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Prehospital Resuscitation of Traumatic Hemorrhagic Shock with Hypertonic Solutions Worsens Hypocoagulation and Hyperfibrinolysis

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Abstract

Impaired hemostasis frequently occurs after traumatic shock and resuscitation. The prehospital fluid administered can exacerbate subsequent bleeding and coagulopathy. Hypertonic solutions are recommended as first-line treatment of traumatic shock; however, their effects on coagulation are unclear. This study explores the impact of resuscitation with various hypertonic solutions on early coagulopathy after trauma. We conducted a prospective observational subgroup analysis of large clinical trial on out-of-hospital single-bolus (250 mL) hypertonic fluid resuscitation of hemorrhagic shock trauma patients (systolic blood pressure, ≤70 mmHg). Patients received 7.5% NaCl (HS), 7.5% NaCl/6% Dextran 70 (HSD), or 0.9% NaCl (normal saline [NS]) in the prehospital setting. Thirty-four patients were included: 9 HS, 8 HSD, 17 NS. Treatment with HS/HSD led to higher admission systolic blood pressure, sodium, chloride, and osmolarity, whereas lactate, base deficit, fluid requirement, and hemoglobin levels were similar in all groups.

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The HSD-resuscitated patients had higher admission international normalized ratio values and more hypocoagulable patients, 62% (vs. 55% HS, 47% NS; $P < 0.05$). Prothrombotic tissue factor was elevated in shock treated with NS but depressed in both HS and HSD groups. Fibrinolytic tissue plasminogen activator and anti–fibrinolytic plasminogen activator inhibitor type 1 were increased by shock but not thrombin-activatable fibrinolysis inhibitor. The HSD patients had the worst imbalance between procoagulation/anticoagulation and profibrinolysis/antifibrinolysis, resulting in more hypocoagulability and hyperfibrinolysis. We concluded that resuscitation with hypertonic solutions, particularly HSD, worsens hypocoagulability and hyperfibrinolysis after hemorrhagic shock in trauma through imbalances in both procoagulants and anticoagulants and both profibrinolytic and antifibrinolytic activities.

Keywords

Hypertonic saline; coagulopathy; hemostasis; physiopathology; underlying mechanisms; tissue factor; tissue factor pathway inhibitor; thrombomodulin; thrombin-activatable fibrinolysis inhibitor; tissue plasminogen activator; D-dimers

Introduction

Despite progress in fluid resuscitation and hemorrhage control in recent years, bleeding remains the leading cause of preventable death in civilian trauma patients and combat casualties (1). Hemorrhage is responsible for almost 50% of deaths occurring within 24 h of injury and up to 80% of intraoperative trauma mortalities (2). The disproportionate burden of bleeding in trauma is explained by the frequent emergence of coagulation abnormalities. Hemostasis requires a balance between coagulation and fibrinolysis, which permits control of bleeding while preventing intravascular thrombosis (3). A variety of altered coagulofibrinolytic parameters are detectable in critically injured patients. These defects, or coagulopathies, impede the normal hemostatic response (4), worsening blood loss and contributing to the morbidity of hemorrhagic shock (5).

Mounting evidence suggests that all resuscitation fluids contribute, in varying degrees, to clinically relevant hemostatic disturbances. In particular, aggressive use of large-volume crystalloids can exacerbate coagulopathy, along with hyperinflammation, cellular injury, and organ dysfunction. Similarly, most colloids are associated with detrimental effects and interfere with hemostasis (6). Small-volume hypertonic-hyperoncotic fluids have several theoretical and practical advantages over isotonic crystalloids (7), and studies in animals and humans show substantial physiologic benefits for treatment of hemorrhagic hypotension with few adverse effects (8). Besides volume expansion, hypertonic fluids exhibit potent immunomodulatory and anti-inflammatory actions (9, 10) that not only justify their use in shock resuscitation but also suggest other therapeutic applications (11), particularly in austere trauma care settings (12). Unfortunately, prospective, randomized, controlled trials of severely injured >patients have failed to demonstrate a survival advantage of hypertonic fluids over normal saline (NS) (13, 14). The potential of hypertonic fluids to modulate the coagulation cascade is less well known, as data are limited and contradictory, especially in shock patients (15). Hypertonic fluids in association with permissive hypotension allow for

