Effects of intravenous administration of formaldehyde on platelet and coagulation variables in healthy horses

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Objectives—To assess safety and determine effects of IV administration of formaldehyde on hemostatic variables in healthy horses.

Animals—7 healthy adult horses.

Procedure—Clinical signs and results of CBC, serum biochemical analyses, and coagulation testing including template bleeding time (TBT) and activated clotting time (ACT) were compared in horses given a dose of 0.37% formaldehyde or lactated Ringer's solution (LRS), IV, in a 2-way crossover design. In a subsequent experiment, horses received an infusion of 0.74% formaldehyde or LRS. In another experiment, horses were treated with aspirin to impair platelet responses prior to infusion of formaldehyde or LRS.

Results—Significant differences were not detected in any variable measured between horses when given formaldehyde or any other treatment. Infusion of higher doses of formaldehyde resulted in adverse effects including muscle fasciculations, tachycardia, tachypnea, serous ocular and nasal discharge, agitation, and restlessness.

Conclusions and Clinical Relevance—Intravenous infusion of formaldehyde at doses that do not induce adverse reactions did not have a detectable effect on measured hemostatic variables in healthy horses. (*Am J Vet Res* 2000;61:1191–1196)

In 1943, Roberts[1] reported that administration of formalin solution to horses resulted in a mean decrease in coagulation time of 75.2%. Adverse reactions observed with higher doses included restlessness, lacrimation, salivation, nasal discharge, frequent defecation, sweating, muscle tremors, and signs of abdominal pain.[1] Despite a lack of controlled studies to confirm efficacy and safety, formaldehyde is still used by practitioners as a treatment for hemorrhage in horses.[2]

Formaldehyde may alter hemostasis through effects on platelet or endothelial function (primary hemostasis), activation of secondary hemostasis, or inhibition of fibrinolysis. Analysis of data from healthy goats and humans suggests that low doses of formaldehyde may activate platelets and enhance primary hemostasis.[3,4] Cross-linking of proteins by formaldehyde may alter protein conformation in a way that activates platelets or endothelium, potentiating primary hemostasis.

In addition to the adverse reactions observed by Roberts,[1] IV administration of formaldehyde has the potential to induce hepatotoxicosis[5-7] or intravascular hemolysis.[8] The liver has a high concentration of formaldehyde dehydrogenase and is responsible for the catabolism of formaldehyde.[6-8] Doses of formaldehyde that may be effective in enhancing hemostasis in horses do not cause hepatotoxicosis after oral administration to rats and dogs.[5,9,10] Similarly, intravascular hemolysis has only been reported at doses higher than those commonly used to enhance hemostasis in horses.[8]

Because formaldehyde has the potential to be used as an economic treatment of uncontrolled hemorrhage in horses, we conducted a series of experiments to assess its safety and effects on primary and secondary hemostasis in healthy horses and horses with impaired platelet function secondary to administration of aspirin.

Materials and Methods

Horses—Seven healthy adult horses that ranged from 8 to 22 years old (mean, 13.85 years) and weighed between 432 and 545 kg (mean body weight, 482 kg) were used in the study. Six horses were used in each experiment. All horses were clinically normal, as determined on the basis of results of physical examination, CBC, and serum biochemical analyses. Horses were maintained standing in stocks and box stalls during experiments but were allowed access to a large paddock between experimental sessions. Horses had ad libitum access to grass hay and water while in the box stalls and paddock. The study protocol was approved by an institutional animal care and use committee.

Sample collection—Prior to each experiment, both jugular veins of each horse were aseptically prepared, and a 14-gauge 3.25-inch catheter[a] was placed in each vein. The left catheter was used for collection of blood samples, and the right catheter was used for infusion of dilute formaldehyde (formaldehyde treatment) or lactated Ringer's solution (LRS; control treatment).

Clinicopathologic analysis—Blood obtained by aspiration from jugular catheters was placed in 10-ml evacuated tubes that did not contain anticoagulant or in tubes that contained sodium citrate or EDTA.[b] A CBC was performed on EDTA-anticoagulated blood by use of an automated hematology analyzer,[c] and differential cell counts were performed manually on stained blood smears. Platelet counts were performed on sodium citrate-anticoagulated blood, using the same automated hematology analyzer. Biochemical analysis

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of the serum fraction of coagulated blood was performed, using a centrifugal chemical analyzer.[d] Variables measured for each horse included **L-iditol dehydrogenase (IDH)**, **γ-glutamyltransferase (GGT)**, and **aspartate transaminase (AST)** activities and BUN, creatinine, glucose, total protein, calcium, phosphorus, sodium, potassium, chloride, and total CO_2 concentrations.

