A Pilot Comparison of Limited Versus Large Fluid Volume Resuscitation in Canine Spontaneous Hemoperitoneum

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ABSTRACT

Treatment for hemorrhagic shock secondary to a spontaneous hemoperitoneum includes restoration of IV volume and surgical control of hemorrhage. This study was designed to determine if limited fluid volume resuscitation (LFVR) with hypertonic saline (HS) and hyperoncotic fluids (hydroxyethylstarch [HES]) results in more rapid cardiovascular stabilization in dogs with spontaneous hemoperitoneum versus conventional resuscitation (CR) with large volume resuscitation. Eighteen client-owned dogs presenting in hemorrhagic shock with a spontaneous hemoperitoneum were enrolled. Dogs were randomized to be fluid resuscitated with up to 90 mL/kg of an isotonic crystalloid (CR group) or up to 8 mL/kg of 7.2% Na chloride (i.e., HS) combined with up to 10 mL/kg of 6% HES. Measurements of vital signs, lactate, packed cell volume (PCV), total solids (TS), and blood pressure were made at standard time points. The primary end point was time to stabilization of hemodynamic parameters (measured in min). Dogs in the LFVR group achieved hemodynamic stabilization significantly faster (20 min; range, 10–25 min) than those in the CR group (35 min; range, 15–50 min; $P = .027$). Future studies are warranted to further investigate potential benefits associated with LFVR in dogs with spontaneous hemoperitoneum. (*J Am Anim Hosp Assoc* 2014; 50:■■■–■■■. DOI 10.5326/JAAHA-MS-6085)

Introduction

Hemorrhagic shock secondary to spontaneous hemoperitoneum, defined as spontaneous hemorrhage within the peritoneal cavity without evidence of trauma, is common in dogs evaluated in an emergency room setting. Immediate treatment goals include restoration of IV volume and prompt surgical control of hemorrhage. Conventional resuscitation (CR) with large fluid volumes with isotonic crystalloids based on the replacement of estimated blood volume (90 mL/kg in dogs) has been recommended, although it has been recommended to start with one-quarter to one-third of this calculated volume and reassess the patient before giving more fluids.[1–3]

Disadvantages of CR include long administration time, rapid redistribution to the interstitial space with potential edema formation, hypothermia, and the potential to exacerbate bleeding by dislodging clots and diluting circulating clotting factors.[2,3] Those concerns have given rise to alternative types of fluid resuscitation during active hemorrhage, such as limited fluid volume resuscitation (LFVR).

LFVR is often also referred to as low-volume or small-volume fluid resuscitation. LFVR protocols attempt to use the smallest volume of fluid possible to restore the IV volume and resolve shock, thus minimizing fluid extravasation into the interstitium and the probability of disrupting a forming blood clot.[4,5] Protocols

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CR *conventional resuscitation;* DR *delayed resuscitation;* HES *hydroxyethylstarch;* HR *heart rate;* HS *hypertonic saline;* HSA *hemangiosarcoma;* HypR *hypotensive resuscitation;* LFVR *limited fluid volume resuscitation;* MAP *mean arterial blood pressure;* PCV *packed cell volume;* pRBC *packed red blood cell;* PT/PTT *partial thromboplastin time;* SAP *systolic arterial blood pressure;* TS *total solids*

often include the use of hypertonic saline (HS) and/or colloids. The blood pressure resuscitation endpoint is lower than with CR, and a mean arterial blood pressure (MAP) of 70 mm Hg or a systolic arterial blood pressure (SAP) of 90 mm Hg (i.e., low/normal to maintain perfusion to vital organs) is acceptable until definitive control of hemorrhage is achieved.[4,5] LFVR should not be confused with either hypotensive resuscitation (HypR) or delayed resuscitation (DR). With HypR or DR, the patient is either permitted to remain hypotensive or fluids are withheld, respectively, until bleeding is definitively controlled.[2,6,7] During HypR, the patient is resuscitated to a MAP of no greater than 60 mm Hg until definitive control of hemorrhage is achieved.[2,6,8,9] During DR, on the other hand, no fluids are given until definitive control of hemorrhage can be achieved.[7] Once bleeding is controlled in either situation, aggressive fluid resuscitation is initiated. Multiple studies in animal models of hemorrhagic shock and in people with naturally occurring hemorrhage have compared various fluids and resuscitation strategies. Although results have been inconsistent, many studies have found that the HS/colloid combinations produce better rises in MAP, O_2 saturation, and cardiac output versus isotonic crystalloids.[7,10–29]

