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Effects of Plasma and Hetastarch Administration on Colloid Oncotic Pressure and Coagulation Variables in Dairy Calves and Goats

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ABSTRACT

Background: Transfusion with fresh frozen plasma (FFP) or hetastarch 6% (HES) is an option for managing decreased colloid oncotic pressure (COP) associated with hypoproteinemia. The effectiveness of HES compared to plasma has not been reported in calves and goats.

Hypothesis: Hetastarch increases COP to levels similar to FFP. There will be no significant adverse clinicopathological changes after administration of HES.

Animals: Seven healthy preweaned calves and 7 juvenile goats from university herds.

Methods: Cohort, clinical trial in a two-way crossover design. Hetastarch and FFP were administered intravenously at 10 and 20 mL/kg, respectively, once. Plasma COP was measured re-transfusion, at 0, 1, 2, 4, 6, 12, 24, 36, 72 h, and 7 days after each transfusion. Coagulation variables were analyzed pre-transfusion, at 0, 24, and 72 h after transfusion. The effects of treatment and time on COP and coagulation variables were determined by multivariate analysis of variance.

Results: Transfusion with FFP and HES increased the COP in calves and goats, with FFP increasing the COP to a greater magnitude in calves (least square mean difference of 1.6 vs. 1 mmHg; $p = 0.03$) but not in goats (least square mean difference of 3.0 vs. 3.0 mmHg; $p = 0.99$). There were no significant changes ($p > 0.05$) in coagulation variables detected after transfusion with FFP or HES.

Conclusions and Clinical Importance: Hetastarch is an alternative colloid to FFP in calves and goats. Adverse changes were not observed in goats and calves after HES administration.

1 | Introduction

Diarrhea secondary to bacterial, viral, or parasitic infections in ruminants can lead to clinically important hypoproteinemia, causing severe sequelae including edema formation and effusion into pleural and abdominal cavities [1]. Fluid resuscitation with isotonic crystalloids alone might be ineffective in these cases. Therefore, colloids are indicated to increase colloid oncotic pressure (COP), maintain fluid within blood vessels, and prevent extravasation into tissues [2]. Fresh

Abbreviations: APTT, activated partial thromboplastin time; COP, colloid oncotic pressure; FFP, fresh frozen plasma; HES, hetastarch; MANOVA, multivariate analysis of variance; PT, prothrombin time; TS, total solids.

frozen plasma (FFP) and hetastarch (HES) are colloid options for ruminants. FFP contains albumin, globulins, and beneficial components like glucose, electrolytes, and clotting factors. The effects of FFP on increasing immunoglobulins or total solids are transient, and animals often require additional colloid support [3]. However, repeated FFP transfusions increase the risk of anaphylactic reactions, especially if cross-matching is not available or multiple donor animals are used [4]. FFP requires donor animals, specialized processing and storage, and can only be used once after defrosting thus potentially limits its availability and use in some veterinary practices [5]. Hetastarch is one formulation of commercially available synthetic colloid that contains large hydroxyethyl starch molecules that maintain oncotic pressure within blood vessels without diffusing out of the vessels [6]. Hetastarch has been associated with adverse effects in other species, including coagulopathies and acute renal injury in compromising or septic conditions [7–11]. Limited research regarding the side effects is available in ruminants. Hetastarch does not contain the additional elements that FFP provides, however, it is easily stored, readily available, and potentially cost-effective because of lower costs to purchase and multiple administrations that can be performed.

The duration of the effect of FFP can be assessed by measuring total solids concentrations before and after transfusion. However, the starch molecules in HES are not accurately measured in the clinicopathologic reference for total solids, either not changing or falsely decreasing values [11, 12]. Hetastarch and FFP increase oncotic pressure, therefore, measuring COP allows the determination of the duration of the effect of colloids in the animal [11]. Determination of the duration of the effect of the colloids might also help predict the approximate time before re-administration in instances where the animal is not maintaining sufficient COP.