reduced volumes of crystalloids, minimizing the risk of dose-related dilution sequelae. Hypertonic fluids may also exert intrinsic effects on hemostasis via direct molecular interactions with coagulation proteins, platelets, or the fibrinolytic system (16). Indeed, *in vitro* and animal studies report anticoagulant effects or impaired platelet function with hypertonic fluids that could aggravate bleeding and acute coagulopathy (17, 18).

As part of a larger prospective clinical trial evaluating prehospital resuscitation of severely injured trauma patients in hypovolemic shock (14), the aim of this ancillary laboratory study was to determine the impact of a single-bolus (250 mL) infusion of hypertonic fluids on the risk of acute traumatic coagulopathy. We hypothesized that shock and resuscitation with hypertonic fluids would differentially modulate posttraumatic chemostatic alterations that contribute to acute coagulopathy. Specifically, this study was designed to 1) characterize the prevalence, time course, and severity of early hemostatic alterations, as measured by standard clotting tests and sensitive bio-markers of coagulation and fibrinolysis; and 2) investigate the impact of 0.9% NaCl (NS) versus 7.5% hypertonic saline, alone or combined with 6% Dextran 70, on the observed posttraumatic coagulofibrinolytic derangements.

Materials and Methods

Study design and setting

This prospective observational study was performed as an *a priori* subgroup analysis of a previously published, multicenter, randomized, controlled, double-blind, 3-arm clinical trial (14). The present trial was designed to evaluate the efficacy of out-of-hospital single-bolus infusion of hypertonic fluids in a cohort of injured patients in hemorrhagic shock. The parent trial was conducted by the Resuscitation Outcomes Consortium (ROC) in 11 centers in the United States and Canada under the USA regulations for Exception from Informed Consent for Emergency Research (21 CFR 50.24) and Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans in Emergency Health Situations (Article 2.8). The protocol was approved by the US Food and Drug Administration, Canadian Institutes of Health Research, and institutional review boards of all participating centers.

Study population and intervention

This subgroup analysis included patients enrolled in two centers (Toronto and Seattle), who had additional laboratory tests done during the initial 24 h of hospitalization. Hypovolemic shock was defined as out-of-hospital systolic blood pressure (SBP) of 70 mmHg or less or SBP 71 to 90 mmHg with a heart rate of 108 beats/min or more. Exclusion criteria were pregnancy, younger than 15 years, more than 2,000 mL of intravenous fluids or blood before enrollment, hypothermia (<28°C), drowning, asphyxia, burns, isolated penetrating head injury, time of call received by dispatch to study intervention longer than 4 h, known prisoners, and transfer from another hospital. Patients randomly received a single bolus of 250 mL of 7.5% hypertonic saline (HS), 7.5% hypertonic saline/6% Dextran 70 (HSD), or standard 0.9% NS as the initial resuscitation fluid at the scene. Additional fluids were allowed after study fluid, as guided by local protocols.

To investigate the effect of hypertonic fluid resuscitation on hemostasis after trauma and hemorrhagic shock, we analyzed age, sex, and factors linked to early coagulopathy: extent of tissue destruction (Injury Severity Score [ISS]), shock (base deficit [BD], lactate), and dilution measured by the amount of fluid administered (19). *Coagulopathy* was defined as an international normalized ratio (INR) 1.3 or higher, prothrombin time (PT) 14 seconds or longer and/or platelet count less than 100×10^9/L. To study the changes in hemostasis, key biomarkers were assayed: tissue factor (TF), thrombin-antithrombin complex (TAT), TF pathway inhibitor (TFPI), thrombomodulin (TM), thrombin-activatable fibrinolysis inhibitor (TAFI), tissue plasminogen activator (tPA), plasminogen activator inhibitor type 1 (PAI-1), and D-dimers. Matching assays were performed in a control group of 20 healthy, asymptomatic, medication-free volunteers (16 male, 4 female; mean age, 35.7 years). This subgroup analysis was not designed or powered for patient outcomes and, hence, the laboratory findings were not correlated with patient outcomes.

