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Low-Molecular-Weight Heparin Dosage in Newborn Foals

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Background: Heparin is used in humans as prophylaxis of hypercoagulable states and disseminated intravascular coagulation (DIC). However, babies need a higher heparin dose than do adults. Septic neonate foals are at high risk of hypercoagulable state and DIC, and there is limited objective information about heparin dose for equine neonates.

Objective: To assess whether neonate foals require higher dosages of low-molecular-weight heparin (LMWH) than adults.

Animals: Eighteen healthy and 11 septic neonate foals.

Methods: Experimental and clinical studies. Firstly, healthy foals were randomly distributed in 2 groups, 1 receiving 50 IU/kg SC of dalteparin and the 2nd group receiving 100 IU/kg SC of dalteparin, once daily for 3 days. Blood samples were collected before and 3, 6, 27, and 51 hours after the 1st LMWH administration. Plasma antifactor-Xa activity was measured, together with hemostatic and hematologic parameters used to assess the risk of bleeding. Subsequently, septic foals were treated blindly either with placebo (saline) or 100 IU/kg of dalteparin for 3 days. Plasma antifactor-Xa activity and other hemostatic parameters were determined before and after treatment.

Results: Plasma antifactor-Xa activity in healthy foals was below prophylactic activity when using the adult dosage (50 IU/kg), whereas prophylactic activities were achieved when using the double dosage (100 IU/kg). No hemorrhagic events and erythrocyte-related complications were observed with either dosage. In the clinical study, only 4/6 septic foals had plasma antifactor-Xa activity adequate for prophylaxis.

Conclusions and Clinical Importance: Equine neonates require higher dosages of LMWH compared with adults to reach prophylactic heparinemia.

Key words: Antifactor-Xa activity; Dose; Heparinemia; Low-molecular-weight heparin.

Sepsis, the systemic inflammatory response to infection, is one of the leading causes of death in human intensive care unit patients[1] and newborn foals.[2] Humans with severe sepsis can have coagulation abnormalities consistent with disseminated intravascular coagulation (DIC),[3–5] which is a major factor influencing mortality in septic human neonates.[3,6] There is clinical evidence in septic human neonates of an association between DIC and renal failure.[7] Furthermore, humans with DIC have histopathologic changes consistent with necrosis and intravascular thrombi in vessels of various organs due to fibrin deposition.[8] Although there is controversy among authors, some have proposed that DIC and consequent fibrin deposition contribute to organ failure.[9,10]

The relationship between septicemia and coagulopathy consistent with thrombotic events and DIC also has been detected and studied in critical equine neonate patients.

Abbreviations:

ADP	adenosine diphosphate
ADP-CT	adenosine diphosphate closure time
aPTT	activated partial thromboplastin time
AT	antithrombin
CT	closure time
DIC	disseminated intravascular coagulation
LMWH	low-molecular-weight heparin
PT	prothrombin time

Septicemia is an important disease and the most common cause of death in neonate foals.[11] The incidence of coagulopathies consistent with DIC in septic foals is up to 50% and it is associated with poor outcome.[12,13] Moreover, massive fibrin deposition and microthrombosis in capillaries of the main organs, such as lung, kidney, and liver, have been observed in most septic foals that died or were euthanized because of poor prognosis in a single study population,[14] and this massive fibrin deposition might be associated with the multiorgan failure syndrome according to similar results in other articles.[15,16]

In recent years, low-molecular-weight heparins (LMWHs) have become one of the anticoagulant drugs used in human pediatric patients, both for primary thromboprophylaxis and the treatment of thromboembolí.[17–19] In horses, heparin therapy has been recommended to treat the hypercoagulable state and DIC associated with severe gastrointestinal tract diseases and endotoxemia in adults, and septicemia in newborn foals.[20–22] Other thrombotic events such as venous thrombosis and thrombophlebitis have been also treated with heparin.[20,21,23] Moreover, it has been observed that LMWH therapy reduces fibrin deposition in capillaries of horses with severe inflammatory gastrointestinal tract disease.[24]

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Human neonates require higher doses of LMWH compared with older children and adults to reach adequate prophylactic concentrations.[19,25] Prophylactic concentrations are those that prevent thromboembolic disease in at-risk patients. LMWH therapy should reach a range of 0.1–0.3 IU/mL antifactor-Xa activity for prophylactic purposes in humans.[26,27] A pharmacokinetic study on LMWH in horses demonstrated that their pharmacokinetic and anticoagulant properties are similar to those in people.[28] A dose of 50 IU/kg of LMWH (dalteparin) in adult horses can be adequate for prophylactic purposes.[29] Pharmacokinetics of LMWH in equine neonates and the dosage needed to reach the prophylactic levels of plasma antifactor-Xa activity have not been determined.