Template bleeding time (TBT)—Hair was clipped over the skin distolateral to the accessory carpal bone of both forelimbs. A template bleeding device[e] was placed vertically against the horse's skin and discharged. Blood from the incision was collected periodically onto filter paper[f] placed approximately 1 cm below the incision. The TBT was measured from discharge of the device until bleeding had stopped.

Coagulation variables—Blood obtained from the catheter in the left jugular vein was used for determination of **activated clotting time (ACT)**, **prothrombin time (PT)**, **partial thromboplastin time (PTT)**, and **fibrin degradation products (FDP)**. For ACT assays, blood was aspirated and placed in 20-ml syringes and quickly injected into 2 warmed (37 C) evacuated tubes containing diatomaceous earth.[g] Tubes were mixed by gentle inversion and incubated at 37 C for 1 minute. Tubes then were removed from the water bath, rocked gently, and returned to the water bath. The ACT was recorded as mean time to initial clotting in each tube. The PT was determined by addition of 0.2 ml of warmed rabbit thromboplastin reagent to 0.1 ml of warmed (37 C) plasma (sodium citrate) and measurement of the interval until clot detection, using a fibrometer.[g] The PTT was determined as follows: 0.1 ml of sample plasma was added to 0.1 ml of warmed actin-activated cephaloplastin reagent, incubated for 3 minutes at 37 C, and mixed with 0.1 ml of warmed $CaCl_2$ solution, and the interval until clot detection was measured.[h] For each time point, PT and PTT were determined in duplicate for each horse and the mean value calculated. Control values for PT and PTT were established, using human plasma (sodium citrate). The FDP were measured, using a commercial latex agglutination test kit.[i]

Experimental design—For each of 3 experiments, 6 horses were used in a randomized 2-way crossover design. Prior to initiation of the first experiment, the following baseline values were obtained for each horse: ACT, TBT, PT, PTT, FDP, CBC, serum biochemical analyses, and platelet count. The ACT, TBT, CBC, serum biochemical analyses, and platelet counts also were determined before experiments 2 and 3. For experiments 1 and 2, clinical variables were recorded including rectal temperature, heart rate, respiratory rate, mucous membrane color (pale, pink, or dark), capillary refill time, auscultation score for the gastrointestinal tract, and appetite (less than normal, normal, or excessive). Auscultation score for the gastrointestinal tract was calculated after auscultation of 4 abdominal quadrants (right upper, right lower, left upper, and left lower). A score of 1 was assigned for each quadrant when sounds were heard in the gastrointestinal tract within 20 seconds after initial auscultation at a site. Total auscultation score for the gastrointestinal tract at each time point ranged from 0 to 4. For all experiments, behavior and demeanor were continuously monitored during and immediately after infusions. Researchers administering the infusions, collecting samples, and performing all assays were not aware of the treatment each horse received.

Experiment 1—Three horses were given 10 ml of 37% formaldehyde in 1 L of LRS (final formaldehyde concentration, 0.37%) that was administered during a period of approximately 15 minutes, and 3 horses were given LRS without formaldehyde (control treatment). Time 0 was defined as the time the infusion was initiated. After a 1-week period, treatments were reversed. Clinical signs were recorded before infusion as well as 7.5 and 40 minutes and 1, 2, and 24 hours after infusion. A CBC and serum biochemical analyses were performed on samples obtained before infusion and 24 hours after infusion. The TBT was measured before infusion and 25 minutes and 1 and 4 hours after infusion. The PT, PTT, FDP, and platelet count were determined at 0, 25, and 60 minutes. The ACT was determined before infusion and 25 and 60 minutes and 4 and 24 hours after infusion.