Blood collection and laboratory analyses

Serial blood samples were collected on hospital admission (within 3 h of resuscitation) and at 12 and 24 h. Routine clinical coagulation tests (INR, partial thromboplastin time (PTT), platelet count) were performed by the hospital laboratories. For the specialized coagulation assays, blood was collected in tubes containing 3.2% (0.109 mol/L) citrate and centrifuged, and aliquots of the platelet-poor plasma were transferred to cryovials and stored frozen (−80°C) until analysis. Soluble coagulation and fibrinolytic biomarkers were analyzed in duplicate using commercially available enzyme immunoassay kits from American Diagnostica Inc. (Stamford, Conn) for TF (IMUBIND), total TFPI (IMUBIND), TAFI (IMUCLONE), TM (IMUBIND), PAI-1 (IMUBIND), and D-dimer (IMUCLONE) according to the manufacturer's instructions. Absorbencies were read using automated microplate photometer (EL340; BIO-TEK Instruments, Winooski, Vt).

All data were kept in a password-encrypted dedicated database. Investigators and technicians performing the assays were blinded to patient identity and treatment arms. Data were analyzed with the patient groups identified only as group A, B, or C, without any indication as to treatment arm.

Statistical analysis

Data were assessed for normality and homogeneity of variance using Kolmogorov-Smirnov test. Demographic data and biomarker levels are expressed as mean ± SD. Univariate and multivariate analyses were used accordingly: intergroup comparisons between dichotomous variables were performed using Student unpaired *t* test (continuous variables) and nonparametric Mann-Whitney *U* test (continuous variables not normally distributed). Serial comparisons between groups were made using repeated-measures analysis of variance (ANOVA) with *post hoc* Bonferroni/Dunn testing. All analyses were 2-tailed, with values of $P < 0.05$ considered statistically significant. This subgroup analysis was not designed or powered for patient outcomes and, hence, the laboratory findings were not correlated with patient outcomes.

Results

Thirty-four injured patients with hypovolemic shock from the larger ROC trial were randomly included in this ancillary study. This patient subset was well matched to the larger ROC cohort, with respect to demographics and clinical status. Nine patients received HS as the initial resuscitation fluid, 8 HSD, and 17 NS. Patients from all three treatment arms had similar ages and sexes (Table 1). On hospital admission, mean SBP was increased compared with qualifying measurements in all groups but was significantly higher for patients treated with HS or HSD compared with NS. As expected, sodium, chloride, and osmolarity were higher for HS and HSD groups compared with NS.

All patients included in this study were severely injured (mean ISS of 22.1 ± 11.9) and in shock (mean BD, −10.1 ± 7.8; mean lactate, 5.2 ± 3.5 mmol/L). However, ISS, BD, and lactate did not differ significantly between the groups (Table 1). Concerning iatrogenic dilution, all treatment groups received similar volumes of prehospital (mean, 1.25 ± 1 L) and 24-h fluid administration (mean, 15.7 ± 15.1 L). Admission hemoglobin and hematocrit levels were lower for HSD-treated patients despite not reaching statistical significance (Table 1).

On admission at the 3-h laboratory time point, approximately half of the patients were coagulopathic: 47% of NS, 55% of HS, and 62% of the HSD patients (Table 1). The HSD-treated patients also had higher mean admission INR. Only one patient had low ($<100 \times 10^9$/L) platelet count on admission.

Tables 2 and 3 display the effect of the different resuscitation fluids on coagulation biomarkers on hospital admission, whereas Figures 1 and 2 display the changes across time. Blood samples from 20 healthy adults were used as control.