Similar to human neonates, equine neonates have some coagulation system peculiarities that might have influenced LMWH pharmacokinetics. Based on human pediatric studies, the dose of LMWH for newborn foals might need to be doubled compared with the dose recommended for adult horses. Thus, the main objective of the present study was to compare 2 different doses of LMWH (the one recommended in adult horses and a double dose) in a population of healthy neonatal foals, in order to assess which of these 2 doses reached prophylactic levels of plasma antifactor-Xa activity. A 2nd objective was to assess whether hemorrhagic risks and erythrocyte-related complications were detected in neonates when the prophylactic dose of LMWH was reached. Finally, plasma antifactor-Xa activity also was determined in a group of septic neonate foals receiving LMWH, in order to assess whether the activity was affected by sickness.

Materials and Methods

Animals

In the experimental study, 18 Andalusian healthy newborn foals from a farm nearby the Equine Teaching Hospital of Barcelona were used, with the owner's informed consent. Foals were determined to be healthy based on clinical history, complete physical examination, and results of additional tests that included measurements of serum IgG concentration, hematology, fibrinogen concentration, and sepsis score. Foals did not receive any medication before or during the study except for LMWH.

Additionally, in the prospective clinical study, those septic neonate foals hospitalized at the Equine Teaching Hospital of Barcelona between February and June 2009, from which their owners' consent was obtained, were enrolled. The diagnosis of sepsis was confirmed by either a positive blood culture, confirmed septic polyarthritis, sepsis score $\geq$14,[30] or postmortem confirmation.

Experimental Study Design

Healthy foals were randomly assigned to 2 groups. One group received the same dose of LMWH as adults (50 IU/kg of dalteparin[a]) once daily, for 3 days; whereas the 2nd group received a double dose of 100 IU/kg of dalteparin once daily, for 3 days. All injections were given SC in the scapular region.

Blood samples were drawn before starting on LMWH (T-0), 3 and 6 hours after the 1st treatment (T-3 and T-6), and 3 hours after the following daily treatments (T-27 and T-51). Samples were collected from the jugular vein into 3 vacuum-evacuated tubes,[b] 1 containing K_3EDTA and 2 citrated (1 : 9, citrate : blood), and immediately refrigerated in a portable refrigerator and processed within 2 hours after sampling. Blood samples collected in EDTA were used for hematologic determinations. One citrated blood tube was centrifuged for 15 minutes at 1,000 $\times$ *g*, and plasma was removed and frozen at -20°C within 2 hours in several aliquots until analyzed for hemostatic variables. The 2nd citrated blood sample was used for assessment of platelet function by determination of closure time (CT) within 3 hours of sampling.

PCV was measured by the microhematocrit method. Hemoglobin concentration and platelet count were determined with a semiautomatic cell counter.[c] Assessment of erythrocyte agglutination was performed by microscopic examination of blood (5 μL) diluted with saline solution (5 drops), as described elsewhere.[29,31,32] Agglutination was then graded (grade 0–3) as previously used[29] (grade 0 = no agglutination, grade 1 = mild erythrocyte agglutination, grade 2 = moderate agglutination, and grade 3 = severe agglutination).

Activated partial thromboplastin time (aPTT) and prothrombin time (PT) were determined in duplicate, with a semiautomatic coagulometer[d] and coagulometric kits,[d] as reported previously.[12]

Platelet function inhibition was assessed with a platelet function analyzer (PFA-100)[e] and the determination of the CT with adenosine diphosphate (ADP) as the platelet agonist (adenosine diphosphate-closure time [ADP-CT]). The system has been described in detail elsewhere[33,34] and used previously in horses.[35] ADP-CT was determined before treatment (T-0) and 3 hours after daily treatment of the 1st and 3rd day (T-3 and T-51, respectively). Finally, heparin concentration in plasma was measured using the antifactor-Xa activity assay[d] by a colorimetric method in a semiautomatic analyzer.[f]

Clinical Study Design

Once the experimental study was finished and analyzed, a clinical study was designed in order to assess whether plasma antifactor-Xa activity achieved in healthy neonates after LMWH therapy was similar to that achieved in sick neonates. Therefore, a double blind, randomized, prospective study was designed. The investigator performing randomization did not have any information of the sick foals, and coded syringes were given to senior clinicians as soon as an eligible septic foal was hospitalized.