Experiment 2—Six horses were assigned to treatment groups as described for experiment 1. A 1-week period was allowed between treatments. Horse 1 was given 1 L of a 1.0% solution of formaldehyde during a period of ≥ 15 minutes. The infusion was discontinued after the horse received only 900 ml of solution because of an adverse reaction. Horses 2 through 6 received a 0.74% solution of formaldehyde in LRS. Horses receiving the control treatment were administered 1 L of LRS. Samples were collected as described for experiment 1, except that PT, PTT, and FDP were not measured, and PCV was determined 1 hour after initiation of infusion.

Experiment 3—Six horses were used in a 2-way crossover study of formaldehyde and control treatments, as described for experiment 1. Aspirin was administered to all horses (20 mg/kg of body weight, PO, 72, 48, and 24 hours prior to time 0 [ie, start of infusion]). Treatment consisted of 1 L of 0.37% formaldehyde in LRS or LRS alone. Data were collected at the same time points as for experiment 1, except that only ACT and TBT were determined. Treatments were reversed and the experiment repeated after a 1-week period.

Statistical analyses—A 2-way repeated-measures ANOVA was performed to identify time and treatment effects, and the Bonferroni post-hoc test was performed when the F statistic was significant. A Mann-Whitney rank-sum test was used to detect differences in TBT at time 0 after treatment with aspirin in experiment 3, compared with values for time 0 in experiments 1 and 2. For all analyses, a value of $P < 0.05$ was considered significant.

Results

Experiment 1—Horses remained calm when receiving formaldehyde and control treatments and did not have overt clinical signs of pain, discomfort, or anxiety. Rectal temperature did not change significantly when horses were given formaldehyde or control treatments during the experimental period. Similarly, significant differences were not detected in heart rate or respiratory rate for formaldehyde or control treatments (**Fig 1**). Other clinical signs monitored during the experiment, including capillary refill time, mucous

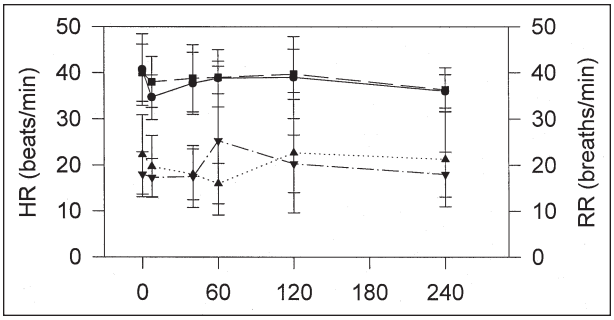

Figure 1—Mean ± SD heart rate (HR) and respiratory rate (RR) of horses given formaldehyde or lactated Ringer's solution (control) treatments in experiment 1. Circles = HR formaldehyde treatment. Squares = HR control treatment. Triangles = RR formaldehyde treatment. Inverted triangles = RR control treatment. Time 0 = Initiation of infusion.

Table 1—Mean ± SD values for serum biochemical analyses of horses given formaldehyde or control treatments in experiment 1

Treatment group	Time (h)	IDH (U/L)	GGT (U/L)	Creatinine (mg/dl)	Calcium (mEq/L)	TCO_2 (mEq/L)
Formaldehyde						
	0	2.00 ± 1.83	27.2 ± 26.0	1.16 ± 0.23	12.2 ± 1.00	27.8 ± 1.3
	24	3.50 ± 1.00	28.5 ± 25.3	1.00 ± 0.19	13.3 ± 0.43	26.7 ± 1.1
Control						
	0	2.80 ± 0.45	28.0 ± 30.1	1.06 ± 0.20	12.2 ± 0.69	28.0 ± 2.3
	24	4.00 ± 1.90	27.2 ± 33.1	0.98 ± 0.22	12.8 ± 0.98	26.5 ± 1.1

IDH = L-Iditol dehydrogenase. GGT = γ-Glutamyltransferase. TCO_2 = Total CO_2. Time 0 = Initiation of infusion.

Table 2—Mean ± SD values for hematologic variables of horses given formaldehyde or control treatments in experiment 1

Treatment group	Time (h)	Platelet count (× 10^5 cells/μl)	PCV (%)	WBC count (× 10^5 cells/μl)
Formaldehyde				
	0	1.52 ± 0.35	33.8 ± 5.8	6.42 ± 0.67
	24	1.40 ± 0.30	37.2 ± 9.1	6.72 ± 1.42
Control				
	0	1.60 ± 0.26	32.0 ± 5.5	6.86 ± 1.26
	24	1.66 ± 0.30	36.2 ± 5.4	7.00 ± 1.10

Time 0 = Initiation of infusion.