The primary objective of this study was to determine safety and efficacy of a LFVR technique compared with a CR technique in dogs with a spontaneous hemoperitoneum. It was the authors' hypothesis that a LFVR technique would achieve faster patient stabilization without compromising either patient safety or outcome compared with a CR technique.

Materials and Methods

Patients

Client-owned dogs that presented to the emergency service at Angell Animal Medical Centerwith hypovolemic shock due to a spontaneous hemoperitoneum were eligible for inclusion. Client consent was obtained for all included dogs. Shock was defined as three or more of the following objective parameters: heart rate (HR) >120 beats/min, respiratory rate (RR) >40 beats/min, body temperature $<37.8°$ C, capillary refill time >2 sec, SAP <90 mm Hg, or lactate >2.5 mmol/L.[2,4,30–35] All dogs had non-clotting blood (packed cell volume [PCV] $>20\%$) detected via abdominocentesis (using a 21 gauge needle). A PCV and total solids (TS) were obtained on the abdominal fluid for each dog. Each dog had a baseline heparinized, whole blood venous blood gas[a], lactate, PCV/TS, prothrombin time/partial thromboplastin time (PT/PTT), complete blood count, and a serum biochemical analysis collected at the time of admission. Coagulopathy was diagnosed on the basis of significant elevations of PT/PTT ($>50\%$ of the high value of the reference range) and/or a platelet count $<40{,}000\times10^9$/L. Dogs were excluded if they were euthanized without treatment, if a primary coagulopathy was present, if they received a packed red blood cell (pRBC) transfusion during stabilization, or died during the initial 1 hr resuscitation period as illustrated in **Figure 1**.

Fluid Resuscitation

Dogs were randomly assigned, via an envelope system, to receive either CR or LFVR. All dogs were triaged immediately to the intensive care unit at the time of presentation. An 18 gauge IV cephalic catheter was placed, and continuous electrocardiographic monitoring commenced. Dogs in the CR group could receive up to 90 mL/kg of crystalloids[b]. Dogs in the LFVR group could receive up to 8 mL/kg HS[c] with up to 10 mL/kg hydroxyethylstarch[d] (HES). All boluses were administered over approximately 5 min, and the patients were then reassessed *q* 5 min for additional crystalloid or hypertonic fluid and/or colloid needs, respectively (**Figure 2**). HR, RR, capillary refill time, and SAP via Doppler

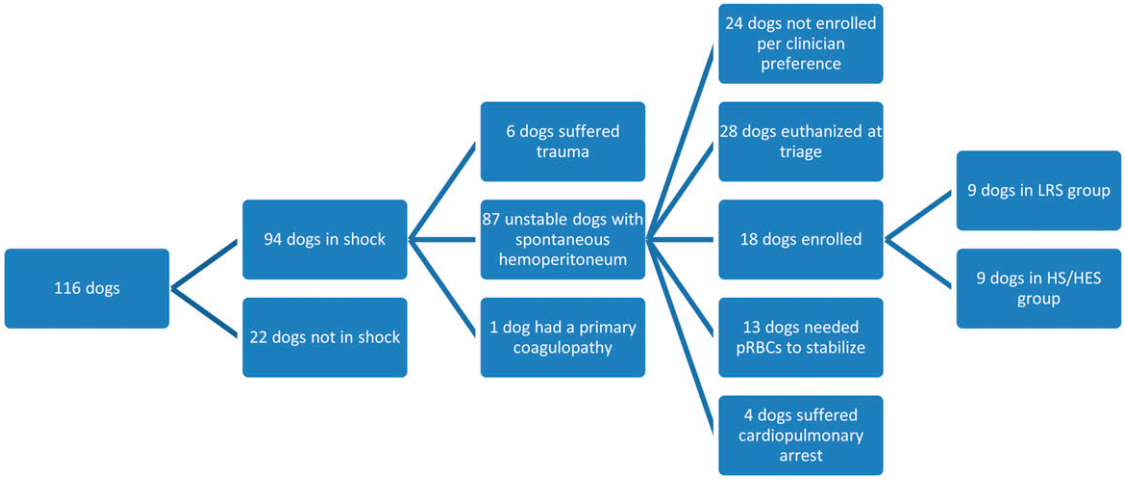

FIGURE 1 *Schematic depicting the exclusion and inclusion of dogs in this study. LRS, lactated Ringer's solution.*