After diagnosis and initial therapy, septic foals were randomly assigned to 2 groups. With the information about antifactor-Xa activity of the experimental study, a decision was made to not assess the 50 IU/kg dose in septic foals. Therefore, 1 group received 100 IU/kg of LMWH (dalteparin) and the other received placebo (saline at the same volume). Placebo was included to compare potential adverse effects with the LMWH group and to confirm the lack of antifactor-Xa activity in nontreated foals. Both treatments were administered SC daily, for 3 days, and foals were daily monitored for assessing any adverse effect associated with LMWH therapy. Foals whose LMWH treatment could not be finished (due to euthanasia performed before finishing the treatment period) or did not have a confirmed diagnosis of sepsis were excluded.

Blood samples were drawn through the jugular catheter, and placed in citrated tubes. They were collected just before treatment (T-0) and 3 hours after each daily treatment (T-3, T-27, and T-51, respectively). Samples were processed identically as samples in the experimental study. In this case plasma antifactor-Xa activity was measured after the same technique as in the experimental study, and clotting times, antithrombin (AT) activity and D-Dimer concentration were additionally determined by techniques described previously.[12]

Statistical Analysis

Commercial software (SPSS, 15.0 version)[g] was used for all the statistical analyses. In the experimental study, a longitudinal

Table 1. Hematological and coagulation variables in healthy foals (n = 18) treated with the adult-dose (50 IU/kg) and the doubled dose (100 IU/kg), just before initiating LMWH treatment, at 3 and 6 hours after the 1st treatment, and at 3 hours after treatment on the 2nd and 3rd day (27 and 51 hours).

Variables	Before Therapy	3 Hours	6 Hours	27 Hours	51 Hours
PCV (%)					
50 IU/kg	36.0 ± 3.1	34.6 ± 3.9	33.5 ± 3.6#	34.5 ± 3.3	33.4 ± 3.0#
100 IU/kg	36.3 ± 5.7	33.9 ± 5.1#	36.5 ± 6.0	36.1 ± 7.0	35.0 ± 5.0#
Hemoglobin (g/dL)					
50 IU/kg	13.7 ± 1.3	12.9 ± 1.4	13.0 ± 1.2	12.6 ± 1.2#	12.5 ± 1.1#
100 IU/kg	13.5 ± 2.9	12.9 ± 2.1	13.3 ± 1.9	12.9 ± 2.0#	12.9 ± 2.0#
Platelet count ($x10^3/\mu L$)					
50 IU/kg	243.7 ± 101.0	224.1 ± 64.6	223.6 ± 28.3	227.6 ± 78.5	217.2 ± 61.1
100 IU/kg	248.7 ± 130.2	219.0 ± 100.5	207.5 ± 104.8	238.0 ± 134.4	234.9 ± 142.2
aPTT (s)					
50 IU/kg	51.0 ± 8.4	57.5 ± 16.8	53.5 ± 8.1	52.9 ± 7.3	50.4 ± 8.5
100 IU/kg	53.0 ± 9.4	57.0 ± 8.4	55.7 ± 6.1	52.1 ± 5.4	52.6 ± 3.9
PT (s)					
50 IU/kg	12.6 ± 1.0	13.1 ± 1.7	13.1 ± 1.4#	12.6 ± 1.0	12.4 ± 0.7
100 IU/kg	13.8 ± 1.7	13.7 ± 1.6	13.8 ± 1.3	13.1 ± 0.7	13.2 ± 0.9*
ADP-CT (s)					
50 IU/kg	69.4 ± 12.7	76.5 ± 15.9	—	—	70.1 ± 19.8
100 IU/kg	66.2 ± 18.5	75.2 ± 21.6	—	—	94.7 ± 73.3
Antifactor-Xa (IU/mL)					
50 IU/kg	0 ± 0	0.012 ± 0.027	0.002 ± 0.005	0.007 ± 0.021	0.024 ± 0.023#
100 IU/kg	0 ± 0	0.126 ± 0.063*#	0.099 ± 0.047*#	0.132 ± 0.063*#	0.121 ± 0.096*#

Results are presented as mean ± SD.
*Significantly different from the 50 IU/kg group at the same sample time.
#Significantly different from baseline (before treatment).

