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ORIGINAL STUDY

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Effect of 7.5% hypertonic saline solution on whole blood coagulation in healthy dogs using thromboelastography

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Abstract

Objective: To evaluate the effects of 7.5% hypertonic saline solution (HSS) on whole blood coagulation in healthy dogs and to compare electrolyte and osmolality measurements between in vivo and in vitro dilution with HSS.

Design: Experimental study.

Setting: University teaching hospital.

Animals: Twelve adult purpose-bred Beagles.

Interventions: All 12 dogs received 5 mL/kg 7.5% HSS at 1 mL/kg/min. After a 14-day washout period, 5 of these dogs were randomly selected and received the same volume of 0.9% NaCl. Blood samples were collected before infusion, immediately after infusion, and at 30, 60, and 90 minutes after infusion for the measurement of coagulation using thromboelastography. For comparison of electrolyte concentrations and osmolality between in vitro dilution and in vivo dilution of HSS, 6-mL blood samples were diluted with 7.5% HSS (1:18 ratio) at baseline.

Measurements and Main Results: None of the thromboelastography variables differed significantly between the 7.5% HSS group and the 0.9% NaCl group. The sodium and chloride levels, and the osmolality, were significantly increased at all postinfusion time points compared to baseline, while those levels were significantly higher with in vitro dilution than all postinfusion time points. However, almost all the values gradually decreased and became similar to baseline values in case of in vivo dilution.

Conclusions: The clinically relevant dose of 7.5% HSS (5 mL/kg) did not affect whole blood coagulation significantly in healthy Beagles. Further studies are necessary to assess the effect of HSS on blood coagulation in canine patients with shock.

KEYWORDS
canine, hypertonic saline, hypocoagulation, osmolality, platelet, thromboelastography

1 | INTRODUCTION

Among crystalloid solutions, hypertonic saline solution (HSS) has the unique ability to provide immediate intravascular volume expansion along osmotic gradients from intracellular and interstitial to intravascular compartments.[1,2] Intravenous administration of a small dose (2.5–5.0 mL/kg body weight) of HSS has been advocated as the first-line resuscitation option for both human and canine patients with hemorrhagic shock or severe hypovolemia.[1-3]

The ideal resuscitative fluid for hypovolemic patients should have the capacity to expand intravascular volume, improve and sustain mean arterial pressure and cardiac output, be able to be administered

Abbreviations: CI, confidence interval; HSS, hypertonic saline solution; MA, maximum amplitude; TEG, thromboelastography.

rapidly, and it should be associated with few or no complications.[2] Many studies have confirmed the volume-expanding ability and cardiovascular effects of HSS.[3-5] Although most of these conditions were experimentally induced, the contexts in which the effects of HSS have been studied in veterinary medicine include hemorrhagic shock, trauma, brain injury, and acute pancreatitis.[6-12] Adverse effects associated with HSS have been reported, however, including hypocoagulable effects and electrolyte and osmolality imbalances.[13-16] Several human in vitro studies have shown that HSS impairs whole blood coagulation and platelet function,[14,15] and diluting blood with HSS reportedly results in hypocoagulability and platelet dysfunction in dogs.[17,18]

Thromboelastography (TEG) is a useful method for assessing clot formation and fibrinolysis[19] and has been used widely in human and veterinary medicine. Many studies in people have used TEG for evaluating hemostatic status in trauma patients, and it has been suggested that the method would be more efficient for the rapid diagnosis of coagulopathy and predicting the need for transfusion than conventional coagulation tests including prothrombin time and activated partial thromboplastin time.[20-22]

Despite several in vitro studies, to the authors' knowledge, no published studies have evaluated the in vivo effect of 7.5% HSS on coagulation in dogs. The aim of the current study was to evaluate the in vivo effects of 7.5% HSS on whole blood coagulation in healthy Beagles using TEG, and to compare electrolyte concentrations and osmolality between in vivo and in vitro HSS dilution. The authors hypothesized that the resuscitation dose of HSS (5 mL/kg) would have minimal impact on blood coagulation in vivo.