were measured at baseline and *q* 5 min until the patient stabilized. The same measurements were repeated 30 min after stabilization. Other supportive care measures, as well as care after stabilization, were at the discretion of the primary clinician. Dogs were considered stable when they achieved objective endpoint goals of resuscitation (HR $<$ 120 beats/min, RR $<$ 40 beats/min, and SAP $>$ 90 mm Hg). In addition, a whole-blood venous blood gas, lactate, and PCV/TS were performed 30 min after achieving the vital endpoints of resuscitation. Dogs were resuscitated until endpoints were reached, not until a specific volume of fluid had been infused. The primary outcome measure was time until objective stabilization (measured in min).

Statistical Analysis

Normally distributed data were displayed as mean ± standard deviation, and nonparametric data were displayed as median (range). Most parameters were not normally distributed; thus, nonparametric statistics were performed. Parameters were compared between the CR and LFVR groups and between survivors and nonsurvivors using a Mann-Whitney test. A P value $<$ .05 was considered significant. Statistics were performed using commercially available software[e].

Results

In total, 166 client-owned dogs with hemoperitoneum were screened for inclusion in this study over an 18 mo period. Of those, 29 dogs did not meet inclusion criteria because 7 dogs did not have spontaneous hemoperitoneum (6 were traumatic, 1 was coagulopathic), and 22 additional dogs were not in hypovolemic shock. Of the 87 remaining dogs, 24 were not enrolled due to clinician preference, 28 were euthanized without treatment, 13 received an immediate pRBC transfusion, and 4 suffered cardiopulmonary arrest (2 dogs in each group) during the initial resuscitation phase (Figure 1). The 18 dogs remaining in the study included 8 males (6 castrated) and 10 spayed females. Breeds included were golden retrievers (n = 7), German shepherd dogs (n = 2), Labrador retrievers (n = 2), and 1 each of seven other breeds. The dogs were an average age of 10.4 yr ± 2.2 yr. The only significantly different baseline parameter between groups was body weight. Dogs in the CR group were significantly heavier (36.9 kg ± 9 kg) than dogs in