The effectiveness of HES and FFP in increasing the COP is reported in horses and camelids [7, 10, 11]. Currently, no peer-reviewed literature is available regarding the effects of HES on COP or a comparison of the effect of HES and FFP on COP in calves or goats. Our objectives were (1) to determine and compare the effects of HES and FFP on COP in healthy calves and goats and (2) to evaluate clinicopathologic changes associated with the administration of HES. We hypothesized that HES would increase COP to levels similar to FFP and that there would be no significant adverse changes in the clinicopathologic variables tested.

2 | Materials and Methods

2.1 | Animals and Study Design

A statistical software was used to calculate the sample size (JMP Pro v.17.0, SAS Institute, Cary, North Carolina). The sample size calculation was based on a COP standard deviation of 1.9 mmHg in healthy calves [6], detection of at least a 1 mmHg magnitude change in COP after administration of HES, type 1 error = 0.05, and power of 80%, and a preferred Cohen's $d \geq 0.5$ for effect size. The minimum required sample was seven animals. Seven preweaned calves and 7 juvenile goats were enrolled in a cross-over design with a 2-week washout period. The sequence of FFP or HES administration was randomized by tossing a coin. Based on the randomization, FFP administration was performed first. Seven dairy bull calves from the university dairy herd were enrolled on a rolling basis as they were born. Calves were fed 4–6 L of colostrum by oroesophageal tubing and housed in individual pens. Seven dairy does from the university goat dairy were enrolled. A physical examination, CBC, and serum biochemical analysis were performed on all animals to confirm their health status before the commencement of the study. The study was approved by the University of California Davis Institutional Animal Care and Use Committee (#23016). Experimental procedures were performed in individual pens for calves, whereas goats were housed in a large pen divided to house two goats.

2.2 | Plasma Administration

Caprine and bovine FFP were purchased from the University of California, Davis Veterinary Medical Teaching Hospital Transfusion Medicine service. The plasma donors were University of California, Davis university-owned goat and dairy cow herds. The plasma donors were screened for blood-borne infectious diseases (anaplasmosis and caprine arthritis and encephalitis virus in goats; anaplasmosis and bovine leukosis in cattle) and examined to confirm their health status before donating plasma. An over-the-wire intravenous catheter (Long-term intravenous catheter, Mila International, Florence, Kentucky) was placed using aseptic technique in the jugular vein and secured using sutures and a bandage before administration of FFP. The catheter patency was maintained by flushing with heparinized saline (1:10 dilution of heparin: 0.9% saline) blocks once daily until removed. The FFP was administered using a fluid pump (INfusia VP7 Volumetric Infusion Pump, Fresenius Kabi, North Andover, Massachusetts) at 20 mL/kg [3, 13, 14]. The transfusion rate was set at 5 mL/kg/h for the first 20 min, then 10 mL/kg/h until finished. Transfusion reactions during administration were monitored by evaluating rectal temperature, heart rate, respiratory rate, mucus membrane color, and demeanor every 15 min. In the event of a transfusion reaction, the transfusion was discontinued for 20 min and resumed at 5 mL/kg/h. A 12 mL syringe was rinsed with heparin (Heparin sodium, Fresenius Kabi, North Andover, Massachusetts) by drawing 1 mL and then flushing the syringe empty. Before sample collection, 10 mL of blood was scavenged into the 12 mL syringe to minimize the sample dilution due to the flushing of the catheters with heparinized saline. Blood samples (4 mL) were each collected into a tube containing lithium heparin or sodium citrate as anticoagulants (BD vacutainer, Beckton and Dickinson Company, Franklin Lakes, New Jersey). The scavenged blood was then returned to the animal through the catheter, and the catheter was flushed with heparinized saline. Blood samples collected in tubes containing lithium heparin were analyzed for PCV, plasma total solids (TS), and COP. Blood collected in tubes containing sodium citrate as an anticoagulant was submitted to the University of California, Davis Veterinary Medical Teaching Hospital Clinical Pathology laboratory for coagulation variable analysis. Coagulation variables evaluated included fibrinogen, fibrin degradation products, prothrombin time (PT), and activated partial thromboplastin time (APTT). Blood samples were collected before transfusion (T_{pre}), immediately after

completion of transfusion (T_0), T_1, T_2, T_4, T_6, T_{12}, T_{24}, T_{36}, T_{48}, T_{72} (h) and 7 days (T_{7d}) after transfusion for PCV, TS, and COP determination. Blood samples were collected at T_{pre}, T_0, T_{24}, and T_{72} (h) after transfusion for CBC and coagulation variable determination. Intravenous catheters were removed after blood collection at 72 h, after which samples were collected directly from the jugular vein.

