[d] with a rejection characteristic of 90% at molecular weight of 10,000. The instrument was calibrated, using a standard solution[e] of known π (20.5 + 0.5 mm Hg), and the 0 value was determined by use of saline (0.9% NaCl) solution. Plasma total protein and albumin concentrations were determined by a biuret method or bromcresol green dye binding technique, respectively, using an automated chemical analyzer.[f]

Data analysis—Plasma globulin concentrations were calculated retrospectively as the difference between plasma total protein and albumin concentrations. **Calculated values for colloid oncotic pressure (π_{A+G})** were determined, using the predictive nomogram developed by Brown et al[34] for horses: $\pi_{A+G} = -4.384 + (5.501A) + (2.475G)$, where A denotes albumin concentration in g/dl, and G denotes globulin concentration in g/dl. Data were expressed as mean ± SD. All statistical analyses, data transformation, and data analysis were performed using statistical software.[g] For all statistical tests, a value of $P < 0.05$ was used to indicate significance.

Paired *t*-tests were used to compare plasma total protein and albumin concentrations, π_{meas}, and π_{A+G} with baseline values at time points during the experimental period. This yielded a static profile of patterns of change. Using the method of feasible generalized least squares[36] in conjunction with the approach by Diggle et al[37] of repeated measures, indicator variables reflecting time of observations and a feasible correlation pattern of the residuals were used to regress π_{meas} on π_{A+G}.[38] The regression model, which was fitted by use of a regression procedure,[39] incorporated intercept and slope components that reflected the degree to which specific period responses deviated from the baseline model. Compared with the customary paired comparison, this approach yielded a dynamic profile of patterns of change.

To capture a composite index of the divergence of π_{meas} from π_{A+G}, concordance was determined.[40] Concordance, unlike either rank or serial correlation, provides a measure of the agreement of the actual values, as opposed to trend, of 2 potentially alternative techniques to estimate the same response. The null hypothesis was that π_{meas} and π_{A+G} measure the same response in horses. Finally, ratios of albumin to globulin concentration were tabulated to locate variations from the reference range (0.7 to 1.2)[35] during the experimental period.

Results

Adverse reactions were not observed during HES infusions. Mean ± SD plasma total protein and albumin concentrations, π_{meas}, and π_{A+G} before and after HES infusion were determined (**Table 1**). Mean plasma total protein and albumin concentrations were less than reference limits for horses at baseline and throughout the study period.[35] Mean π_{meas} and π_{A+G} were less than π (24.1 ± 3.6 mm Hg) reported for clinically normal horses.[33] There was no significant difference between

Table 1—Mean ± SD total protein concentration, albumin concentration, calculated colloid oncotic pressure (π_{A+G}), and measured colloid oncotic pressure (π_{meas}) in plasma of blood samples obtained immediately before (baseline), at the end of, and 6, 12, 24, and 48 hours after IV infusion of hydroxyethyl starch (HES; 8 to 10 ml/kg [3.6 to 4.5 ml/lb] of body weight) in hypoproteinemic horses (n = 11)

Variable	Baseline	End infusion	6 h	12 h	24 h (n = 9)	48 h
Total protein (g/dl)	4.54 ± 0.76	3.87 ± 0.74*	4.06 ± 0.87*	4.05 ± 0.84*	4.21 ± 0.79*	4.19 ± 0.82
Albumin (g/dl)	1.85 ± 0.38	1.58 ± 0.32*	1.66 ± 0.41*	1.64 ± 0.40*	1.68 ± 0.42*	1.69 ± 0.42
π_{A+G} (mm Hg)	12.4 ± 3.0	9.9 ± 2.8*†	10.7 ± 3.3*†	10.6 ± 3.3 *†	11.1 ± 3.2*†	11.1 ± 3.3
π_{meas} (mm Hg)	11.8 ± 3.5	13.3 ± 3.7*†	13.5 ± 4.6*†	12.8 ± 4.3†	12.7 ± 4.6†	12.5 ± 4.1

*Significantly ($P < 0.05$) different from baseline. †Significant ($P < 0.05$) difference between π_{meas} and π_{A+G} at corresponding time.