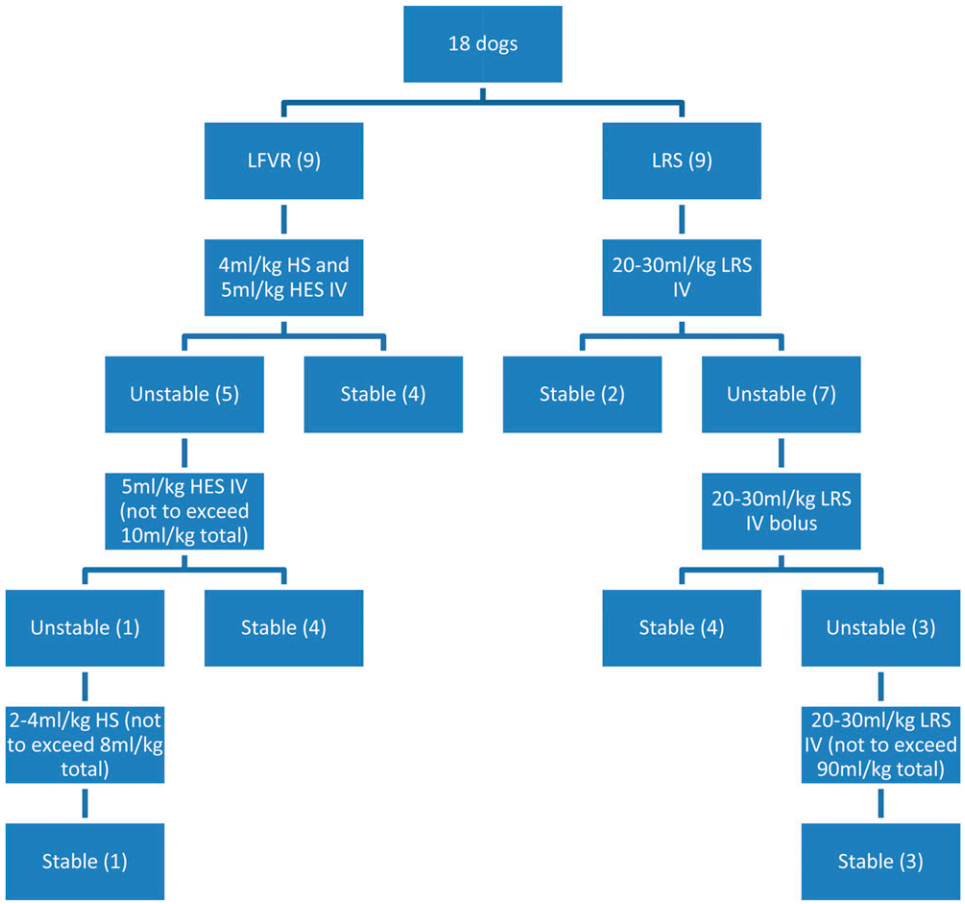

FIGURE 2 *Schematic depicting the fluid resuscitation protocols. LRS, lactated Ringer's solution.*

the LFVR group (25.2 kg ± 8.1 kg). There were no significant differences in baseline temperature, HR, RR, SAP, PCV, TS, or lactate between the two groups as described in **Table 1**. The CR group dogs were initially given between 18.1 mL/kg and 30.8 mL/kg of crystalloids via pressure bag inflated to 300 mm Hg and were then reassessed *q* 5 min for additional crystalloid needs (90 mL/kg maximum). The LFVR dogs received approximately 5 mL/kg of HES via pressure bag inflated to 300 mm Hg and approximately 4 mL/kg of HS was administered concurrently via the needle port of the T connector set[f] and then reassessed *q* 5 min for additional HS and/or HES needs (8 mL/kg HS and 10 mL/kg HES maximum). The 9 dogs in the CR group received an average of 52.8 mL/kg (20–92.3 mL/kg) of crystalloids. The 9 dogs in the LFVR group received an average of 4.5 mL/kg HS (4–6.8 mL/kg) and 7.9 mL/kg HES (5–10.3 mL/kg). Dogs in the LFVR took significantly less time to reach stabilization endpoints compared with CR dogs (mean, 20 min; range, 10–25 min versus mean, 35 min; range, 15–50 min, respectively; $P = .027$). All dogs received O_2 via facemask during stabilization. No dog required an external heating device. Fifteen dogs received 0.05 mg/kg of hydromorphone[g] IV during initial resuscitation (8 in the CR group and seven in the LFVR group). All dogs had three-view thoracic radiographs and none showed obvious metastatic disease. All dogs had an abdominal ultrasound performed by a board-certified radiologist (described below). Two dogs had an echocardiogram performed by a board-certified cardiologist with no evidence of right atrial hemangiosarcoma (HSA). All diagnostic imaging was performed after patients were deemed stable. Fluid cytology on the abdominal effusion was not performed.

All dogs were deemed stable following the aforementioned fluid resuscitation; however, 30 min after achieving stabilization endpoints, 4 dogs became tachycardic again (HR > 120) with HRs ranging from 132 beats/min to 168 beats/min. Those dogs were treated with pRBCs. All dogs were in the CR group. Overall, the HRs were not significantly different between groups 30 min after achieving vital endpoints of resuscitation (median HR in the