On admission, evidence of activation of hemostasis (thrombin generation) was remarkable with TAT levels 5- to 15-fold higher in hypovolemic shock patients compared with healthy volunteers. The plasma levels of the procoagulant TF antigen were significantly lower in the HSD group compared with those in healthy volunteers, whereas the opposite was observed in the NS group. No significant difference was observed across all groups concerning TM levels, but the other anticoagulant TFPI was significantly higher in hypovolemic shock patients compared with that in healthy control and notably higher in HSD patients. Thus, HSD patients had both lower procoagulant and higher anticoagulant levels compared with other groups.

On admission, evidence of activation of fibrinolysis was also noted, as mean $_D$-dimer levels were 25- to 50-fold higher in patients with hypovolemic shock compared with healthy controls. The HSD patients had the highest levels of crosslinked fibrin degradation products ($_D$-dimer). The mean levels of the profibrinolytic tPA were three to five times higher in shock patients than those in healthy controls, with the highest levels observed in HSD-treated patients (25.2 ± 3.1 ng/mL). The antifibrinolytic PAI-1 activity was also higher in shock patients than that in healthy controls, with the lowest levels observed in the HSD group. Unexpectedly, TAFI activity in shock patients was lower than that in healthy controls despite the massive release of the profibrinolytic tPA. The lowest levels of the

antifibrinolytic TAFI occurred in the HSD group as well (80.5% ± 11.4%). Thus, HSD patients seem to have more evidence of fibrinolysis than the other groups—the highest levels of the profibrinolytic tPA and the lowest levels of the antifibrinolytic PAI-1 and TAFI (Tables 2 and 3).

During the first 24 h after injury, the prothrombotic TF only varied significantly in the NS group, where the already elevated levels on admission continued to rise, followed by a slight drop by 24 h (Fig. 1A). The anticoagulant TM rose continuously across time in all groups, whereas TFPI increased in both HSD and NS groups and decreased for HS-treated patients. The antifibrinolytic TAFI, which was lower on admission in all shock groups compared with healthy volunteers, continued to decrease, reaching its lowest levels at 24 h. D-dimer fragments remained high in the HS and HSD groups but declined in the NS group (Fig. 2). Table 3 displays a summary of the changes in the measured biomarkers.

Discussion

As first described in Vietnam casualties (20) and civilian transfusion patients (21), trauma-associated coagulopathy results from a combination of intrinsic physiologic derangements and iatrogenic factors. This has classically been attributed to the *lethal triad* of hypothermia, acidosis, and loss of clotting factors from hemorrhage and hemodilution caused by excessive volume replacement (22). Recent clinical studies demonstrate that fully 25% of trauma victims present with coagulation abnormalities on hospital admission. These defects occur before receiving large amounts of intravenous fluids and before the appearance of hypothermia and acidosis (23). Moreover, this subgroup of patients exhibits a 4-fold greater risk of mortality, increased transfusion requirements, longer hospital stay, and a higher incidence of multiple organ dysfunction (24). Accordingly, acute traumatic coagulopathy is recognized as an endogenous condition that is intrinsically linked to the degree of shock and severity of injury itself.

The etiology of early trauma-induced coagulopathy is not fully understood, but two main pathogenic mechanisms are proposed. The first involves systemic anticoagulation and hyperfibrinolysis secondary to tissue hypoperfusion (25). In response to hypoperfusion, endothelial-bound TM complexes with thrombin to activate protein C to APC. Then, APC inactivates factors (F)V and FVIII (26), potentiating the anti-coagulated state, while enhancing consumption of antifibrinolytics (27), including PAI-1 and TAFI (25). Derepression of profibrinolytic activity allows unimpeded activation of plasmin (28) and release of tPA (29). The resultant hypocoagulability and hyperfibrinolysis (30) accelerate bleeding and clot dissolution with generation of D-dimer fibrin degradation products (31). The second mechanism poses that inflammation-mediated endothelial disruption (32) initiates the extrinsic pathway by procoagulant TF exposure (33). The activated TF/FVIIa complex catalyzes conversion of prothrombin to thrombin and fibrinogen to fibrin. This culminates in disseminated intravascular coagulation, with factor consumption (26) and release of the TAT complex and TFPI. Thus, a congruent understanding of the development of traumatic coagulopathy is essential to improve patient outcomes.