2 | MATERIALS AND METHODS

2.1 | Animals

Twelve healthy adult Beagles (8 males, 4 females), ranging in age from 20 to 48 months and weighing 7.8 to 15.0 kg (median 10.2 kg), were included in the study. For inclusion in the study, dogs were considered healthy based on complete history, physical examination, CBC, serum biochemistry profile, prothrombin time, activated partial thromboplastin time, fibrinogen concentration, and D-dimer concentration. Dogs did not have any history of anesthesia or recent illness, and had not been administered any types of fluids, including synthetic colloids and blood products, or any drugs, including steroids, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, or anticoagulants during the 3 months prior to the study. The study was conducted in accordance with the Guidelines for the Care and Use of Laboratory Animals and was approved by the Experimental Animal Committee of Chungnam National University (approved no. CNU-00628).

2.2 | Experimental design

Twelve purpose-bred Beagles were used for the study. All 12 dogs were included in the treatment group, and 5 of these dogs were subsequently randomly selected and included in the control group (1 male, 4 females).

Each dog in the treatment group was administered 5 mL/kg 7.5% HSS via a 20-Ga over-the-needle catheter* in the cephalic vein at 1 mL/kg/min. After a 2-week washout period, dogs in the control group received 0.9% NaCl,† corresponding to the volume of HSS, and at the same speed. The experimental solution was 7.5% HSS, which was generated by combining 25 parts 11.7% hypertonic saline‡ and 14 parts distilled water§ and filtering this solution directly through a 0.2-μm nylon sterile syringe filter** just prior to infusion.

To compare the effects of in vivo and in vitro dilution of HSS on electrolytes and osmolality, whole blood was diluted with HSS; 1 part 7.5% HSS and 18 parts of whole blood, which matched the in vivo dilution following resuscitation volume using 5 mL/kg of fluids based on an assumed blood volume of 90 mL/kg in adult dogs.[23]

Prior to each experiment, the dogs were fasted for 12 hours but allowed access to water ad libitum. The dogs' vital signs were continuously monitored throughout the experimental period, as were their mental status, signs of active bleeding, and clinical signs of hypernatremia such as restlessness, nausea, vomiting, lethargy, as well as confusion, coma, seizures, muscle weakness, and myoclonus. The IV catheter was removed at the end of the experiment.

2.3 | Sample collection

Blood samples were drawn via jugular venipuncture atraumatically using a 20-Ga butterfly needle with extension†† before the infusion (baseline), immediately after infusion, and 30, 60, and 90 minutes after the start of the infusion. Blood samples for TEG analysis were collected into vacutainer tubes containing 3.2% buffered sodium citrate‡‡ with a final concentration of 1 part citrate to 9 parts whole blood, which were kept at room temperature for 30 minutes. For electrolyte and osmolality analyses, 6 dogs (3 males, 3 females) were randomly selected from the treatment group, and their blood samples were collected into plain tubes§§ at all postinfusion time points. For in vitro measurement of electrolyte concentrations and osmolality, the blood samples for baseline in vivo TEG were diluted and mixed gently to achieve a blood to HSS ratio of 18:1.

2.4 | Thromboelastography analysis

Kaolin-activated TEG analysis was performed using a TEG commercial analyzer.*** First, 1 mL of citrated whole blood was activated with kaolin by transferring it into a kaolin-coated vial.††† Then, 20 μL of calcium chloride and 340 μL of the kaolin and blood sample mixture were placed into a TEG cup.‡‡‡ From the TEG tracing, reaction time (R), clotting time (K), alpha angle (α), maximum amplitude (MA), and global clot strength (G) were measured. The TEG results were compared with the reference interval derived from 40 healthy Beagles.

2.5 | Electrolyte and osmolality

Analyses of serum sodium, potassium, and chloride were performed via a commercial electrolyte analyzer§§§ using an ion-selective electrode method. Serum osmolality was determined via an osmometer**** using

TABLE 1 TEG variables at baseline and 4 time points in healthy Beagles administered 7.5% HSS (n = 12) and 0.9% normal saline (n = 5)