2.3 | Hetastarch Administration

After the 2-week washout period, a physical examination was performed on all animals to confirm their health status. An over-the-wire intravenous catheter was placed in the opposite jugular vein used during the plasma transfusion, similar to procedures during FFP administration. Intravenous catheter maintenance was similar to the procedures during FFP transfusion. Hetastarch 6% (Hetastarch 6%/NaCl 0.9%, Hospira, Lake Forest, Illinois) was administered using a fluid pump at 10 mL/kg at a rate of 2 mL/kg/h [15–17]. Monitoring during transfusion, sample collection, and analysis was similar to the procedures for FFP transfusion.

2.4 | Sample Analysis

The PCV was measured using a microhematocrit reader (CritSpin microhematocrit centrifuge, Iris International Inc. Westwood, Massachusetts). Blood collected in tubes with lithium heparin as an anticoagulant was centrifuged at 2800 × *g*, and plasma was harvested. The plasma TS was determined using an optic refractometer (Master refractometer, Atago, Bellevue, Washington). The COP was determined using an oncometer (Onkometer BMT 923, BMT MESSTECHNIK GMBH, Germany) according to the manufacturer's recommendations, with plasma as the recommended sample type. Briefly, the reference chamber was filled with 100 μL of 0.9% NaCl (saline) and then aspirated by an internal vacuum in the instrument to calibrate the instrument to zero. The chamber was then filled with the first 100 μL sample and aspirated. The chamber was then filled with a second 100 μL of the same sample to acquire a COP reading. The COP reading in mmHg was acquired within 60 s. The chamber was rinsed three times with saline between each sample reading. The error of measurement of the oncometer was ± 0.2 mmHg. The platelet count was determined on the CBC.

2.5 | Statistical Analysis

Data were checked for normality using the Shapiro–Wilk test. Mean ± SD was reported when data were normally distributed, whereas median (range) was reported when data were not normally distributed. Descriptive data, including age, body weight, dropout rate, and complications associated with the treatment procedures, were reported. The effect of treatment (FFP or HES transfusion) and time on plasma oncotic pressure, total solids, and coagulation variables were compared using a 2-factor multivariate analysis of variance (MANOVA) when data were normally distributed or the multivariate Kruskall-Wallis test [18] when data were not normally distributed. Treatment and time were considered fixed effects, whereas age was considered a random effect. When appropriate, interactions between treatment and time were considered. The initial comparisons determined the changes in COP, PCV, TS, and coagulation variables between T_{pre} and T_0. This was followed by comparing COP, PCV, and TS among time points from T_0 to T_{7d} and T_0 to T_{72} for coagulation variables. Fibrinogen concentrations and platelet counts were log-transformed before analysis.

3 | Results

Five Holstein, one Jersey bull calves, and one Holstein freemartin heifer were enrolled. Calf mean age at enrollment was 9 days (range 4–15 days). The mean ± SD weight for calves at enrollment was 34.8 ± 6.6 kg. Six Saanen and one La Mancha does were enrolled. The mean age for goats at enrolment was 7.7 months (range 7–9 months). The mean ± SD weight for goats was 38.4 ± 3.3 kg. All calves and goats completed the study, and no transfusion reactions were observed.

3.1 | Effect of FFP and HES Administration in Calves

The pre-transfusion (T_{pre}) least square means for COP were 20.1 and 17.0 mmHg for FFP and HES, respectively. The post-transfusion (T_0) least square means for COP were 21.7 and 18.0 for FFP and HES, respectively. Transfusion increased the COP, but the increase was significantly higher when FFP was administered than HES (least square mean difference of 1.6 vs 1 mmHg; $p = 0.03$). There were no significant differences ($p = 0.99$) in the COP among time points from T_0 to T_{7d} or interactions between time and treatment ($p = 0.99$). The calf's age was not associated with changes in COP after transfusion ($p = 0.153$). The changes in COP after FFP and HES administration are depicted in Figure 1.