TABLE 1

Comparison Between the CR and the LVFR Group of Dogs*

	CR group	LVFR group	*P* value
Baseline temperature (°C)	37.8 (36.9–38.9)	37.8 (36.8–38.3)	.688
Baseline HR (beats/min)	152 (128–191)	140 (128–200)	.424
Baseline RR (breaths/min)	40 (32–48)	40 (28–52)	.753
Baseline SAP (mm Hg)	110 (80–163)	100 (75–170)	.479
Baseline PCV (%)	25 (19–44)	29 (19–40)	.505
Baseline TS (g/L)	57 (47–60)	57 (50–74)	.564
Baseline lactate (mmol/L)	8.7 (4.1–11)	6.7 (2.3–12.9)	.596
Postresuscitation HR	128 (97–168)	120 (104–150)	.723
Postresuscitation RR	28 (24–32)	40 (24–48)	.821
Postresuscitation SAP	129 (100–158)	118 (100–164)	.423
Postresuscitation PCV	16 (11–23)	15 (13–22)	1
Postresuscitation TS	43 (26–52)	47 (24–59)	.269
Postresuscitation lactate	4.25 (2.6–7)	3.7 (1.1–9.6)	.860
Δ HR	−30 (−79–12)	−20 (−92–0)	.825
Δ RR	−16 (−20 to −2)	−10 (−24–0)	.891
Δ SAP	28 (−34–70)	25 (−50–55)	.725
Δ PCV	−8 (−24 to −5)	−12 (−20 to −6)	.421
Δ TS	−13 (−33 to −.60)	−14 (−26 to −.30)	.965
Δ lactate	−3.9 (−6.7 to −.8)	−1.4 (−6.6 to −.7)	.658
Δ lactate (%)	−45 (−19.5 to −72)	−45 (−12.7 to −73.1)	.563
Time to stabilization (min)	**35 (15–50)**	**20 (10–25)**	**.027**
pRBCs (mL/kg)	13 (6.0–21.4)	16.3 (8.4–36.9)	1
Days in hospital (survivors)	3.5 (3–4)	3.5 (2–4)	.874
Cost to client (survivors) in USD	5,477 (4,892–6,050)	4,938 (4,461–5,825)	.31

*All data are presented as median (range).
Δ, change in; CR, conventional resuscitation; HR, heart rate; LFVR, limited fluid volume resuscitation; PCV, packed cell volume; pRBCs, packed red blood cells; RR, respiratory rate; SAP, systolic arterial blood pressure; TS, total solids; USD, US Dollars.

LFVR group was 120 beats/min; range, 104–128 beats/min and median HR in the CR group was 128 beats/min; range, 97–168 beats/min).

Lactate reduction was not significantly different between groups ($P = .66$). The CR group had a median lactate reduction of 3.9 mmol/L (0.8–6.7 mmol/L) and the LFVR group had a median lactate reduction of 1.4 mmol/L (0.7–6.6 mmol/L). Median percent reduction in lactate was 45% in both groups (CR range, 19.5–72%; LFVR range, 12.7–73.1%; $P = .563$) as shown in Table 1. Six dogs in this study had cardiac arrhythmias (three with ventricular premature contractions and three with sustained ventricular tachycardia) postresuscitation. Five dogs were in the CR group and 1 dog was in the LFVR group. The 3 dogs with sustained ventricular tachycardia were all successfully treated with 2 mg/kg of lidocaine[h] via IV bolus followed by a constant rate infusion at 50 μg/kg/min. Postfluid resuscitation pRBC transfusion requirements were similar between the two groups during their hospital stay (mean, 17.2 mL/kg in the CR group; mean, 22.9 mL/kg in the LFVR group; $P = 1$).

Six dogs in the CR group underwent exploratory celiotomy. One was euthanized intraoperatively due to suspected diffuse neoplasia, 1 was euthanized postoperatively after an episode of collapse, and four survived to discharge. Three dogs were euthanized without surgery due to suspicion of diffuse metastatic neoplasia on abdominal ultrasound (i.e., due to the presence of multiple cavitated hepatic and omental nodules). Necropsies were offered but declined. Of the 4 dogs that survived until discharge, 3 had splenic HSA and 1 had a hyperplastic splenic nodule. Two of the dogs with HSA were alive 28 days postoperatively, as was the dog with the hyperplastic splenic nodule. The third dog with HSA was lost to follow-up.