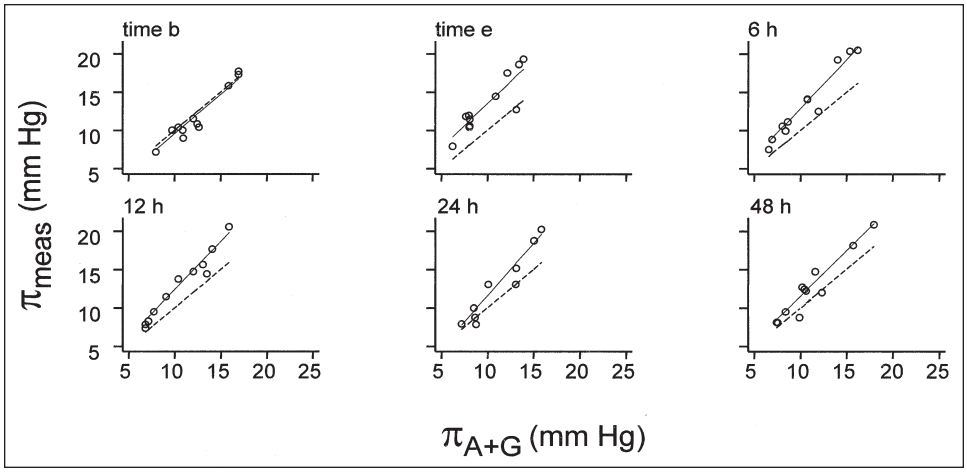

Figure 1—Regression analysis (solid line) of measured colloid oncotic pressure (π_{meas}) on calculated colloid oncotic pressure (π_{A+G}) for plasma in blood samples obtained immediately before (time b), at the end of (time e), and 6, 12, 24, and 48 hours after IV infusion of hydroxyethyl starch (HES; 8 to 10 ml/kg [3.6 to 4.5 ml/lb] of body weight) in hypoproteinemic horses (n = 11). The regression line (dashed line) representing a perfect model with the equation = a + bx, where = π_{meas}, x = π_{A+G}, intercept (a) = 0, and slope (b) = 1, was also determined.

Table 2—Regression and concordance analysis of π_{meas} on π_{A+G} in plasma of blood samples obtained immediately before (baseline), at the end of, and 6, 12, 24, and 48 hours after IV infusion of HES in hypoproteinemic horses (n = 11)

Variable	Baseline	End infusion	6 h	12 h	24 h (n = 9)	48 h
β_j	−0.70 ± 1.05	2.69 ± 0.95*	0.80 ± 1.14	0.59 ± 1.22	−1.30 ± 1.36	0.41 ± 1.34
β_κ	1.03 ± 0.08	0.12 ± 0.08	0.25 ± 0.09*	0.22 ± 0.10*	0.34 ± 0.11*	0.16 ± 0.11
ρ_c	0.93 ± 0.04	0.54 ± 0.12	0.73 ± 0.09	0.80 ± 0.07	0.82 ± 0.10	0.87 ± 0.06
a	−0.70 ± 1.05	1.99 ± 0.83*	0.10 ± 0.77	−0.11 ± 0.77	−2.00 ± 0.93	−0.29 ± 0.87
b	1.03 ± 0.08	1.15 ± 0.08	1.28 ± 0.07*	1.25 ± 0.07*	1.37 ± 0.08*	1.19 ± 0.07

β_j = Coefficient of the intercept (± SE). β_κ = Coefficient of the slope (± SE). ρ_c = Concordance (± SE). a = Intercept (± SE) of the regression equation. b = Slope (± SE) of the regression equation.
See Table 1 for key.

the means of π_{meas} and π_{A+G} at the beginning of HES infusion. For individual horses, approximately 73% of baseline π_{A+G} values were within 10% of π_{meas}, and the greatest observed difference between π_{A+G} and π_{meas} was 2.2 mm Hg. (**Fig 1**, baseline)

After HES infusion, mean π_{meas} increased significantly from baseline for 6 hours. Mean plasma total protein and albumin concentrations and π_{A+G} decreased significantly from baseline for 24 hours (Table 1). Differences between the means of π_{meas} and π_{A+G} after HES infusion were significant for 24 hours.