Transfusion with FFP or HES did not have a significant effect (T_{pre} vs. T_0) on PT (least square mean difference = 0.5 s; $p = 0.657$), APTT (least square mean difference = 0.3 s; $p = 0.651$), fibrinogen concentrations (least square mean difference = 7 mg/dL; $p = 0.338$), and platelet count (least square mean difference = 112×10^3 cells/μL; $p = 0.793$). There were no significant differences in PT ($p = 0.138$), APTT ($p = 0.293$), fibrinogen ($p = 0.257$), and platelet counts ($p = 0.807$) among time points from T_0 to T_{72}. The calf's age was not associated with PT ($p = 0.250$), APTT ($p = 0.201$), fibrinogen concentrations ($p = 0.498$), and platelet counts ($p = 0.276$) after transfusion. Fibrin degradation products were excluded from the analysis because the concentrations (< 5 μg/mL) were similar between treatments and all time points. The changes in PT, APTT, fibrinogen, and platelet counts are summarized in Table 1.

Transfusion with FFP or HES (T_{pre} vs. T_0) did not significantly affect the PCV (least square mean difference = 1.7%; $p = 0.324$). There was no significant difference ($p = 0.99$) in the PCV among the time points from T_0 to T_{7d}. The calf's age was not associated with PCV after transfusion ($p = 0.621$). Transfusion with FFP or HES (T_{pre} vs T_0) did not significantly affect the TS (least square mean difference = 0.5 g/dL; $p = 0.618$). There was no significant difference ($p = 0.99$) in the TS among the time points from T_0 to

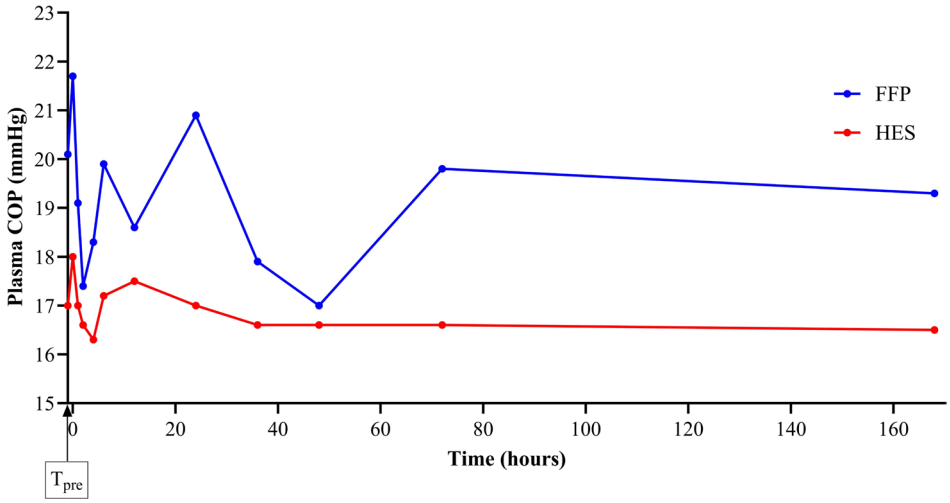

FIGURE 1 | Least squares mean of plasma colloid oncotic pressure after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 dairy calves. Colloid oncotic pressure (COP) was measured before transfusion (T_{pre}), immediately after completion of transfusion (T_0), T_1, T_2, T_4, T_6, T_{12}, T_{24}, T_{36}, T_{48}, T_{72} (h), and 7 days (168 h).

TABLE 1 | Least squares mean ± standard error of the mean for fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (APTT), and platelets before transfusion (T_{pre}), immediately after transfusion (T_0), T_{24}, and T_{72} h after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 dairy calves.