General Linear Model that considered the intraindividual variability for the levels of studied parameters was used to evaluate the differences between treatment groups at each sample time for all the hematological and hemostatic variables assessed. An unstructured working matrix for the estimation of foals' intravariability was used.

Results were expressed as estimated means and their standard deviation (SD) for each time of follow-up and, only for description purposes, the median also was used in the text. In the clinical study, a Wilcoxon test for paired measures was used to compare differences of plasma antifactor-Xa activity and hemostatic parameters before and after treatment. For the clinical study, results were expressed as median and interquartile range. For statistical significance, a type I error was set at 0.05 (2-tailed) for all analyses.

Results

Experimental Study

Eight healthy foals were included in the adult dose group (50 IU/kg), whereas 10 healthy foals were enrolled in the double dose group (100 IU/kg). In the 50 IU/kg group, 6 foals were males and 2 were females. Their mean ± SD age was 5.5 ± 5.5 days (median, 4 days). In the 100 IU/kg group, there were 7 females and 3 males. Their mean ± SD age was 6.9 ± 7.0 days (median, 3.5 days).

Only the high-dose group (100 IU/kg) achieved plasma heparin concentrations above 0.1 IU/mL (measured by antifactor-Xa activity) (Table 1 and Fig 1). Antifactor-Xa activity in the high-dose group (100 IU/kg) increased significantly ($P < .001$) compared with baseline (T-0) at all time points; whereas in the adult dose group (50 IU/kg) it increased significantly ($P < .005$) only at T-51, but did not reach the minimum prophylactic antifactor-Xa activity (0.1 IU/mL)[26,27] during treatment. Mean antifactor-Xa activities in the high-dose group (100 IU/kg) were

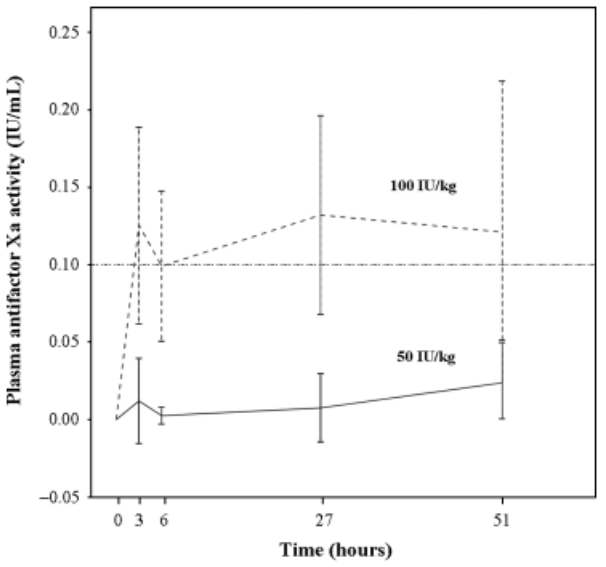

Fig 1. Plasma antifactor-Xa activities for doses of low-molecular-weight heparin (LMWH) of 50 and 100 IU/kg in the experimental study (n = 18) at each sampling time: just before initiating LMWH therapy (0 hours), 3, and 6 hours after the 1st treatment, and 3 hours after daily treatment for the next 2 days (27 and 51 hours). Horizontal dashed line indicates minimum prophylactic antifactor-Xa activity. Results are presented as mean and standard deviation.

Table 2. Plasma antifactor-Xa activity, clotting times (aPTT and PT), D-Dimer concentration, and antithrombin activity (AT) in septic foals treated with the dose of 100 IU/kg dalteparin (n = 6) or placebo (n = 5), just before initiating therapy and at 3 hours after treatment during 3 days (3, 27, and 51 hours).