Variables	Fluid type	Baseline	Immediately after infusion	30 min	60 min	90 min
R (min)	7.5% HSS	4.11 ± 0.66	4.23 ± 0.97	4.06 ± 0.95	4.47 ± 0.91	4.18 ± 1.05
	0.9% NaCl	4.16 ± 0.42	4.48 ± 0.61	4.46 ± 0.70	4.18 ± 0.45	4.38 ± 1.24
K (min)	7.5% HSS	1.67 ± 0.29	2.08 ± 0.67	1.64 ± 0.37	1.6 ± 0.32	1.52 ± 0.23
	0.9% NaCl	1.54 ± 0.47	1.54 ± 0.22	1.56 ± 0.30	1.44 ± 0.23	1.34 ± 0.18
α (deg)	7.5% HSS	66.48 ± 3.79	63.78 ± 6.1	66.42 ± 4.63	66.66 ± 5.37	67.53 ± 3.22
	0.9% NaCl	68.04 ± 5.93	70.24 ± 4.21	66.5 ± 4.66	68.72 ± 3.27	70.52 ± 3.59
MA (mm)	7.5% HSS	60.89 ± 4.02	56.96 ± 5.62	61.55 ± 3.61	60.40 ± 4.24	60.69 ± 5.09
	0.9% NaCl	64.84 ± 5.29	62.62 ± 6.40	63.74 ± 3.19	63.46 ± 4.85	64.26 ± 4.47
G (Kdyn/cm^2)	7.5% HSS	7.91 ± 1.31	6.80 ± 1.52	8.11 ± 1.28	7.75 ± 1.30	7.91 ± 1.67
	0.9% NaCl	9.48 ± 2.13	8.92 ± 1.95	8.88 ± 1.31	8.89 ± 1.93	9.15 ± 1.70

freezing point depression. All analyses were performed within 2 hours of blood collection.

2.6 | Statistical methods

All variables were analyzed using SPSS for Windows version 22.0.[††††] Repeated measures ANOVA was performed on the TEG data from the treatment group that received 7.5% HSS and the control group. Cohen's f^2 effect size for each TEG variable signified approximately medium or large effect sizes, according to Cohen's guidelines; the values for R, K, α, MA, and G were 0.101, 0.495, 0.417, 0.563, and 0.579, respectively.[24] The Shapiro–Wilk test was performed to verify normal data distributions NaN.[‡‡‡‡] The predetermined significance level was P <0.01, which was corrected using Bonferroni correction to control for type-I error.

To compare electrolytes and osmolality at baseline and specific time points, repeated measures ANOVA was employed, and the P-value deemed to indicate statistical significance was <0.013, which was adjusted via Bonferroni correction. Paired t-test was used for comparison of electrolytes and osmolality at specific time points and with the 1:18 in vitro dilution ($P < 0.05$). All data are reported as mean ± SD.

3 | RESULTS

Table 1 presents the TEG variables at baseline and the 4 time points in the treatment group (administered 7.5% HSS) and control group (administered 0.9% NaCl). There were no significant differences in any of the TEG variables between the treatment group and the control group at any time point (Figure 1). Electrolytes and osmolality values at baseline, the 4 time points after the administration of HSS, and 1:18 in vitro dilution with HSS, which were provided for the 6 randomly selected dogs in the treatment group, are shown in Table 2. Sodium and chloride levels at all the postinfusion time points were significantly higher than those at baseline ($P < 0.013$). Potassium levels decreased immediately after 7.5% HSS infusion but had almost returned to baseline levels after 30 minutes. Osmolality was significantly increased at all postinfusion time points compared with baseline ($P < 0.013$). The sodium and chloride concentrations and osmolality were significantly higher in case of in vitro dilution than for in vivo dilution at each postinfusion time point ($P < 0.05$). Potassium levels after the 30-minute time point were significantly higher than those of the 1:18 in vitro dilution ($P < 0.05$).

4 | DISCUSSION

In the current study, the effect of 7.5% HSS on whole blood coagulation in healthy Beagles was compared to those of 0.9% NaCl using TEG. None of the TEG parameters were significantly influenced by IV injection of 7.5% HSS. Several human and canine in vitro studies have reported that HSS affects blood coagulation.[14,15,17] When human plasma was diluted with HSS, activated partial thromboplastin time was prolonged at 5% volume replacement, and prothrombin time was extended and platelet aggregation impaired at 10% volume replacement.[14] Another human in vitro study showed that R was increased and α was decreased when 7.5% of whole blood volume was replaced with HSS.[15] In canine blood samples diluted 1:22 with 7.2% HSS, which is approximately equivalent to 4 mL/kg infusion, closure time measured via a platelet function analyzer was prolonged.[17] An in vitro study using human blood samples revealed that calcium signaling in platelet was attenuated by HSS. Consequently, platelet aggregation was impaired and platelet death resulted from membrane scrambling, triggering osmotic shock.[25] Based on the discrepancy between the results derived from the previous in vitro studies and the present in vivo study, the authors hypothesize that hyperosmolality resulting from administration of HSS has possibly less impact on clotting factors, including platelets, through unknown in vivo mechanisms.

