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*Original Article*

# The effect of intravenous fresh frozen plasma administration on fibrinogen and albumin concentrations in sick neonatal foals

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## Summary

**This study investigated the immediate (6 h or less) effects of fibrinogen and albumin contained in transfused equine origin fresh frozen plasma on those proteins when measured in sick neonatal foals. Fibrinogen and albumin concentrations were measured in the administered plasma and in 31 sick foals at admission to a referral neonatal intensive care unit. Additional samples were obtained from the foals at 2 and 6 h following transfusion. No changes in albumin concentration were recognised. The main determinant of fibrinogen concentration following transfusion was the concentration of fibrinogen in the foal at admission. Importantly, intravenous transfusion of equine fresh frozen plasma did not result in immediate (6 h or less) increases or decreases in the fibrinogen concentration in the recipient foals. Fibrinogen from the donor contained within transfused plasma will not directly affect fibrinogen concentrations measured at later times.**

## Introduction

Transfusions of fresh frozen plasma (FFP) are frequently administered to healthy foals as treatment for failure of passive transfer or as prophylaxis for *Rhodococcus equi* infection and to critically ill neonatal foals as part of their therapy (Becht and Semrad 1985; LeBlanc 1987; White 1990; Madigan *et al.* 1991; Wilkins and Dewan-Mix 1994; Giguère *et al.* 2002, 2011). Little is known regarding the effect on the plasma concentrations of the other components of transfused FFP in healthy or critically ill foals. Fibrinogen (FIB) is a plasma protein component that is frequently monitored in critically ill foals as a measure of the acute inflammatory response and as an indicator of response to treatment. Fibrinogen concentration ([FIB]) normally increases from birth to age 4–7 days, when it reaches mature values (Barton *et al.* 1995). Increasing or increased [FIB] is found in cases with inflammation and infection while decreasing [FIB] is thought to occur with resolution of inflammation or infection. Fibrinogen concentration monitoring is used to determine efficacy of treatment of patients with inflammatory disease, in conjunction with other clinical parameters, and can play a key role in guiding case management.

Fresh frozen plasma contains, amongst other clotting factors and proteins, FIB from the donor animal. It is currently unknown whether the FIB contained in the administered FFP affects the recipient foal's [FIB], potentially confounding the interpretation of changes in [FIB].

The specific aim of the study was to investigate the immediate (within 6 h) effect of FFP transfusion on [FIB] and albumin concentration ([ALB]) in critically ill neonatal foals. We hypothesised that i.v. administration of equine FFP to critically ill equine neonates will cause changes in the recipient's plasma [FIB] proportional to the [FIB] of the administered plasma. Albumin concentration was concurrently assessed because it is present in plasma at a larger concentration, has a longer half-life and should be less affected by acute changes in the inflammatory status of the foal.

## Materials and methods

### *Animals*

Consecutively admitted critically ill neonatal foals (age <2 weeks) of various breeds and either gender, admitted for evaluation and treatment and receiving commercially available equine origin FFP as a part of their treatment, were enrolled following informed owner consent. All procedures were approved by the Institutional Animal Care and Use Committee.

### *Study design*

This was an observational prospective clinical study.

### *Fresh frozen plasma*

Commercially available equine origin FFP was stored according to the instructions of the manufacturer (HiGamm-Equi)[a]. Frozen plasma was thawed slowly in warm water baths immediately prior to administration. Each lot of plasma was assayed for albumin and fibrinogen concentrations prior to administration, using citrated plasma sample(s) provided by the manufacturer. Plasma lots are prepared by collection of a single large volume from one horse that is thoroughly mixed. We had previously established that there was excellent correlation ($R^2 = 0.97$; $P<0.001$) between [ALB] measured in citrated or heparinised plasma (data not shown) allowing us to use the provided citrated plasma samples to determine [ALB] and [FIB] in the administered plasma.

### *Fresh frozen plasma administration*

Fresh frozen plasma was administered at the discretion of the attending veterinarian as part of the treatment plan for each foal. No effort was made to standardise timing of FFP administration following patient admission or rates and composition of i.v. administered isotonic crystalloid fluids. FFP transfusion was performed using a i.v. administration set and a continuous i.v. fluid infusion pump (Alaris Gemini IV)[b]. After an initial observation period, the administration rate would then be increased if no reaction had occurred. Transfusion duration was not recorded.