Shock resuscitation strategies are continuously evolving (34), driven by intensive experience from the combat theater. The recognition that many injured patients are coagulopathic on presentation (35) has led to a shift toward damage-control principles (36), emphasizing prompt bleeding control and restoration of tissue perfusion (37) and the correction of early coagulation defects using fresh plasma and other blood products in near equivalent ratios (38), along with prohemostatic agents such as tranexamic acid (39). This approach also recommends restricting fluids to limit hemodilution (40) and other deleterious effects of the lethal triad (41). Still, some fluids are required to replenish circulating volume and oxygen-carrying capacity in the prehospital phase when blood component therapy is limited (37). Yet, the optimal fluid composition, volume, and timing for shock resuscitation remain controversial (34); debate continues over the relative merits of crystalloids versus colloids (42) and their potential to worsen coagulopathy (6).

Fluid resuscitation is essential for the management of traumatic hemorrhagic shock but may worsen hemostatic impairments and increase bleeding (43). The impact of different fluids on early trauma coagulopathy is poorly understood, and there is no consensus on the ideal fluid for resuscitation. We studied the postinjury coagulation and fibrinolytic responses to prehospital resuscitation with two hypertonic fluids (HS, HSD) and the standard of care (NS). This study found that a single bolus of hypertonic fluid, particularly HSD, worsens the hypocoagulability and hyperfibrinolysis that follow traumatic hemorrhagic shock through imbalances in procoagulant/anticoagulant and profibrinolytic/antifibrinolytic activities.

The importance of diagnosing and treating hemostatic defects increased significantly in recent years with the recognition of early trauma coagulopathy as being intrinsically linked to shock and injury severity and carrying a high mortality. In our study of severely injured patients (mean ISS, 22) in hypovolemic shock, 50% to 62% were coagulopathic on hospital admission. This figure is higher than reported for the general trauma populations of 25% but comparable to recent studies reporting that approximately 50% of the critically injured patients have early coagulopathy defined by an INR of 1.3 or greater (44). In contrast, it is notable that, despite being a high-risk group, at least 40% of the patients were not coagulopathic on hospital admission.

The worst laboratory evidence of hypocoagulability (INR values) occurred in patients resuscitated with HSD (Table 1). Hypertonic-hyperoncotic fluids are known to worsen hemostatic impairments (45) and bleeding and HSD to prolong PT/INR but not PTT. Both HS and HSD inhibit *in vitro* platelet aggregation, reduce clot formation, and enhance fibrionolysis. Some of these effects are nonspecific and caused by hemodilution and improvements in venous flow. The addition of Dextran may account, at least in part, for the different results between HS and HSD. Dextran 70 is a volume expander known to inhibit primary hemostasis and enhance fibrinolysis through a combination of mechanisms, including inhibition of platelet activation/aggregation via cleavage of von WiIlebrand factor and platelet protease–activated receptor 1 for thrombin, blockade of tPA uptake, and changes in FVIII structure and function. Nonetheless, a growing number of *in vitro* and animal studies also suggest relatively less impairment of the plasmatic coagulation system by hypertonic fluids compared with hydroxyethyl starch and gelatin, along with fewer safety concerns with hypertonic saline than artificial colloids.