The concentrations of both sodium and chloride, and also the osmolality, reached a peak at a time point immediately after the administration of 7.5% HSS in the current study; the levels decreased as time passed. These findings are similar to those of previous canine studies with healthy Beagles or Beagles with hemorrhagic shock.[6,16] Although the electrolyte concentrations, except for potassium, and

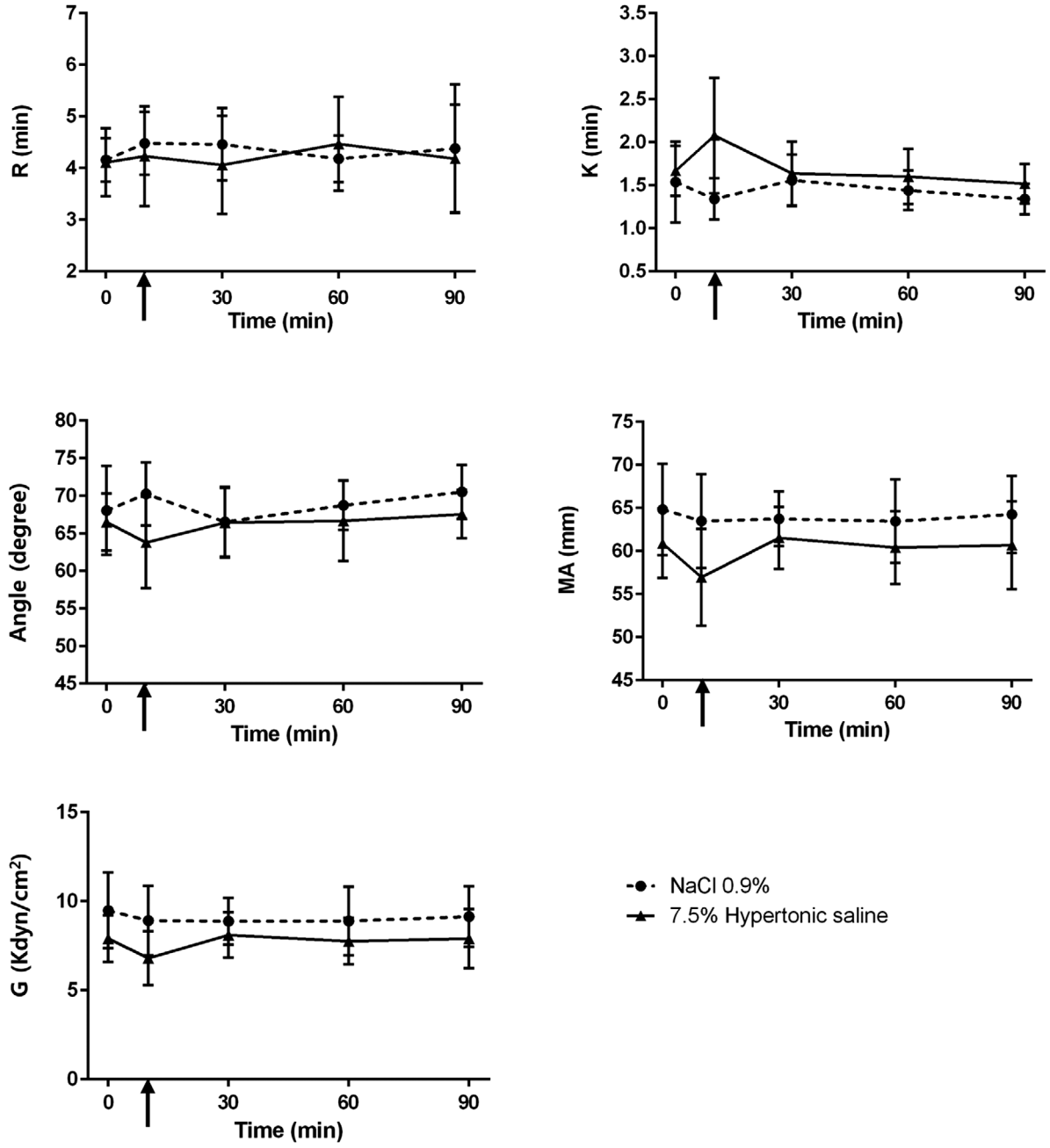

FIGURE 1 Comparison of thromboelastography variables in healthy Beagles before and after the administration of 5 mL/kg 7.5% HSS or 0.9% NaCl, where "↑" indicates the time point just after administration. There were no significant differences between the 2 groups at any time point. All values are reported as mean ± SD. R, reaction time; K, clotting time; α, angle; MA, maximum amplitude; G, global clot strength

osmolality values were significantly higher at all time points than those at baseline in case of in vivo dilution, the values were significantly lower than those associated with in vitro dilution (Table 2); the sodium load and hyperosmolality induced by HSS were likely compensated in vivo. The coagulation process is complex, composed of various factors that include anticoagulants, procoagulants, platelets, endothelium factors, and fibrinolysis.[26] In vitro coagulation might not reflect the activity of the endothelium, as well as the buffering system and electrolyte homeostasis; therefore, some differences exist between in vitro and in vivo coagulation.[27,28] Some studies have drawn opposing conclusions regarding the effects of hypertonic saline and mannitol on canine whole blood coagulation in vitro and in vivo.[18,29] Certain mechanisms might be related to coagulation during in vivo dilution with HSS, as they happen in electrolytes and osmolality, but these were not revealed in the current study.