### *Sample acquisition*

Admission blood samples were obtained during i.v. catheter placement at the time of admission (Arrow Central Venous Catheter)[c]. The whole blood sample was distributed as routine aliquots into multiple glass blood tubes with a variety of anticoagulants, including a 3.2% citrate tube used for this study. Additional whole blood samples were obtained at 2 and 6 h following completion of the FFP transfusion by direct venipuncture or by aspiration through the i.v. catheter after withdrawal of an appropriate presample and placed in 3.2% citrated tubes.

### *Fibrinogen and albumin concentration determination*

Fibrinogen (nephelometry technique; ACL 7000)[d] and albumin (bromcreosol green dye reflectance photometry dry chemistry slide technique; Vitros 350 Chemistry System)[e] concentrations were routinely measured by the hospital clinical pathology laboratory.

### *Statistical analyses*

Kruskal–Wallis and regression analyses were used to assess differences between groups, sample periods and associations. Statistical significance was defined as $P \leq 0.05$. [FIB] to [ALB] ratios, change (Δ) in [FIB] and [ALB] between sample times, and percent Δ in [FIB] and [ALB] between sample times were calculated in the administered plasma and at each sampling time for the enrolled foals. Analyses were performed using commercially available software (Minitab 16)[f].

## Results

Data were not normally distributed and are summarised using median and 25–75 percentile interquartile ranges with numbers of foals provided as n. Transfusion reactions were not observed in any foal.

### *Fibrinogen*

Fourteen lots of plasma were used. Median $[FIB]_{Plasma}$ was 2.45 g/l (range 1.52–3.78 g/l). Admission $[FIB]_{Foal}$ was determined in 31 foals. Not all data at later sample points were available for all foals.

Neither $\Delta[FIB]_{Foal}$ nor percent Δ[FIB] over any time period were significant (**Fig 1**, **Tables 1** and **2**). Linear regression demonstrated that [FIB] of the foal at Admission was the primary determinant of [FIB] 2 and 6 h after FFP transfusion ($R^2$ = 82.6%, P<0.001; $R^2$ = 86.7%, P<0.001, respectively; **Fig 2**). $[FIB]_{Foal}$ at 2 h was impacted by $[FIB]_{Plasma}$ to a small degree ($R^2$ = 14.8%, P = 0.043).

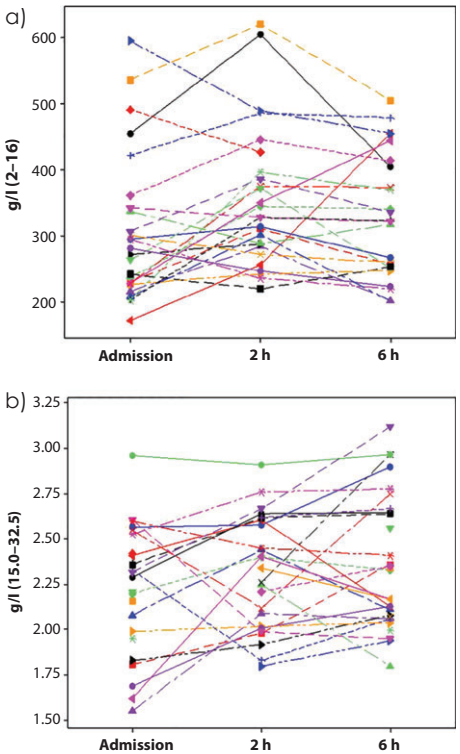


***Fig 1: Line plots showing individual foal values for (a) fibrinogen (g/l) and (b) albumin (g/l) concentrations in sick foals treated with equine origin fresh frozen plasma at admission and at 2 and 6 h following plasma transfusion. Two foals with extremely high fibrinogen concentrations have been removed from the plot in (a) to allow improved ease of viewing detail. There were no differences between sample times for either fibrinogen or albumin concentration.***

**TABLE 1: Summary data for fibrinogen concentration (g/l) and albumin concentrations (g/l) from 31 foals receiving fresh frozen plasma transfusion**

| | Admission | 2 hours | 6 hours |
|---|---|---|---|
| Fibrinogen | 2.95 (2.28–455) (n = 31) | 3.28 (2.81–4.31) (n = 30) | 3.23 (2.53–414) (n = 27) |
| Albumin | 22.9 (19.7–24.8) (n = 25) | 23.7 (2.02–26.2) (n = 26) | 23.4 (20.7–26.5) (n = 30) |

Foals were sampled at the time of admission to the hospital and at 2 and 6 h following completion of plasma transfusion. Results are presented as median (25–75th interquartile range) (n = number sampled). Differences were tested using Kruskal–Wallis with no significant differences detected for either protein between any sample timepoints. Statistical significance was set at $P \leq 0.05$.