Graphs of regression analysis of π_{meas} on π_{A+G} at each observation time were determined (Fig 1). The regression line representing a perfect model with the equation = a + bx, where = π_{meas}, x = π_{A+G}, intercept (a) = 0, and slope (b) = 1 was determined.[41] The coefficient of the intercept ($\beta_j \pm$ SE), coefficient of the slope ($\beta_k \pm$ SE), and concordance correlation coefficient ($\rho_c \pm$ SE) were determined at each observation time (**Table 2**, **Fig 2**). Also determined were the resulting intercept (a ± SE) and slope (b ± SE) of the regression line equation, $\pi_{meas} = a + b\pi_{A+G}$. The intercept of the regression line was significantly increased from baseline at the end of HES infusion (time e). The slopes of the regression lines were significantly increased from baseline at 6, 12, and 24 hours after HES infusion.

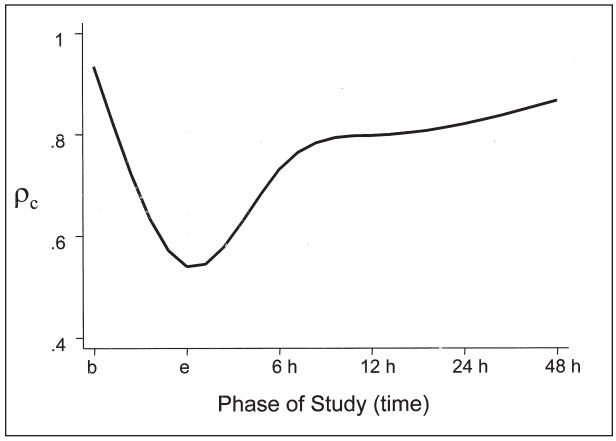

Figure 2—Concordance correlation coefficient (ρ_c) between π_{meas} and π_{A+G} for plasma in blood samples obtained immediately before (time b), at the end of (time e), and 6, 12, 24, and 48 hours after IV infusion of HES (8 to 10 ml/kg [3.6 to 4.5 ml/lb]) in hypoproteinemic horses (n = 11).

Distribution of the albumin-to-globulin ratios (low < 0.7; 0.7 ≤ reference range ≤ 1.2; high > 1.2) was determined (**Table 3**). Analysis of 64 plasma samples throughout the study period indicated that the albumin-to-globulin ratio was low in 37 samples, within reference limits in 27 samples, and high in none of the samples.

Table 3—Pattern of distribution of the albumin-to-globulin ratio in plasma of blood samples obtained immediately before (baseline), at the end of, and 6, 12, 24, and 48 hours after IV infusion of HES in hypoproteinemic horses (n = 11)

Time	Low (< 0.7)	Normal (≥ 0.7 but ≤ 1.2	High (> 1.2)	Total No. of samples
Baseline	5	6	0	11
End infusion	6	5	0	11
6 h	7	4	0	11
12 h	7	4	0	11
24 h	6	3	0	9
48 h	6	5	0	11

Discussion

Thomas and Brown[33] investigated the relationship between π and plasma total protein concentration in several species, including horses. The most commonly used predictive nomogram for people, the Landis-Pappenheimer equation, describes a cubic relation between π and plasma total protein concentration.[2,5,29,31,33] This equation substantially underestimated measured π in bovine, feline, and equine plasma samples, supporting the view that predictive nomograms are species-specific.[33] The difference between measured π and estimates of π determined by use of the Landis-Pappenheimer equation may be related in part to species variability in the albumin-to-globulin ratio.[33,34] Albumin exerts a greater oncotic effect than globulin at equivalent concentrations as a result of the anionic charge and relatively smaller size of albumin molecules.[3,4,29,31,33,34] Therefore, substantial changes in the albumin-to-globulin ratio can alter the strength of the relationship between π and total protein concentration.[3,4,29,31,33,34] Furthermore, in addition to species-specific differences, wide variations in the albumin-to-globulin ratio are commonly encountered clinically, as was observed in the horses in our study.[29,31,34] To account for the dependence of π on the albumin-to-globulin ratio, Brown et al[34] developed for several species a predictive nomogram, π_{A+G}, which incorporates albumin and globulin concentrations. Use of this equation for calculating π of serum samples obtained from a population of hospitalized horses yielded results that correlated well (R^2 = 0.88) with direct measurements of π.[34] However, as a result of systematic and random errors, this method of calculation did not provide consistently accurate estimates of π. The authors of this study concluded that for clinical use direct measurement was superior to a predictive nomogram for determination of π.[34]