To understand the complex system of hemostasis, we measured key coagulo-fibrinolytic parameters implicated in the hemostatic response to injury. On hospital admission, patients in hemorrhagic shock had markedly elevated thrombin generation (TAT), 5 to 15 times higher than healthy controls, indicating the overactivation of hemostasis as would be expected in bleeding patients. It would be reasonable to expect that the hemostatic response to bleeding and shock would include an increase in prothrombotic cofactors (i.e., TF) and a decrease in anticoagulants, such as TM and TFPI (19, 33). The expected rise in TF was observed in shock patients receiving NS but not in those receiving hypertonic fluids. The lowest TF levels were registered in HSD patients. The analysis of the anticoagulant response is less clear, but the highest levels (TAT, TFPI) were observed in HSD-treated patients, which may account for the higher numbers of hypocoagulable patients in this group. The increase in TF (and decrease in TFPI) after HSD resuscitation likely reflects the release of preformed TF from tissues such as circulating monocytes, microparticles, or endothelial cells secondary to severe vascular injury and hypoperfusion (32, 33). The role of circulating TF and TFPI in hemostasis and thrombosis in traumatic coagulopathy is controversial, with uncertainty about the relative contributions of extravascular cell surface–bound circulating microparticle and soluble TF. The mechanism by which resuscitation fluids influence endothelial damage, inflammation, and coagulation system requires further investigation.

D-dimer levels were 25 to 50 times higher in shock patients than those in healthy controls, suggesting very active fibrinolysis. This is consistent with previous reports in severely injured trauma patients (15, 27). However, other causes for the elevated levels cannot be excluded. The highest levels were also observed among HSD-treated patients, which could indicate higher breakdown of fresh clots in a group of patients already hypocoagulable. Recent studies report hyperfibrinolysis to occur in less than 3% of all injured patients but associated with increased mortality rates (28). Our findings would suggest that fibrinolysis may be much more common. All patients included in this study had tPA levels above those of healthy controls, with mean levels three to five times higher. Once again, the group of patients with the highest tPA levels was that treated with HSD. The expected response to the high tPA levels would be a proportionally high antifibrinolytic activity of PAI-1 and TAFI (25). Although PAI-1 was higher in shock patients compared with controls, the lowest increase in this antifibrinolytic response was noted in HSD-treated patients. Interestingly, shock patients were unable to mount an antifibrinolytic response with TAFI, which remained below healthy control levels for the entire 24 h after trauma. Even here, the lowest TAFI levels were in the HSD group.

This observational study has limitations. The first is that the small number of patients included restricts the power of our observations. This subgroup analysis included patients enrolled in only 2 of 11 enrolling centers (Toronto and Seattle) and was not designed or powered for outcome correlation with laboratory coagulopathy data. We acknowledge that the study group is modest, and we would like to have had more patients enrolled in this subgroup analysis. However, given the number of patients that were enrolled and the completeness of the data set, reasonable conclusions are able to be drawn from the analysis. A further limitation of the study is that only patients who survived for greater than 3 h were enrolled in the study. With limited resources, for a thorough coagulopathy analysis for 24 h and to allow enough time to see a treatment effect, patients who succumbed early to their

traumatic injuries were not included in this analysis. After study enrollment, during the ensuing 24 h, the fluid administration per group was statistically very similar at approximately 15 L per patient (bottom of Table 1). The amount of fluid administered between study enrollment and HS/HSD/NS administration and the first blood draw could be variable, however, as shown in Table 1; by 24 h after admission, all of the groups received the same amount of overall fluid. This is the very reason that the study was done for a 24-h period to see if there were any coagulopathy effects based on time and resuscitation volume.

Another significant limitation is inherent to all descriptive laboratory studies where causality cannot be directly determined. It is possible that the coagulation laboratory changes between the groups reflect the amount and type of blood products administered and the time to definitive hemorrhage control. Although the cohorts received similar overall fluid resuscitation at 24 h after study enrollment, the time to hemorrhage control was uniformly unable to be extracted from the patients' records with scientific certainty because of the timing of hemorrhage control and the need for ongoing resuscitation. Unfortunately, the time to definitive hemorrhage control is not uniformly available for us to incorporate into the subgroup analysis.

We also simplified a very complex process where hemostatic cofactors/enzymes often have many different roles under specific conditions accelerating thrombosis while simultaneously activating anticoagulation and/or fibrinolysis. Thus, although the description of a coagulation parameter as procoagulant or anticoagulant might facilitate understanding of a complex process, it may also be imprecise. Finally, further studies are necessary to elucidate the molecular mechanisms underlying the observed effects of HS versus HSD solutions on coagulation and fibrinolysis observed in resuscitated hemorrhagic shock patients.