		T_{pre}	T_0	T_{24}	T_{72}
Fibrinogen (mg/dL)	FFP	347 ± 33.1	354 ± 61.7	362 ± 57.8	361 ± 30.7
	HES	306 ± 27.8	290 ± 27.4	257 ± 27.5	264 ± 38.8
PT (sec)	FFP	23.6 ± 0.9	22.0 ± 0.8	23.5 ± 0.9	23.2 ± 0.3
	HES	23.0 ± 0.6	23.5 ± 0.6	23.5 ± 0.5	23.5 ± 0.4
APTT (sec)	FFP	41.0 ± 1.6	37.9 ± 1.7	55.4 ± 11.6	40.3 ± 3.1
	HES	37.0 ± 1.7	40.1 ± 1.6	46.5 ± 3.8	65.4 ± 14
Platelets (cells/μL)	FFP	657,658 ± 272,350	918,332 ± 213,449	746,448 ± 233,727	1,051,962 ± 150,585
	HES	862,979 ± 98,051	826,037 ± 106,679	829,850 ± 109,146	787,045 ± 94,309

Note: There were no significant differences ($p > 0.05$) in fibrinogen, PT, APTT, and platelets among the time points.

T_{7d}. The TS increased with age ($p = 0.008$). The changes in PCV and TS after transfusion are summarized in Table 2.

3.2 | Effect of FFP and HES Administration in Goats

The pre-transfusion (T_{pre}) least square means for COP were 23.1 and 20.6 mmHg for FFP and HES, respectively. The post-transfusion (T_0) least square means for COP were 26.1 and 23.6 for FFP and HES, respectively. Transfusion increased the COP (overall least square mean difference = 3.0 mmHg; $p = 0.042$), but the increase was not significantly different between FFP and HES (mean difference 3.0 vs. 3.0 mmHg; $p = 0.99$). Age was not associated with changes in COP after transfusion ($p = 0.252$). There were no significant differences ($p = 0.899$) in the COP among time points from T_0 to T_{7d} or interactions between time and treatment ($p = 0.243$). The changes in COP after FFP and HES administration are depicted in Figure 2. Transfusion increased the fibrinogen concentrations, but the increase was observed when FFP was administered and not with HES (least square mean difference of 68 vs. 3 mg/dL; $p = 0.002$). Transfusion with FFP or HES did not have a significant effect (T_{pre} vs. T_0) on PT (least square mean difference = −0.9 s; $p = 0.206$), APTT (least square mean difference = −2.4 s; $p = 0.892$), and platelet count (least square mean difference = 87×10^3 cells/μL; $p = 0.934$). There were no significant differences in PT ($p = 0.997$), APTT ($p = 0.840$), fibrinogen ($p = 0.190$), and platelet counts among time points from T_0 to T_{72}. Age was not associated with PT ($p = 0.923$), APTT ($p = 0.943$), fibrinogen concentrations ($p = 0.675$), and platelet counts ($p = 0.309$) after transfusion. Fibrin degradation products were excluded from the analysis because the concentrations (< 5 μg/mL) were similar between treatments and all time points. The changes in PT, APTT, fibrinogen, and platelet counts are summarized in Table 3.

The pre-transfusion (T_{pre}) least square means for PCV were 38% and 31% for FFP and HES, respectively. The post-transfusion (T_0) least square means for PCV were 30% and 29% for FFP and HES, respectively. Transfusion decreased the PCV, but the magnitude

of the decrease was greater when FFP was administered than HES (least square mean difference of 8 vs. 2%; $p=0.02$). There was no significant difference ($p=0.422$) in the PCV among the time points from T_0 to T_{7d}. Age was not associated with PCV after transfusion ($p=0.379$).

The pre-transfusion (T_{pre}) least square means for TS were 6.7 and 6.3 g/dL for FFP and HES, respectively. The post-transfusion (T_0) least square means for TS were 7.7 and 6.5 g/dL for FFP and HES, respectively. Transfusion increased the TS, but the magnitude of the increase was greater when FFP was administered than HES (least square mean difference of 1 vs. 0.2 g/dL; $p=0.005$). There was no significant difference ($p=0.561$) in the TS concentrations among the time points from T_0 to T_{7d}. Age was not associated with changes in TS ($p=0.161$). The changes in PCV and TS after transfusion are summarized in Table 4.

TABLE 2 | Least squares mean ± standard error of the mean for PCV and plasma total solids (TS) before transfusion (T_{pre}), immediately after transfusion (T_0), and T_1, T_2, T_4, T_6, T_{12}, T_{24}, T_{36}, T_{48}, T_{72} (h), and 7 days (T_{7d}) after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 dairy calves.