Of the 7 dogs in the LFVR group that underwent exploratory celiotomy, 2 were euthanized intraoperatively, 1 was euthanized postoperatively, and 4 survived to discharge. Two dogs did not go to surgery based on suspicion of metastatic disease on abdominal ultrasound. One was euthanized and the other was managed medically and survived to discharge. The dog euthanized postoperatively was found to have had metastatic carcinoma of the spleen from a primary renal mass in surgery. That dog had signs of an acute abdomen (i.e., sudden tachycardia, abdominal pain, vomiting, bloody diarrhea) and was humanely euthanized 3 days after surgery while still hospitalized. In total, 4 dogs in the CR group survived to discharge. Three had splenic HSAs and 1 had a splenic hematoma. All 3 dogs with HSA were alive 28 days postoperatively and the hematoma dog was lost to follow-up. Time to discharge was similar between the two groups (mean time to discharge in the CR group, 3.5 days; range, 3–4 days; mean time to discharge in the LFVR group, 3.25 days; range, 2–4 days; $P = .874$). Cost was similar between groups for the dogs that survived until discharge after stabilization and surgery ($5,165 in the LFVR and $5,474 in the CR groups; $P = .34$) as shown in Table 1.

When survivors were compared with nonsurvivors (i.e., those euthanized), the only differences were in the abdominal fluid TS and plasma lactate at baseline. Dogs that were euthanized had significantly lower abdominal fluid TS (47 g/L ± 9.0 g/L) than dogs that survived to discharge (56.6 g/L ± 7.4 g/L), with a P value of .027. Additionally, dogs that did not survive to discharge had significantly higher baseline lactate (8.8 mmol/L ± 3.8 mmol/L) than survivors (6.13 mmol/L ± 2.8 mmol/L), with a P value of .027.

Discussion

This study compared CR using isotonic crystalloids to a LFVR strategy using HS in combination with HES in dogs with hypovolemic shock due to hemoperitoneum. Consistent with previous reports, the majority of dogs in this study had splenic HSA. This study also found that dogs stabilized significantly faster with a LFVR protocol versus CR. Reducing the median resuscitation time by 15 min may be important because it reduces the amount of time that vital organs are inadequately perfused and, therefore, have compromised O_2 delivery. Furthermore, dogs treated with a LFVR strategy were ready for surgical intervention sooner.

Dogs in both groups had similar overall outcomes in survival until discharge despite the difference in initial stabilization. From a hospital efficiency standpoint, an LFVR protocol might be considered advantageous over a CR using a larger fluid volume resuscitation protocol because it can be accomplished faster with less technician support without compromising patient safety. Those conclusions are similar to those made about LFVR versus CR for cases of experimentally induced gastric dilatation-volvulus in previous studies.[10,16] There were positive findings in the short term in that dogs were resuscitated faster with less fluid, but overall survival was the same. In addition, in that study, dogs in the LFVR group had a higher cardiac output and less hemodilution.[10]

LFVR techniques using hypertonic crystalloids and colloids expand plasma volume for 2–3 hr. In contrast, with resuscitation using only isotonic crystalloids, only 10–25% remains within the vasculature 1 hr later.[36] In fact, it has been suggested that that isotonic crystalloids should not be used as the sole type of fluid resuscitation during hemorrhagic shock.[4] Additional theoretical benefits of LFVR include a decreased risk of hypothermia, dilutional coagulopathy, rebleeding, and interstitial edema formation when compared with CR. In addition, LFVR protocols have

beneficial cardiac effects and have also been shown to reduce ischemia-reperfusion injury versus isotonic crystalloids.[19–23,37–42]

That said, LFVR techniques are not without potential side effects that must be acknowledged. Side effects of HS can include occasional ventricular premature contractions, bradyarrhythmias, transient hypotension, and bronchoconstriction if given faster than 1 mL/kg/min.[43,44] It should also be kept in mind that HS administration will cause transient hypernatremia and preclude the ability to accurately trend endogenous serum Na levels in the immediate few hr after resuscitation. Hemolysis and subsequent hemoglobinuria can also be seen when HS is injected into small peripheral veins.[14] Furthermore, HS rapidly improves cardiac output and blood pressure, which, along with the Na load, may increase the risk of either congestive heart failure or neurologic signs in some patients. Also, there is concern that LFVR may also promote blood loss at the site of vascular injury due to a breakdown of an ill-formed blood clot (rebleeding). However, as mentioned previously, rebleeding is not a concern unique to hypertonic fluids and can theoretically occur with any type of fluid resuscitation. Changes in Na, chloride, potassium, bicarbonate concentrations, and osmolality can be seen with HS use, but they are transient and of minimal clinical importance in appropriately selected candidates.[31]