Variables	Before Therapy	3 Hours	27 Hours	51 Hours
Antifactor-Xa (IU/mL)				
Placebo	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
100 IU/kg	0 (0–0)	0.07 (0.03–0.24)[#]	0.08 (0.02–0.17)	0.1 (0.02–0.21)
aPTT (s)				
Placebo	84.8 (75.4–95.1)	87.1 (67.9–111.1)	78.7 (60.2–87.6)	64.4 (55.8–95.5)
100 IU/kg	59.0 (57.6–102.5)	68.4 (55.6–93.8)	74.8 (54.6–93.1)	64.5 (52.3–85.5)
PT (s)				
Placebo	15.4 (13.0–17.0)	20.0 (15.2–23.0)	15.8 (14.5–18.5)	14.0 (13.5–19.1)
100 IU/kg	15.3 (12.0–19.0)	17.8 (12.1–25.9)[#]	16.4 (13.0–21.5)	14.1 (12.6–18.8)
D-Dimer (ng/mL)				
Placebo	278 (255–426)	432 (209–1462)	603 (396–3720)	1722 (557–4015)
100 IU/kg	474 (300–1583)	341 (312–2519)	564 (314–1499)	922 (361–1707)
AT (%)				
Placebo	134 (118–151)	138 (116–155)	157 (140.5–181)	168 (147–182)
100 IU/kg	154 (117.5–205.5)	159 (118–191)	168 (108.5–185.5)	169 (105.5–189)

Results are presented as median, interquartile range.
[#]Significantly different from baseline (before treatment).

significantly higher ($P < .001$) when compared with those in the 50 IU/kg group at all sampling times during treatment. Although mean values of the high-dose group (100 IU/kg) were above the minimum prophylactic antifactor-Xa activity (0.1 IU/mL), some individuals did not reach this minimum value during treatment.

Sixty-eight out of 72 samples from both groups had absent or mild red cell agglutination. Only 3 samples of the adult dose group (50 IU/kg) and 1 sample of the high-dose group (100 IU/kg) showed an agglutination grade higher than 1. No relationship between this mild agglutination and the dosage of heparin administered was detected.

PCV decreased mildly but significantly ($P < .05$) in both treatment groups when compared with those values before treatment (T-0), although values always stayed within reference range (Table 1). Hemoglobin concentration also decreased mildly but significantly at T-27 and T-51 in both groups compared with baseline samples. No differences were observed for platelet count, aPTT and ADP-CT (Table 1). Statistical differences were observed for PT during treatment, although values remained within normal limits. No other variations were detected.

None of the foals showed swelling at the injection site. Only foal #15 (belonging to the high-dose group) had signs of either jugular hematoma or phlebitis from the 1st sampling because of difficulties in this foal's management and subsequent repeated sampling. No other adverse effects related to treatment or sample collection were detected in any foal.

Clinical Study

Eleven septic foals were finally enrolled in the prospective study, of which 5 foals received placebo (saline) and 6 foals received heparin therapy. Four other foals were excluded because the initial clinical diagnosis of sepsis was not confirmed, and another 4 septic foals were also excluded because they died or were euthanized before finishing the treatment period. Foals receiving placebo were 3 males and 2 females, with a mean ± SD age of 0.7 ± 0.4 days (median, 1 day). They were 3 Andalusians, 1 Lusitanian, and 1 Arabian. Foals receiving LMWH were 4 males and 2 females, with a mean ± SD age of 6.7 ± 6.8 days (median, 4.5 days). They were 2 Andalusians, 2 Arabians, and 2 Warmblood foals.

No adverse effects associated with LMWH therapy were observed in these foals. Antifactor-Xa activity was always absent at all sampling times in the placebo group, whereas it increased significantly ($P < .05$) at T-3 compared with baseline in the LMWH group (Table 2). Median activities at T-27 and T-51 did not reach statistically differences compared with baseline.

Discussion

In the present study, healthy neonate foals required double dose of LMWH (100 IU/kg of dalteparin) of adult horses to reach the same prophylactic plasma antifactor-Xa activity. Septic foals in the LMWH group reached prophylactic plasma antifactor-Xa activity, and some foals did not reach prophylactic activities at all the sample times. Therefore, results of this study demonstrate that newborn foals require higher doses of LMWH than do adults for thromboprophylaxis; however, the final recommended dose for septic foals remains to be determined.