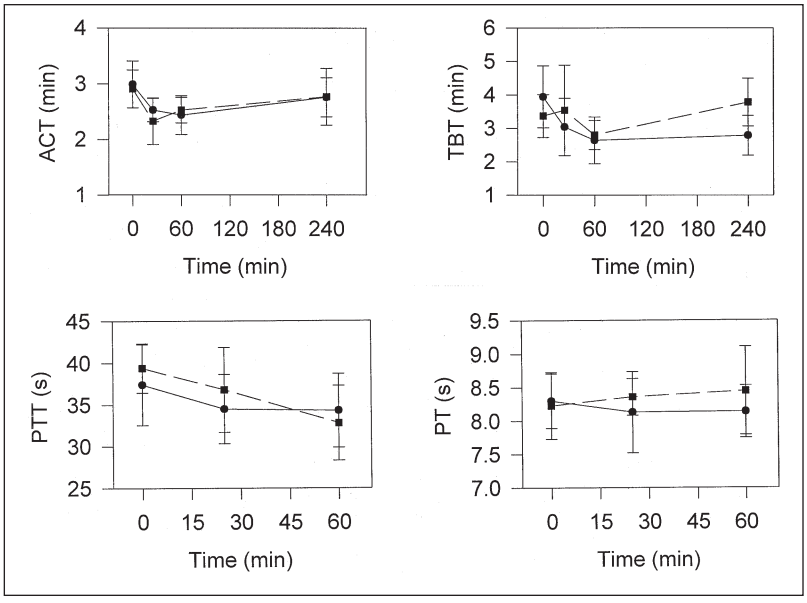

Figure 2—Mean ± SD values for coagulation variables of horses given formaldehyde (circles) or control (squares) treatments in experiment 1. ACT = Activated clotting time. TBT = Template bleeding time. PTT = Activated partial thromboplastin time. PT = Prothrombin time.

membrane color, appetite, and auscultation score for the gastrointestinal tract remained within acceptable limits, and we did not detect significant differences between formaldehyde and control infusions (data not shown).

Significant differences were not detected in results of serum biochemical analyses. In particular, serum IDH and GGT activities and serum creatinine, calcium, and total CO_2 concentrations at time 0 and at 24 hours were not significantly different between control and formaldehyde treatments (**Table 1**). The PCV, RBC count, RBC indices, total WBC and differential counts, platelet count, plasma total protein concentration, and fibrinogen concentration remained relatively constant for each horse. Significant differences in hematologic variables were not observed between formaldehyde and control treatments (**Table 2**).

Mean TBT were calculated at each time for control and formaldehyde treatments (**Fig 2**). Mean ± SD TBT was not significantly different between treatments at 20 minutes (formaldehyde, 3.04 ± 0.86 minutes; control treatment, 3.54 ± 1.35 minutes) or 60 minutes (formaldehyde, 2.64 ± 0.70 minutes; control treatment, 2.80 ± 0.43 minutes). The ACT was not significantly different between horses given formaldehyde or control treatments throughout the experiment.

The PT and PTT for control and formaldehyde treatments were calculated (Fig 2). Significant differ-