### *Albumin*

Median $[ALB]_{Plasma}$ was 24.3 g/l (range 19.6–27.0). $\Delta[ALB]_{Foal}$ was not significant over any time period (**Fig 1**, **Tables 1** and **2**). Similar to [FIB], Admission [ALB] was a significant (P = 0.019) determinant of 2 h [ALB] (**Fig 2**). Different from [FIB], $[ALB]_{Foal}$ at 2 h was not impacted by $[ALB]_{Plasma}$ ($R^2$ = 0.4%, P = 0.769). No differences were identified between the FFP calculated

**TABLE 2: Percent change in fibrinogen concentration ([FIB]) between sampling times**

| | Admission to 2 h % change | Admission to 6 h % change | 2 h to 6 h % change |
|---|---|---|---|
| Fibrinogen (ALL) | 15.5 (−9.5 to 44.2) (n = 28) | −2.8 (−8.1 to 29.6) (n = 25) | −6.8 (−16.3 to −0.9) (n = 25) |
| Fibrinogen (increased group) | 34.1 (15.5 to 50.1) (n = 18) | 11.7 (−5.3 to 61.6) (n = 17) | −7.17 (−23.7 to −0.85) (n = 17) |
| Fibrinogen (decreased group) | −12.8* (−18.3 to −7.9) (10) | −9.9* (−22.8 to −5.1) (8) | −4.6 (−6.9 to 6.8) (8) |

Foals were sampled at the time of admission to the hospital (Admission) and at 2 h and 6 h following completion of plasma transfusion and grouped as having increased or decreased [FIB] at 2 h post transfusion. Results are presented as Median (25–75th interquartile range) (n = number of foals). Differences in percent change [FIB] were tested using Kruskal–Wallis. Statistical significance was set at $P \leq 0.05$.

*Significant differences were found from admission to 2 h and admission to 6 h between foals that had increased fibrinogen concentration at 2 h compared to admission (increased group) vs. foals that had decreased fibrinogen concentration at 2 h compared to admission (decreased group). This difference between the 'increased' and 'decreased' groups was not present when evaluated between groups for the 2–6 h period. Admission to 2 h P = 0.001; admission to 6 h P = 0.003; 2 h to 6 h P = 0.268. No significant differences were found between sampling periods when all foals were considered.

fibrinogen:albumin ratio and those calculated for the foals at any sample time.

## Discussion

The results of this study show that [FIB] in commercially produced equine FFP should not impact [FIB] measured in sick foals following FFP transfusion to a clinically significant extent in the immediate post-transfusion period. If longer-term effects on $[FIB]_{foal}$ are found, they are very unlikely to be not a direct consequence of the [FIB] of the administered FFP. However, the immediate (within ~6 h) impact of FFP transfusion on both [FIB] and [ALB] was not readily predictable in an individual sick foal (**Fig 1**).

The data set was also investigated more closely using 2 groups that had either increased or decreased [FIB] at the 2 h sample time following transfusion when compared to admission [FIB] by evaluating the percent change in [FIB] over that and the subsequent 6 h sample time (**Table 2**). The percent change was utilised due to the large range of [FIB] in the foals of the study. Foals having decreased [FIB] at the 2 h sample time had higher [FIB] at admission when compared to foals that had an increase in [FIB] at the 2 h sample time, suggesting that, in those foals, FIB had been diluted in the foal's vascular space or that FIB had been consumed. Physiological (post gestational age related) and pathophysiological (dehydration, haemorrhage, septic shock) responses affecting the intravascular volume of the sick foal may result in changes in [FIB] and [ALB] (Brace 1998; Palmer 2004). Additionally, normal neonatal foals have substantially larger fluid volumes relative to their body mass than do mature horses (Fielding *et al.* 2011). Large fluid volumes might be required for volume expansion in sick foals, but the proportion of the administered fluids ultimately retained in the vascular space might be small. Very fast rates of i.v. crystalloid fluid administration, and large volumes, would have been required in some foals in this report to restore perfusion and could effectively dilute existing FIB. An additional cocontributor to decreased [FIB] could be disease severity. A near 2-fold increase in FIB degradation, with unchanged FIB synthesis, has been described after 4–6 h of induced acidaemia in pigs (Martini and Holcomb 2007). While severe acidaemia is uncommon, except in very ill foals, some foals might have been significantly acidaemic at admission. Coagulopathy, resulting in FIB loss, is relatively common in critically ill foals and could also contribute to decreased [FIB] (Cotovio *et al.* 2008; Bentz *et al.* 2009; Dallap-Schaer *et al.* 2009).