	PCV (%)		TS (g/dL)	
	FFP	HES	FFP	HES
T_{pre}	27.5 ± 1.2	29.6 ± 1.0	4.5 ± 0.5	5.6 ± 0.4
T_0	24.2 ± 1.1	29.2 ± 1.0	5.6 ± 0.1	5.5 ± 0.1
T_1	25.4 ± 1.3	26.6 ± 1.1	4.9 ± 0.2	5.4 ± 0.3
T_2	25.1 ± 1.3	26.3 ± 1.0	4.8 ± 0.4	5.6 ± 0.2
T_4	26.5 ± 1.6	26.1 ± 0.9	5.9 ± 0.3	5.1 ± 0.2
T_6	25.6 ± 1.5	28.8 ± 1.2	5.8 ± 0.1	5.3 ± 0.2
T_{12}	28.8 ± 0.9	28.7 ± 1.5	5.2 ± 0.1	5.3 ± 0.2
T_{24}	27.3 ± 1.7	28.7 ± 1.1	5.0 ± 0.2	5.0 ± 0.3
T_{36}	26.4 ± 1.4	29.1 ± 1.5	4.5 ± 0.5	5.3 ± 0.5
T_{48}	27.9 ± 1.2	29.0 ± 1.2	4.9 ± 0.3	5.0 ± 0.3
T_{72}	29.5 ± 1.6	28.3 ± 1.1	5.2 ± 0.4	5.8 ± 0.2
T_{7d}	28.4 ± 1.4	30.5 ± 1.3	5.0 ± 0.2	5.6 ± 0.2

Note: There were no significant differences ($p>0.05$) in PCV or TS among the time points.

4 | Discussion

Our study demonstrated that HES administration increased plasma COP comparable to FFP in healthy calves and goats, which is consistent with our hypothesis. In our study, administration of HES was not associated with coagulopathies. In calves, the increase in COP was higher for FFP than HES, but no sustained changes in COP were observed after T_0. This finding contrasts with studies of healthy camelids that reported increased COP values above pre-transfusion values for up to 96 h [9]. A similar reduced duration of effect of 3 h was reported after tetrastarch administration in healthy neonatal foals [19]. This finding might be due to the healthy status of the calves in our study, resulting in effective compensation for the increased fluid volume administered as FFP or HES. In sick animals, which are often experiencing fluid deficits and have low oncotic pressure, the magnitude of change and duration of change are anticipated to be greater. The non-significant changes in the PCV and TS support the effective fluid compensation after the administration of FFP or HES in healthy calves. Despite the increase in COP after HES or FFP administration, there was no significant corresponding elevation in TS in calves. However, previous studies reported increased TS up to 24 h after FFP administration at 34 mL/kg.[3] Thus, TS measurement might not be effective in assessing changes in plasma total solids after HES or FFP administration at the dose used in our study. This highlights the importance and usefulness of measuring COP. The increase in TS concentration in calves is expected because calves have low TS concentrations at birth, which increase after colostrum ingestion and endogenous production of proteins.

Although FFP and HES administration increased COP, there was no significant difference in the magnitude of increase between the FFP and HES treatments in goats, which is in contrast