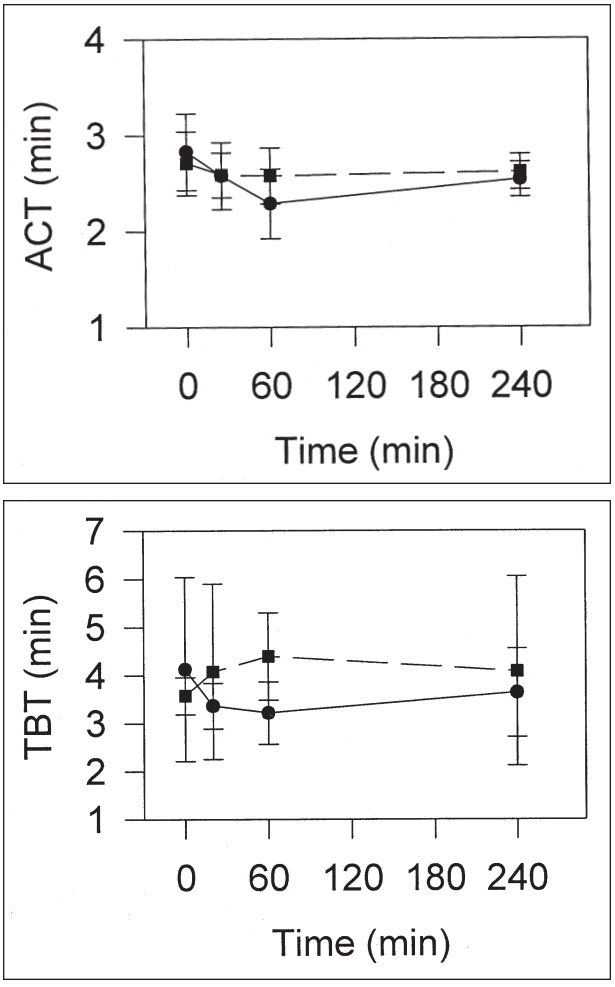

Figure 3—Mean ± SD values for coagulation variables of horses given formaldehyde (circles) or control (squares) treatments in experiment 2.

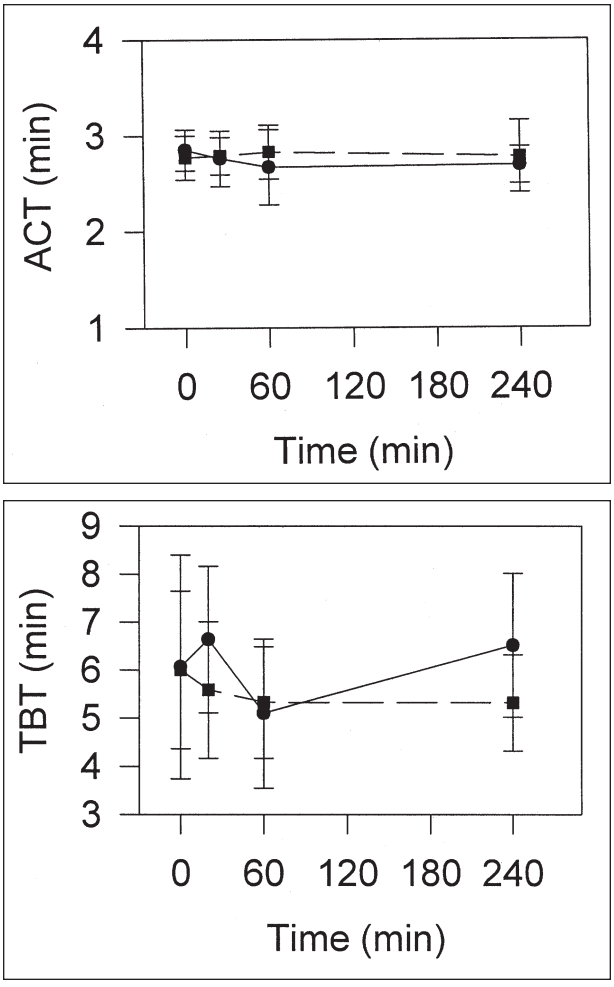

Figure 4—Mean ± SD values for coagulation variables of horses given formaldehyde (circles) or control (squares) treatments in experiment 3.

ences in PT, PTT, or concentration of FDP were not observed between formaldehyde and control treatments.

Experiment 2—Because of adverse effects, horse 1 received only 900 ml of 1% formaldehyde solution, and horses 2 and 3 received only a portion (650 and 550 ml, respectively) of the 0.74% solution of formaldehyde in LRS. The remaining 3 horses received 1 L of 0.74% formaldehyde in LRS. Because of the obvious adverse reactions in horses given formaldehyde treatment, observers were aware of treatments received by those horses. The most consistent observations included muscle tremors throughout the entire body, tachycardia (heart rate increased to as high as 75 beats/min), tachypnea, serous ocular and nasal discharge, agitation, and restlessness. Other behaviors observed during formaldehyde infusion included kicking at the flank, head tossing, chewing, pawing, blepharospasm, and urination. All clinical signs of toxicosis resolved within a few minutes after the formaldehyde infusion was discontinued. In the 3 horses that received 1 L of 0.74% formaldehyde in LRS during a period of 15 to 20 minutes, mild signs of discomfort were observed, including nasal and ocular discharge and mild restlessness; however, these signs disappeared almost immediately after completion of the infusion. Significant differences in ACT or TBT were not observed between formaldehyde and control treatments (**Fig 3**). Similar to experiment 1, results of hematologic and serum biochemical analyses were not significantly different between formaldehyde and control treatments (data not shown).