Nonetheless, this laboratory study reports findings that are relevant for the understanding of the mechanisms responsible for the multiple changes in coagulation that occur after trauma and resuscitation. We found evidence supporting the association between shock and tissue destruction and two coagulation defects: hypocoagulability and hyperfibrinolysis. We also found that, despite the high injury severity and shock, many patients (at least 40%) did not have evidence of being coagulopathic on hospital admission. A key finding was that a single administration of 250 mL of hypertonic saline in the initial phase of resuscitation of injured patients with hypovolemic shock seems to significantly worsen the hemostatic response. We found evidence that HS and particularly HSD were associated with higher rates of hypocoagulability (lower levels of prothrombotic and higher levels of anticoagulant cofactors) and fibrinolysis (higher profibrinolytic and lower antifibrinolytic cofactor levels). Although the primary injury mechanisms differ between civilian and military trauma victims, the common pathogenesis of resuscitated hemorrhagic shock makes these findings generally relevant to both populations. In conclusion, hypertonic solutions, particularly when combined with Dextran, seem to worsen the hypocoagulability and hyperfibrinolysis that occur after hemorrhagic shock in the cohort of trauma patients evaluated in our study. Although HS and HSD increased the SBP above that of NS, they may not have corrected the shock because acidosis persisted despite the BP normalization.

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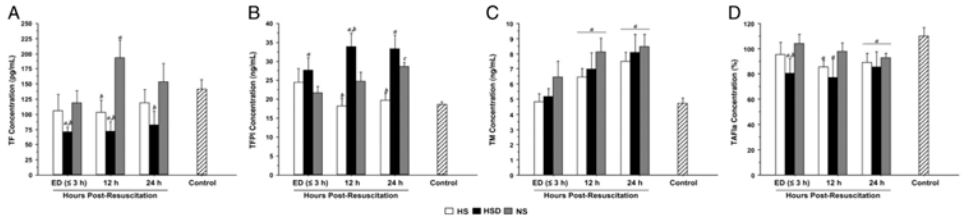

Fig. 1. Plasma concentrations of TF (A), TFPI (B), TM (C), TAFI (D) were determined on emergency department (ED) admission (≤3 h) and at 12 and 24 h after resuscitation in trauma patients treated prehospital with HS (n = 9), HSD (n = 8), or NS (n = 17) and in healthy controls (n = 20)

Data are shown as mean ± SEM; $^{a}P < 0.05$ vs. age-matched controls; $^{b}P < 0.05$ vs. time-matched NS-treated patients; $^{c}P < 0.05$ vs. time-matched HS-treated patients, by ANOVA.