LMWHs are known to cause fewer hemostatic alterations and bleeding risks than unfractioned heparins in humans.[19,36] LMWH did not cause thrombocytopenia or inhibit platelet function in foals in the present experimental study. Moreover, LMWH did not cause prolongation of clotting times in foals in both experimental and clinical studies, even at the dose of 100 IU/kg, which is in agreement with other studies where LMWH at a regular adult dose did not affect platelet count,

clotting times, and template bleeding time.[29,37,38] Thus, no increased risk of bleeding was associated with LMWH at the higher dose used in this study. Other studies in adult horses also demonstrated that LMWH has little or no effect on PCV, erythrocyte count, and hemoglobin concentration of treated horses.[22,29] The mild decrease observed in PCV and hemoglobin concentration compared with baseline values in the present study was statistically significant but clinically irrelevant, since none-to-mild erythrocyte agglutination was observed. A higher number of foals might help to determine whether this decrease was related to LMWH or due to familiarization of the foals to repeated sampling.

None of the foals of this study showed any complication or adverse effect related to treatment when giving LMWH at 100 IU/kg, except 1 foal in the experimental study that had mild signs of either jugular hematoma or phlebitis due to difficulties in that foal's management and repeated sampling. Difficult management was considered the main cause of the mild jugular complication seen, because it was already observed immediately after the 1st sampling and before LMWH treatment.

This study had some limitations. Originally, the experimental study was designed as a cross-over design, in which each foal would have received both doses of LMWH (50 and 100 IU/kg) during their neonatal period (<21 days) in a randomized fashion. Eventually, this design could not be followed mainly because most foals unfortunately were sold or moved to different facilities before finishing the cross-over study, but also because the hemostatic system could have variations associated with age during the neonatal period.[39] This fact could produce some bias on the results when comparing foals at 2 different ages. In this study, differences seen on the hemostatic tests could be caused by either age or treatment, and both effects would have been indistinguishable. One possibility to reduce the bias related with age could be to treat all foals at 2 fixed ages. However, movements of animals out of the study made it impossible.

In the clinical study, the actual age difference between placebo and LMWH treated septic foals due to random allocation is worth noting. The small number of cases made unpractical the subclassification of the foals according to age. Therefore, the physiologic hemostatic differences that foals of different ages had might slightly affect the results reported.

Another limitation could be related to the sampling times chosen. The possibility that peak plasma antifactor-Xa activities occurred before or after sampling time (3 and 6 hours after LMWH administration) cannot be ruled out, and the possibility that the 100 IU/kg group reached prophylactic activities before or after sampling exists. However, sampling design was decided using information from previous studies, in which peak plasma activity was measured between 2 and 6 hours.[17] Thus, although not impossible, it seems certainly improbable that significantly higher antifactor-Xa activities would have been missed in the present study.

Finally, in the clinical study plasma antifactor-Xa activity increased in the LMWH group during treatment. However, because of the low number of septic foals recruited and the variability of antifactor-Xa activity seen in some neonates, the results only were statistically significant at T-3 (3 hours) compared with baseline. Most of the variability seen in the LMWH group was mainly because of 1 foal that never reached prophylactic antifactor-Xa activity. Interestingly, this foal had the lowest AT activity at all time points, which was probably the cause of its low antifactor-Xa activity and subsequently contributed to the variability seen. Moreover, clinical signs such as epistaxis and multiple petechiae, clinicopathological results and postmortem findings such as multiple petechiae and echymosis in different organs, and different thrombi confirmed a severe DIC status in that foal. Regarding the hemostatic profile in the clinical study, no relevant differences were detected comparing baseline values and treatment values. Hemostatic profile of these septic animals showed similar alterations to those reported previously.[11–13] A prospective randomized clinical study with a larger group of animals is warranted in order to confirm tendencies seen in this preliminary clinical trial, as well as to assess the effect of heparin therapy on outcome.

In conclusion, newborn foals need higher doses of LMWH than adult horses in order to reach the plasma antifactor-Xa activity level of LMWH recommended for thromboprophylactic therapy. Its administration at a dose of 100 IU/kg in foals is safe and did not produce bleeding risks, thrombocytopenia or erythrocyte agglutination. Further studies are warranted to determine the recommended dose for thromboprophylaxis in septic foals.

Footnotes

[a] Fragmin, Kabi Pharmacia AB, Stockholm, Sweden
[b] Venoject, Terumo Europe, Leuven, Belgium
[c] Advia 120 Analyzer, Bayer Lab, New York, NY
[d] Stago ST4, Stago Diagnostics, Asnières-Sur-Seine, France
[e] PFA-100 System, Siemens Healthcare Diagnostics, Deerfield, IL
[f] Olympus AU400, Olympus Diagnostics, Hamburg, Germany
[g] SPSS Inc, Chicago, IL

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