Experiment 3—Only ACT and TBT were measured in experiment 3. As expected, administration of aspirin significantly ($P < 0.001$) prolonged baseline TBT values (6.04 minutes), compared with values for horses that did not receive aspirin in experiments 1 and 2 (3.76 minutes; **Fig 4**). Formaldehyde administration did not result in significant differences in TBT between treatments at 20 minutes (formaldehyde, 6.64 ± 1.53 minutes; control treatment, 5.59 ± 1.42 minutes) or 60 minutes (formaldehyde, 5.10 ± 1.55 minutes; control treatment, 5.33 ± 1.16 minutes). Similarly, significant differences in ACT were not observed between treatments at any times throughout the study.

Discussion

Doses of approximately 10 ml of a 37% solution of formaldehyde or 30 to 150 ml of buffered 10% forma-

lin in 1 L of isotonic fluids have been recommended for control of hemorrhage in horses.[4] To the authors' knowledge, the only report of formaldehyde use in horses described administration of 4 to 50 ml of 4 to 12% formalin solutions in 40 to 500 ml of distilled water, with a mean decrease in coagulation time of 75.2%.[1] The final concentration of formalin in those infusions is not reported, but the amount of formalin in the injections, rather than the concentration of the solution, was believed to have had the greatest effect on coagulation time.[1]

Although formaldehyde is historically recommended for treatment of purpura hemorrhagica, it anecdotally has been reported to be effective for control of many types of bleeding. Administration of formalin to goats decreased bleeding time for a period of approximately 30 minutes after infusion,[3] suggesting a possible effect on primary hemostasis through enhanced endothelial or platelet activation. This hypothesis is supported by observations that formaldehyde can enhance coagulative functions of human platelets[4] and induce expression of activation-dependent platelet membrane proteins.[11] In the study reported here, we investigated the effects of IV administration of formaldehyde on coagulation variables and bleeding time in healthy horses and horses with prolonged bleeding times secondary to aspirin administration to determine whether formaldehyde is safe and efficacious for enhancement of hemostasis.

Significant differences were not detected in any of the measured variables when horses were treated with a 0.37% solution of formaldehyde. Analysis of these results suggests that formaldehyde has little effect on primary or secondary hemostasis in healthy horses. There are at least 4 possible explanations for these observations. First, there may have been a lack of sensitivity of the assays used. Second, effects may only be evident in horses that are hypotensive and hypovolemic secondary to blood loss. Third, cytokines or other inflammatory mediators may be a critical cofactor for formaldehyde to activate platelets, endothelium, or soluble coagulation factors. Fourth, formaldehyde may not have effects on blood coagulation at doses that are safe for use in horses.

Primary hemostasis is the process by which platelets interact with damaged endothelium to achieve a temporary plug at the site of a vascular defect. Exposure of subendothelial collagen triggers platelet adhesion through interactions between endothelial von Willebrand factor and receptors on the surface of platelets. Platelet adhesion is followed by release of mediators to attract additional platelets (aggregation) to the site of vessel injury. Platelet aggregation provides the necessary environment for accumulation and activation of the intrinsic and extrinsic coagulation systems (secondary hemostasis). The TBT is an indirect measure of primary hemostasis and is dependent on the number and functional ability of circulating platelets, the availability of von Willebrand factor, and vascular integrity. Typically, TBT varies in horses, depending on the technique and site of incision, and there can be profound variation between horses as well as within a horse from day to day.[12,13] Variability was minimized in these experiments by having a single investigator (ELT) perform each measurement and through the use of each horse as its own control on the day of an experiment. Although mean TBT was relatively consistent throughout each experiment, SD were comparatively large and may have masked small treatment effects. To detect an effect of formaldehyde on TBT with a statistical power of 0.80 in experiment 1, a difference in mean TBT of 1.25 to 1.5 minutes would have been required. Effects of formalin infusion on clotting time in goats are large (baseline, 150 ± 4.6 seconds; formalin, 28 ± 2.2 seconds).[3] Assuming comparable effects were evident in horses, they should have been detectable with this sample size, despite the large SD.