Colloids containing resuscitative regimens are designed to maintain or increase π during plasma volume expansion.[3-9] In our study, the observed increases in π_{meas}, in the face of decreases in plasma total protein and albumin concentration resulting from hemodilution, reflect these effects. However, ongoing protein losses or the concurrent administration of plasma products and crystalloids can confound the interpretation of changes in these variables. The use of the predictive nomogram π_{A+G} obviated this concern, because a consequential change in π_{A+G} accounted for the various effects of hemodilution, protein loss, and plasma administration on plasma total protein and albumin concentrations. Close inspection of the nomogram equation reveals that π_{A+G} is dependent on the concentrations of albumin and globulin. It follows that these concentrations are dependent on the total circulating amounts of each protein fraction and the plasma volume. The contribution of administered plasma on the albumin and globulin fractions results in an increase in their respective concentrations and a proportional increase in π_{A+G}. Conversely, expanding plasma volume with crystalloid administration results in a decrease in plasma protein concentrations and a proportional decrease in π_{A+G}. The predictive nomogram did not, however, account for the oncotic contribution of synthetic colloids[7,29,32] and serves as the basis for comparison of estimates of π with π_{meas}. Determining the difference between π_{meas} and π_{A+G} prior to and after HES infusion provided a way to approximate the oncotic effect of HES in the horses studied. Results of our study revealed that the means of π_{meas} (11.8 ± 3.5) and π_{A+G} (12.4 ± 3.0) were similar immediately prior to HES infusion. Results of regression analysis indicated that there was an excellent agreement (ρ_c = 0.93 ± 0.04) between π_{meas} and π_{A+G} at baseline. Estimates of π within 10% of π_{meas} are considered to have clinical usefulness.[29,30,34] Approximately 73% of π_{A+G} values prior to HES infusion satisfied this criterion (Fig 1, baseline).

After the administration of HES and other replacement fluids, π_{meas} increased, whereas π_{A+G} decreased as a result of reductions in plasma total protein and albumin concentrations. The difference between π_{meas} and π_{A+G} was most likely attributable to the oncotic effect of HES. The difference between the means of π_{meas} and π_{A+G} was greatest at the end of infusion (3.4 mm Hg) and decreased to 1.4 mm Hg by 48 hours after infusion. Inspection of regression analysis further supports this assumption. Although the slopes of the regression lines at the beginning (1.03 ± 0.08) and end (1.15 ± 0.08) of HES infusion were similar, the y-axis intercept increased significantly from baseline (–0.70 ± 1.05 mm Hg) to the end of infusion (1.99 ± 0.83 mm Hg). The resulting deviation from the predictive model was indicated by a dramatic deterioration in the concordance correlation coefficient (ρ_c = 0.54 ± 0.12). There was a steady improvement in the agreement of the regression lines with the model throughout the remainder of the study period, which was reflected by an increase in ρ_c. These findings are consistent with a gradual decline in the oncotic effect of HES as a result of its elimination from the intravascular space.

The magnitude and duration of oncotic effects following HES administration depends on the number of oncotically active polymers retained within the vasculature and their rate of elimination.[4,21,24,25] Pharmacokinetic properties of these polydispersed solutions are directly related to the molecular mass distribution and molar substitution ratio (the number of hydroxyethyl groups per molecule of glucose) of HES polymers they contain.[4,21,24,25] Hetastarch (HES 450/0.70) has a weight average molecular weight of approximately 450,000 and a molar substitution rate of 0.70, with the molecular mass of 80% of the polymers ranging from molecular weights of 30,000 to 2,400,000.[4,21,24,25] Following infusion, smaller HES poly-

mers (mol wt, < 70,000) are filtered by the kidneys, whereas larger HES polymers are hydrolyzed by α-amylase and eventually excreted in the urine or extravasated and phagocytized by the reticuloendothelial system.[21,24,25] Intravascular hydrolysis by α-amylase, increasing the number of HES molecules, serves to reinforce the oncotic effect.[4,24]