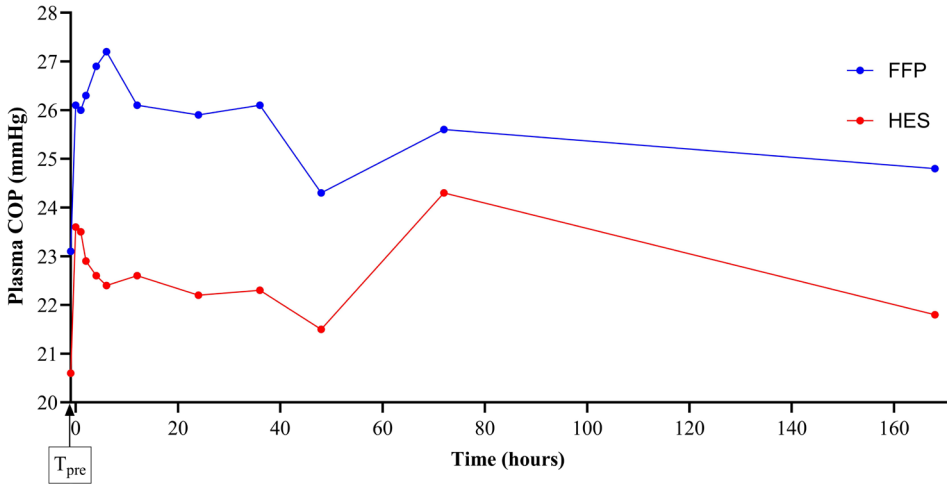

FIGURE 2 | Least squares mean of plasma colloid oncotic pressure after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 goats. Colloid oncotic pressure (COP) was measured before transfusion (T_{pre}), immediately after completion of transfusion (T_0), T_1, T_2, T_4, T_6, T_{12}, T_{24}, T_{36}, T_{48}, T_{72} (h) and 7 days (168 h).

TABLE 3 | Least squares mean ± standard error of the mean for fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (APTT), and platelets before transfusion (T_{pre}), immediately after transfusion (T_0), T_{24}, and T_{72} (h) after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 goats.

		T_{pre}	T_0	T_{24}	T_{72}
Fibrinogen (mg/dL)	FFP[a]	199 ± 14.2	269 ± 14.2	275 ± 14.6	246 ± 18.0
	HES	165 ± 9.2	162 ± 9.6	174 ± 7.3	200 ± 8.8
PT (sec)	FFP	19.8 ± 0.3	18.3 ± 0.2	18.9 ± 0.2	18.8 ± 0.4
	HES	19.8 ± 0.4	19.5 ± 0.4	20.4 ± 0.3	19.0 ± 0.4
APTT (sec)	FFP	25.2 ± 1.7	20.9 ± 0.3	23.4 ± 0.9	19.9 ± 0.8
	HES	23.1 ± 0.3	22.6 ± 0.6	23.0 ± 0.8	20.8 ± 0.7
Platelets (cells/μL)	FFP	288,403 ± 76,768	169,824 ± 57,318	173,780 ± 64,703	257,039 ± 49,583
	HES	275,422 ± 46,669	223,872 ± 54,286	275,422 ± 50,626	316,227 ± 65,870

Note: There were no significant differences ($p > 0.05$) in PT, APTT, and platelets among the time points. $p < 0.05$ denotes a significant difference.
[a]Transfusion (T_{pre} vs. T_0) increased the fibrinogen concentrations, but the increase was observed when FFP was administered and not with HES (least square mean difference of 68 vs. 3 mg/dL; $p = 0.002$).

TABLE 4 | Least squares mean ± standard error of the mean for PCV and plasma total solids (TS) before transfusion (T_{pre}), immediately after transfusion (T_0), and T_1, T_2, T_4, T_6, T_{12}, T_{24}, T_{36}, T_{48}, T_{72} (h), and 7 days (T_{7d}) after administration of fresh frozen plasma (FFP) or hetastarch (HES) in 7 goats.

	PCV (%)[a]		TS (g/dL)[b]	
	FFP	HES	FFP	HES
T_{pre}	38 ± 1.0	31 ± 1.1	6.7 ± 0.2	6.3 ± 0.2
T_0	30 ± 1.3	29 ± 1.7	7.7 ± 0.2	6.5 ± 0.1
T_1	30 ± 0.7	31 ± 1.6	7.9 ± 0.2	6.6 ± 0.2
T_2	31 ± 1.2	33 ± 1.3	7.8 ± 0.2	6.5 ± 0.2
T_4	35 ± 1.2	29 ± 1.2	8.1 ± 0.2	6.4 ± 0.1
T_6	33 ± 1.3	30 ± 0.9	8.1 ± 0.2	6.4 ± 0.2
T_{12}	34 ± 1.2	32 ± 1.0	8.0 ± 0.4	6.4 ± 0.1
T_{24}	33 ± 1.3	31 ± 1.1	7.5 ± 0.1	6.3 ± 0.2
T_{36}	33 ± 1.3	32 ± 0.9	7.7 ± 0.2	6.5 ± 0.2
T_{48}	32 ± 1.3	30 ± 1.2	7.3 ± 0.1	6.3 ± 0.1
T_{72}	38 ± 3.1	37 ± 1.4	7.8 ± 0.2	6.9 ± 0.1
T_{7d}	39 ± 1.1	40 ± 1.9	7.3 ± 0.2	6.8 ± 0.1