In the present study, 0.9% NaCl was used as the control solution, similar to many previous studies.[1-3,5,15] However, this solution does have some effect on coagulation. Both in vitro and in vivo hemodilution with normal saline can increase the coagulability of whole blood, while the changes depend on the extent of hemodilution.[30,31] Another

TABLE 2 Electrolytes and osmolality results from 6 healthy Beagles administered 7.5% HSS; at baseline, 4 time points after the administration of HSS, and 1:18 in vitro dilution with HSS

	Baseline	Immediately after infusion	30 min	60 min	90 min	In vitro
Sodium (mEq/L)	149.17 ± 1.61	164.08 ± 1.57[a,b]	159.35 ± 1.62[a,b]	157.82 ± 1.41[a,b]	157.30 ± 1.71[a,b]	222.15 ± 4.92
Potassium (mEq/L)	4.25 ± 0.13	3.43 ± 0.09[a]	3.95 ± 0.05[b]	4.02 ± 0.07[b]	3.90 ± 0.09[b]	3.41 ± 0.23
Chloride (mEq/L)	111.85 ± 0.27	127.97 ± 0.74[a,b]	123.28 ± 0.68[a,b]	121.40 ± 0.64[a,b]	120.85 ± 0.42[a,b]	175.93 ± 1.14
Osmolality (mOsm/kg)	310.00 ± 1.75	336.00 ± 2.41[a,b]	330.33 ± 1.93[a,b]	327.33 ± 1.02[a,b]	324.17 ± 1.01[a,b]	451.33 ± 4.33

HSS, hypertonic saline solution.
[a]Significant difference compared with baseline values ($P < 0.013$).
[b]Significant difference compared with in vitro value ($P < 0.05$).
Electrolyte reference intervals are based on the following manufacturer-supplied information: Sodium 145–155; Potassium 2.7–5.0; Chloride 96–122.

human in vitro study has shown that resuscitation fluids, including 0.9% NaCl, affect the time to peak, clot rate, and activated clotting time measured by a platelet function analyzer.[32] While the dose of 0.9% NaCl used in the current study is only 5 mL/kg, the slight tendency (despite no significant differences) toward hypocoagulation in the 7.5% HSS group compared with the 0.9% NaCl group is considered to be possibly due to the hypercoagulability of 0.9% NaCl. The potential impact of 0.9% NaCl on coagulation should be considered for interpretation of the results.