Recently normal foals younger than 24 h were shown to have a blood volume of ~160 ml/kg bwt with a plasma volume of ~100 ml/kg bwt (Fielding *et al.* 2011), similar to values reported for 2-day-old foals in earlier studies (Persson and Ullberg 1979; Spensley *et al.* 1987). The normal, prototypic 50 kg foal would therefore have a circulating blood volume of 8 l with a 5 l plasma volume. Addition of one litre of FFP would theoretically expand the plasma volume by up to 20% and, should $[FIB]_{Plasma}$ be lower than $[FIB]_{Foal}$, effectively dilute $[FIB]_{Foal}$. Similarly, i.v. administration of large volumes (2–4 l) of crystalloid fluids to a hypotensive and/or hypovolaemic foal would dilute $[FIB]_{Foal}$, effectively mitigating any potential increase in $[FIB]_{Foal}$ due to FFP administration in the immediate (6 h or less) post transfusion period. Most neonatal foals with critical illness present at age 1–3 days, making these fluid volumes relevant to our case population (Borchers *et al.* 2012)

Some foals had increased [FIB] at one or both sample times following transfusion, relative to admission. Post-FFP administration increases in [FIB] suggest addition of FIB to the vascular space, possibly due to endogenous production in response to the primary disease process, or to transfused FIB followed by translocation of any added free water to the interstitial space, effectively concentrating fibrinogen in the vascular space. Coordinated transcription of 3 fibrinogen genes is upregulated 2- to 10-fold in response to stimuli including inflammation, infection and tissue injury, mainly by interleukin-6 and glucocorticoid signalling pathways (Gabay and Kushner 1999; Redman and Xia 2001). Although fibrinogen has been considered an acute phase reactant protein, values generally increase only moderately at 24 h after induction of inflammation and might not peak for 2–3 days in the horse (Shalm 1979; Jacobsen *et al.* 2005; Pollock *et al.* 2005; Borges *et al.* 2007). The kinetics of fibrinogen synthesis make it unlikely that FIB produced *de novo* as a result of FFP transfusion in the foal resulted in important increases in [FIB] within the time frame of the study. That stated, steady production resulting from existing stimulation was likely to be a contributor to some observed [FIB]

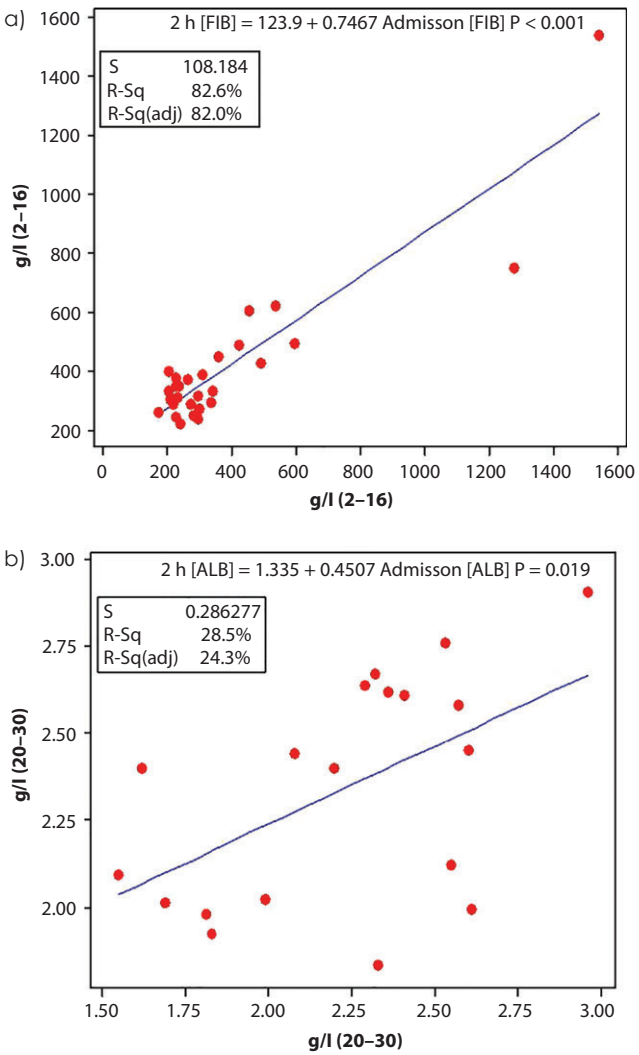


***Fig 2: Linear regression analysis fitted line graph of relationship between admission and 2 h [FIB] (a) and [ALB] (b) demonstrating influence of [FIB] and [ALB] at admission on subsequent 2 h [FIB] and [ALB]. While [FIB] in the foal at admission has a large and statistically significant impact on [FIB] at 2 h ($R^2$ = 82.6%; P<0.001); only a minor relationship is identified for [ALB] ($R^2$ = 28.5%; P = 0.019).***

increases post-FFP transfusion, particularly in foals with well-established disease.