The rate of HES elimination is influenced by species-specific differences in plasma amylase activity.[42,43] In hypoalbuminemic dogs, which have high plasma amylase activity, rapid metabolism and elimination of HES results in a short duration of oncotic effects (< 12 hours) following infusion.[42,44] Elimination of HES from the vascular space in people is more prolonged, resulting in 23% of the peak plasma concentration (end infusion) remaining 8 days after administration to clinically normal subjects.[45] In a controlled pharmacokinetic study of a medium molecular weight (200/0.5) HES in horses, the half-life of the second phase of elimination was approximately 4 times longer than in humans, presumably because of the lower activity of amylase in equine plasma.[43] Infusions of 10 and 20 ml/kg (4.5 to 9.0 ml/lb) of hetastarch in 2 groups of clinically normal ponies resulted in significant increases in π, compared with baseline, throughout the 120-hour observation period.[28] In our study, comparison of π_{meas} to π_{A+G} suggests that a significant oncotic effect of HES persisted for 24 hours in hospitalized horses. The elimination kinetics of hetastarch in horses has not been investigated; however, accumulated evidence suggests there is prolonged intravascular retention of oncotically active polymers after HES infusion.[28,43]

The oncotic effectiveness of colloids, that is, their ability to maintain the capillary-to-interstitial oncotic gradient ($\pi_c - \pi_i$), is dependent on **capillary permeability (σ)** as given by the Starling-Landis equation.[1-7,11,46] Accordingly, systemic circulation (σ = 0.95) is more sensitive than pulmonary circulation (σ = 0.70) to the effects of changes in π on transcapillary fluid exchange (Q).[4-7,11,14,15] However, when vascular permeability is increased by the release of inflammatory mediators in conditions such as sepsis and endotoxemia, the reflection coefficient is reduced and oncotic effectiveness of colloids is diminished.[4,22,46-48] Examination of regression analysis revealed that the slopes of the regression lines were significantly increased from the baseline (1.03 ± 0.08) at 6, 12, and 24 hours after HES infusion (Table 2, Fig 1). A positive increase in slopes reflected the tendency for π_{meas} to diverge from the model as π_{A+G} increased within the range (6.6 to 16.2 mm Hg, x-axis intercepts) determined at these observation times. These results suggest that the oncotic effect of HES was better preserved in horses with higher plasma protein concentrations. Furthermore, this finding supports the concept that pathologic conditions resulting in a loss of intravascular proteins may also accelerate the rate of capillary filtration of smaller molecular weight fractions of HES.[4,46-48] However, results of experimental studies suggest that the oncotic effectiveness of high molecular weight (> 100,000) polymers of HES is superior to plasma proteins when vascular permeability is increased by the administration of endotoxin.[22,46] Increased vascular retention of HES polymers is attributed in part to their larger molecular size relative to albumin (mol wt, 69,000) but also may be related to the ability of HES to modify the endothelial inflammatory response and attenuate the permeability dysfunction associated with this syndrome.[22,46-49]

In conclusion, there was good agreement between plasma π_{meas} and π_{A+G} in blood samples obtained from hypoproteinemic horses prior to infusion of HES. Use of a predictive nomogram did not, however, account for the oncotic effect of HES. Comparison of π_{meas} to π_{A+G} after HES infusion suggests that a significant oncotic effect was maintained for 24 hours in the study horses. The potential benefits of the oncotic effect of HES in the horses remain to be established.

[a]Hespan, McGaw Inc, Irvine, Calif.
[b]Vacutainer, Becton, Dickinson, & Co, Franklin Lakes, NJ.
[c]4420 colloid osmometer, Wescor Inc, Logan, Utah.
[d]SS-057 wet-packed, pre-mounted membrane, Wescor Inc, Logan, Utah.
[e]Osmocoll,Wescor Inc, Logan, Utah.
[f]Vitros 250 analyzer, Johnson & Johnson Clinical Diagnostics Inc, Rochester, NY.
[g]Stata, version 6, Stata Corp, College Station, Tex.

Appendix

Starling-Landis Equation

$$Q = \kappa S [(P_c - P_i) - \sigma (\pi_c - \pi_i)]^{1,2}$$

Q = Total transcapillary fluid exchange
κ = Capillary hydraulic conductivity
S = Capillary surface area
P_c = Capillary hydrostatic pressure
P_i = Interstitial hydrostatic pressure
σ = Capillary reflection coefficient
π_c = Capillary colloid oncotic pressure
π_i = Interstitial colloid oncotic pressure

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