Potential disadvantages of synthetic colloids use include cost, increased risk of volume overload, potential exacerbation of coagulopathies, interference with crossmatching, and possible contribution to the development of edema in animals with vasculitis.[45] Reports of anaphylactic reactions to administration of HES have been reported in people, but there are no known reports in animals. The effect of synthetic colloids on coagulation is an ongoing subject of debate in both human and veterinary medicine. Bleeding complications have been repeatedly reported in people after HES use, and the hemostatic effects appear dose dependent.[45,46] Studies investigating the use of HES have found decreases in von Willebrand factor and factor VIII as well as increases in PTT above and beyond that which could be attributed to hemodilution alone.[46–48] Thrombocytopathia has also been reported with the use of HES and is thought to be due to decreased platelet adhesion by multiple mechanisms, including decreased circulating levels of von Willebrand factor and factor VIII, as well as decreases in platelet aggregation.[49] In addition, HES has been associated with an increased incidence of acute renal injury/failure in human septic patients, likely due to renal tubular damage.[50]

Weaknesses of this study include those inherent in a small, prospective clinical trial. A small sample size and short follow-up period makes conclusions about long-term outcome difficult. More importantly, there was a wide range of fluids given (i.e., 5–10 mL/kg HES in the LFVR group and 20–92 mL/kg of crystalloids in the CR group), making direct comparison of fluid volume infused problematic. Last, because all of the nonsurvivors were euthanized, evaluating outcome is essentially impossible. Unfortunately, this pilot study was not sufficiently powered to detect differences in transfusion requirements, days in hospital, or cost to client between the two groups. Nonetheless, based on the data presented herein, the authors determined that future studies would require 16 dogs in each group for sufficient power to detect differences in pRBC transfusion requirements, 16 dogs in each group to detect differences in days in hospital, and 62 dogs to detect differences in cost (α, .05; power, .8). In addition, it is possible that by excluding dogs that were coagulopathic at admission, some dogs with disseminated intravascular coagulation, a condition commonly reported in dogs with HSA, might have been excluded. In the current study, only 1 dog was excluded due to coagulopathy. It was determined later that the dog in question had ingested rodenticide.

Studies in the future could include patient enrollment at multiple institutions to attain a greater number of dogs and allow a meaningful statistical comparison between the groups to determine if one fluid resuscitation protocol results in lower transfusion requirements, fewer days in hospital, less cost to the client, or a better overall outcome. Also, serial lactate measurements and more comprehensive evaluation of coagulation parameters could be obtained. In addition, all supportive care measures (O_2, heat, analgesics) would be standardized to limit any confounding factors.

Conclusion

In this small pilot study, dogs with a spontaneous hemoperitoneum in hemorrhagic shock were stabilized significantly faster with HS/HES versus large volumes of crystalloids with similar clinical course and case outcome. Further investigation is warranted.

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FOOTNOTES

[a] Stat Profile Critical Care Xpress; Nova Biomedical, Waltham, MA

[b] Lactated Ringer's solution; Baxter Laboratories, Deerfield, IL

[c] 7.2% NaCl; AmTech Group Inc., St. Joseph, MO

[d] Hetastarch (6% hydroxyethyl starch 450/.7 in .9% Na chloride injection); Hospira Inc., Lake Forest, IL

[e] IBM SPSS Statistical Software, version 21.0; SPSS Inc., Chicago, IL

[f] 18cm MicroCLAVE Smallbore T-connector; Abbott Laboratories, Abbott Park, IL

[g] Hydromorphone; West-Ward, Eatontown, NJ

[h] Lidocaine; Sparhawk Laboratories, Inc., Lenexa, KS

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