The administration of HSS has the potential to induce several adverse reactions associated with hypernatremia, hypokalemia, and hyperosmolality.[13,16] In the current study, only 2 dogs exhibited nausea while receiving HSS, and it improved immediately as the infusion rate decreased. No other side effects were observed in any of the dogs. The adverse reaction was more likely caused by vagal stimulation due to rapid administration of HSS rather than due to true hypernatremia[13,33]; therefore, they may be avoided or reduced in severity if a small dose of 7.5% HSS is administered slowly under careful monitoring.

TEG provides information on the global viscoelastic properties of blood clot formation.[19] The TEG parameters fall into 2 categories: the R, K, α, MA, and G values provide measures of coagulation, while LY30 and LY60, which are percent lysis at 30 and 60 minutes after MA, respectively, represent fibrinolysis.[34] In the present study, the focus was on evaluating the effect of HSS on coagulation; therefore, the LY30 and LY60 parameters were not examined. Fibrinolytic dysregulation could manifest as reduced or elevated fibrinolysis following trauma; hyperfibrinolysis is predominantly recognized.[35,36] A human in vitro study showed that replacement of 10% of whole blood with HSS decreased LY30.[15] Therefore, measurement of LY30 or LY60 would be useful to identify the impact of HSS on fibrinolysis, particularly in trauma patients.

While TEG is a simple and rapid method, it is not as sensitive as platelet aggregometry or flow cytometry for the assessment of platelet function in human medicine.[37,38] Although only the TEG analysis was performed to evaluate whole blood coagulation in the current study, other techniques may provide useful information pertaining to the effects of HSS on platelet function.

Another limitation is that only 12 healthy Beagles were used in the experiments. The treatment group, administered 7.5% HSS (n = 12), showed some tendency for hypocoagulability compared with the control group, administered 0.9% NaCl (n = 6), but there were no significant differences in any of the TEG variables, which were within or close to the reference ranges. Nonetheless, a larger sample size would provide more reliable results. In addition, the current study did not reflect a shock state associated with an inability to maintain normal homeostasis.[39] Experimental models of hemorrhagic shock could raise ethical issues, even when the study design and implementation has been approved by a relevant ethics committee and all legal and ethical standards are complied with.[40] Other factors, including availability and costs, should also be considered. For these reasons, only a few studies have incorporated experimentally induced hemorrhagic shock in dogs.[6,7] Prospective investigation of the impact of HSS on coagulation in canine patients with hemorrhage is warranted.

In conclusion, the IV administration of 7.5% HSS did not affect whole blood coagulation significantly in healthy Beagles, compared with 0.9% NaCl. Sodium and chloride concentrations and osmolality associated with in vivo dilution were significantly higher at all timepoints compared with baseline values. Further studies are necessary to clarify the effect of HSS on blood coagulation in critically ill canine patients.

ENDNOTES

[*] BD insyte IV catheter, Becton Dickinson, Sandy, UT.
[†] 11.7% hypertonic saline, Daihan Pharm. Co., Seoul, Korea.
[‡] Distilled water, Daihan Pharm. Co., Seoul, Korea.
[§] Daihan Pharm. Co., Seoul, Korea.
[**] ADVANTEC MFS, Inc., Dublin, CA.
[††] Scalp Vein Set, J.M.S.(K) Medical Supply Co., Seoul, Korea.
[‡‡] BD Vacutainer Plus plastic citrate, Becton, Dickinson and Company, Franklin Lakes, NJ.
[§§] BD Vacutainer plain tube, Becton, Dickinson and Company, Franklin Lakes, NJ.
[***] TEG 5000 Thrombelastograph Hemostasis Analyzer System, Haemonetics Corporation, Haemoscope Division, Niles, IL.
[†††] Haemonetics Corporation, Haemoscope Division, Niles, IL.
[‡‡‡] Plain cups and pins, Haemoscope Co., Niles, IL.
[§§§] EasyLyte, Medica Corporation, Bedford, MA.

**** Advanced Model 3300 Micro-Osmometer, Advanced Instruments, Inc., Norwood, MA.

†††† SPSS version 22.0, SPSS, Inc., Chicago, IL.

‡‡‡‡ SAS Online v.9.1.3, SAS Institute, Cary, NC.

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CONFLICT Of INTEREST

The authors declare no conflict of interest.

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