Note: $p < 0.05$ denotes a significant difference.
[a]Transfusion (T_{pre} vs. T_0) decreased the PCV, but the magnitude of the decrease was greater when FFP was administered than HES (least square mean difference of 8 vs. 2%; $p = 0.02$).
[b]Transfusion (T_{pre} vs. T_0) increased the TS, but the magnitude of the increase was greater when FFP was administered than HES (least square mean difference of 1 vs. 0.2 g/dL; $p = 0.005$).

to the findings in calves. The increased COP was also not sustained past T_0, similar to the results in calves. In contrast to the calves, administration of FFP and HES resulted in a decreased PCV but increase in the TS in goats. A possible reason for this finding might be that the dose per animal of FFP or HES administered was sufficient to cause a decrease in PCV and a simultaneous increase in the TS. The higher magnitude of the decrease in PCV observed after transfusion with FFP was most likely due to the higher dose rate (20 mL/kg) than HES (10 mL/kg). Previous studies reported increased PCV and TS after FFP administration in severely anemic goats, although the dose per animal was not indicated [20]. The difference between our study and a previous study [19] is likely due to the healthy status of the goats enrolled. Our results suggest COP is a more appropriate method for assessing response to treatment than TS. The COP changes were not sustained in calves or goats, however, both treatments increased COP, and further investigation into the duration of effect is needed. Hetastarch can be administered as a bolus at a lower rate of 3 mL/kg/h in dogs, consistent with our study design [16]. A lower rate of administration has been recommended in dogs and cats to decrease risks associated with coagulopathies [21].

The administration of FFP or HES did not have a significant effect on all coagulation variables evaluated in our study except for increased fibrinogen concentrations in goats. A possible reason for the increased fibrinogen concentrations in goats after the administration of FFP is the presence of immunoglobulins. The formation of immunoglobulin aggregates, especially immunoglobulin G, during the preparation of plasma might activate complement in the recipient, resulting in an inflammatory process [22] leading to elevated fibrinogen concentrations. The coagulopathies associated with the administration of HES reported in other species were not observed in our study. Newer formulations of synthetic colloids with low molecular weight, including tetrastarch, have been reported to have the potential for fewer adverse effects than HES. However, the new formulations are more expensive, eliminating the potential cost-saving benefits [23]. While there are sufficient reports describing the adverse effects of HES in humans, including the restrictions on its use, the literature is limited in veterinary species [24].

Our study has several limitations. We enrolled healthy calves and goats. Therefore, the risk for transfusion reactions to HES and FFP or HES-associated coagulopathies was less likely compared to sick animals that might be experiencing coagulopathies

associated with inflammation. Future studies should focus on the effect of HES and FFP administration in sick animals. The calves were enrolled based on availability; therefore, the weight and age of the calves were variable. The variability in weight and age in the healthy cohort of animals in our study limited the evaluation of changes in COP associated with age or weight. The goats were older than the calves, therefore, comparison of the treatment effect between the species is not effective. Although our design was a cross-over with the animals acting as their own controls, further studies should include a large population of sick cattle and goats with variable ages and weights. Monitoring of renal function was not performed in our study, therefore, this should be considered in future studies because of reported renal complications with HES administration in sick animals in other species. We measured coagulation variables that are readily available in most clinical pathology laboratories, but more sensitive tests, such as thromboelastography, should be considered in future studies [25].

5 | Conclusions

The administration of HES and FFP increased the COP in healthy calves and goats. The magnitude of the COP increase was higher after FFP administration than HES in calves. In goats, there was no significant difference in the magnitude of the increase of COP between HES and FFP administration. There were no transfusion reactions observed during HES or FFP administration. There were no significant changes in coagulation variables observed after HES administration. Hetastarch might be considered a colloid alternative to FFP.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

University of California Davis Institutional Animal Care and Use approval, protocol: #23016. Authors declare human ethics approval was not needed.

Conflicts of Interest

Munashe Chigerwe serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in the review of this manuscript. The other authors declare no conflicts of interest.

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