Aspirin administration results in an increase in bleeding time in horses as a result of irreversible inhibition of cyclo-oxygenase.[12-14] Treatment of horses with aspirin (17 mg/kg, PO, q 24 h, for 3 days) resulted in impaired platelet function and prolonged TBT for 3 to 4 days.[12] Aspirin administration prior to infusion significantly prolonged TBT in the horses reported here. However, treatment with formaldehyde did not return TBT toward baseline values (Fig 4).

Prothrombin time, PTT, and ACT are indicators of the quantity and functional capacity of soluble mediators of coagulation (secondary hemostasis). Prothrombin time is primarily a measure of the extrinsic and common pathways of coagulation, whereas PTT is a measure of the intrinsic and common pathways. Activated clotting time will be prolonged when there are deficiencies in the quantity or activity of factors VIII, IX, prothrombin, or fibrinogen. Severe thrombocytopenia also can affect ACT. None of these measurements of secondary hemostasis was altered by treatment with formaldehyde.

The hemostatic activity of formaldehyde in sick horses, potentially with substantial blood loss, depletion of coagulation factors, hypotension, and vasoconstriction, may differ from its activity in healthy horses. Because it requires a profound decrease in function of coagulation factors to prolong bleeding time, the effects of formaldehyde on secondary hemostasis may not be fully appreciated in a healthy horse with typical concentrations of coagulation factors. In addition, when a horse is actively bleeding, that horse may become hypotensive and have potent vasoconstrictive responses that play a role in primary hemostasis. Coexisting inflammation, painful stimuli, and shock cause the release of cytokines and other inflammatory mediators that could contribute to the dynamics of hemostasis and may be affected by formaldehyde. The vasoconstrictive response to profound hypovolemia may exacerbate effects of formaldehyde infusion on hemostasis, explaining a lack of effect in hemodynamically normal horses.

It is possible that enhanced hemostasis was not observed in the experiments reported here because of administration of an inadequate dose of formaldehyde. Administration of a 5% solution of formalin to goats (1.1 ml/kg, IV) markedly decreased clotting time and bleeding time for a period of approximately 30 minutes after injection.[2] This would be equivalent to adminis-

tering 135 ml of 37% formaldehyde diluted in 1 L of saline (0.9% NaCl) solution to a 500-kg horse. However, administration of 1 L of LRS containing formaldehyde at concentrations of 0.74 to 1% caused adverse reactions in the horses described here. If higher doses or more concentrated solutions of formaldehyde were administered, the rate of infusion would have to be substantially slower, perhaps negating the hemostatic effects. If the pH of the solution was responsible for adverse effects, use of buffered formalin rather than the much more acidic formaldehyde may enable safe administration of higher doses. However, pH of the formaldehyde infusions administered varied from approximately 5.75 to 5.90, whereas pH of routinely used saline (0.9% NaCl) solution is 5.5, suggesting that pH alone is not important in causing the toxic effects associated with formaldehyde infusion.

Infusion of formaldehyde at doses that are safe for horses does not appear to substantially enhance primary or secondary hemostasis. Although effects in hemodynamically impaired horses cannot be ruled out entirely, formaldehyde treatment for hemostasis in horses cannot be recommended at this time.

[a]Angiocath, Becton-Dickinson, Infusion Therapy Systems Inc, Sandy, Utah.
[b]Vacutainer, Becton-Dickinson, Rutherford, NJ.
[c]Baker 9010 hematology analyzer, BioImmunochem, Allentown, Pa.
[d]CobasMiraplus, Roche, Sommerville, NJ.
[e]Surgicutt, International Technidyne Corp, Edison, NJ.
[f]No. 2 qualitative circles (150 mm), Whatman International Ltd, Kent, UK.
[g]Simplastin, Organon Teknika Corp, Durham, NC.
[h]Dade actin-activated cephaloplastin reagent, Dade International Inc, Miami, Fla.
[i]Thrombo-Wellcotest, Murex Biotech Limited, Kent, UK.

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