Differences in both directions, increased or decreased [FIB] relative to admission, were of greater magnitude and more frequent between groups at 2 h than at 6 h post transfusion (**Table 2**). In fact, by inspection over all foals, there was small negative percentage of change in [FIB] from admission at 6 h, supporting the premise that any observed changes were due to either treatment or disease processes inherent in the foal, not due to FFP transfusion. This is also supported by the observation the [FIB] in the foal at admission was the major determinant of post transfusion [FIB] (**Fig 2**). The reasons for any observed differences are undefined, in part due to study limitations, but in some cases the differences were large enough potentially to impact case management, if fibrinogen concentration were measured at unusually short intervals, with FIB kinetics and effects of i.v. fluid administration not being considered.

Albumin concentrations have been reported as relatively constant in foals for the first 3 months of life, increasing to mature concentrations by age one year (Rose *et al.* 1979; Rumbaugh and Adamson 1983). Albumin is a primary determinant of colloid osmotic pressure, with Thoroughbred foals having lower measured colloid osmotic pressure than mature horses (Landis and Pappenheimer 1963; Runk *et al.* 2000). We had anticipated that [ALB] would be a useful comparative protein to investigate the impact of FFP transfusion on [FIB], using the [FIB]:[ALB] ratio, but this did not prove to be the case, possibly due to the 5- to 10-fold larger [ALB] obscuring any potential but relatively smaller changes in [FIB] and its effect on colloid osmotic pressure, drawing water into the vascular space.

This study could have been improved by controlling timing of FFP transfusion relative to admission and by carefully recording times and volumes of additional crystalloid administration. More complete recording of admission and subsequent clinical pathology data, including blood gas analyses, might have allowed for more detailed query of the results and should be considered in any subsequent studies of this topic in sick foals.

Using samples obtained immediately prior to FFP transfusion rather than blood samples obtained at admission would have limited the variability present in our results associated with treatment prior to institution of FFP transfusion and should be considered in future studies. However, we believe that this study does provide answers to questions related to the potential for acute (6 h or less) clinically important changes in [FIB] associated with FFP transfusion: minimal changes will be observed, generally of low magnitude and in unpredictable directions, and should not interfere with the use of [FIB] as a monitoring tool in sick equine neonates. Importantly, any observed changes in the time frame of this study could not be related to [FIB] of the transfused FFP and were more likely to be associated with underlying disease and administration of other i.v. fluids.

In summary, i.v. transfusion of equine FFP did not result in important acute changes in [FIB] in the recipient foals. Observed changes in [FIB] in the foals of this report were not of a magnitude that should interfere with monitoring of [FIB] as an indicator of response to treatment, particularly if performed at more appropriate intervals of approximately 48 h. This study did not investigate the impact of FFP transfusion on other indicators of inflammation or on inflammatory mediators in these foals, a potentially interesting and clinically relevant question.

## Authors' declaration of interests

No conflicts of interest have been declared.

## Ethical animal research

The study was approved by the Institutional Animal Care and Use Committee at New Bolton Center, Department of Clinical Studies, University of Pennsylvania School of Veterinary Medicine. Informed client consent was obtained for each foal enrolled in the study.

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## Antimicrobial stewardship policy

Some of the foals in this study were treated with ceftiofur sodium as part of their therapy determined by the clinician in charge of the case.

## Acknowledgement

Portions of the results of this study were presented in abstract at the 2010 American College of Veterinary Medicine Annual Forum.

## Authorship

All authors equally participated in study design and execution. P. A. Wilkins and R. C. Boston performed data analysis, interpretation was provided by all authors. A. R. Hollis, P. A. Wilkins, B. Tennent-Brown, J. E. Palmer and R. C. Boston prepared the majority of the manuscript and all authors approved the final version of the manuscript.

## Manufacturers' addresses

[a]Lake Immunogenics, Inc., Ontario, New York, USA.
[b]CareFusion Corporation, San Diego, California, USA.
[c]Teleflex Medical, Research Triangle Park, North Carolina, USA.
[d]Instrumentation Laboratory, Bedford, Massachusetts, USA.
[e]Ortho Clinical Diagnostics, Rochester, New York, USA.
[f]Minitab Inc., State College, Pennsylvania, USA.

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