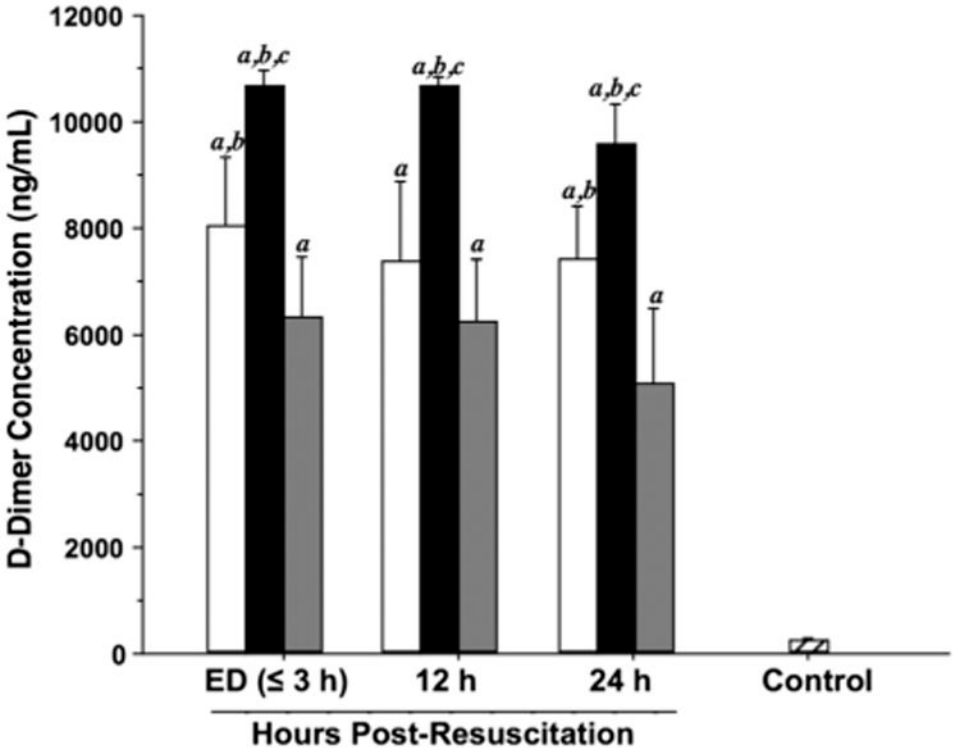

Fig. 2. Plasma D-dimer levels determined on emergency department (ED) admission (≤3 h) and at 12 and 24 h after resuscitation in trauma patients treated prehospital with HS (n = 9), HSD (n = 8), or NS (n = 17) and in healthy controls (n = 20)

Data are shown as mean ± SEM; [a]$P < 0.05$ vs. age-matched controls; [b]$P < 0.05$ vs. time-matched NS-treated patients; [c]$P < 0.05$ vs. time-matched HS-treated patients, by ANOVA.

Table 1
Characteristics of the study patients stratified according to resuscitation fluid treatment

	Resuscitation groups			
Variables	**All patients (n=34)**	**HS (n = 9)**	**HSD (n = 8)**	**NS (n = 17)**
Demographics				
Age, years	42.7 (20.3)	43.2 (22.8)	42.9 (18.5)	42 (21)
Male sex, %	25 (73.5)	8 (88.9)	5 (62.5)	12 (70.6)
Admission SBP, mmHg	123.1 (29.3)	141 (30.7)†	126 (24.6)	112.1 (26.8)
ISS	221.1 (11.9)	24.5 (16.8)	21.3 (9)	21.2 (10.6)
Admission biochemistry and coagulation				
Sodium, mEq/L	142.4 (7.5)	147.9 (1.9)†	147.6 (2.4)†	136.9 (7)
Chloride, mEq/L	108.6 (8.8)	114.9 (5.4)†	109.1 (7.8)	104.9 (9.1)
Osmolarity, mmol/L	317.7 (34.4)	334 (29.6)	335 (29.6)	303.1 (34.8)
Hemoglobin, g/dL	10.2 (2.2)	10.7 (2.7)	9.7 (2.9)	10.2 (2.6)
Hematocrit, L/L	0.3 (0.007)	0.32 (0.08)	0.28 (0.08)	0.3 (0.07)
BD, mEq/L	−10.1 (7.8)	−9.2 (5.6)	−13.1 (12.2)	−9.4 (6.7)
Lactate, mmol/L	5.2 (3.5)	5.3 (3.5)	4.8 (1.1)	5.3 (4.3)
INR	1.3 (0.6)	1.3 (0.3)	1.6 (1.2)	1.2 (0.1)
PT, s	15.2 (2.1)	16.2 (2.8)	14.7 (1.6)	15 (1.9)
Platelet ($\times 10^9$/L)	217.2 (13)	195.7 (21.7)†	179.6 (11.7)†	248.1 (33)
Coagulopathic, n (%)*	18 (53)	5 (55.6)	5 (62.5)	8 (47.1)
INR ≥1.3, n (%)	14 (41.2)	3 (33.3)	4 (50)	7 (41.2)
Fluids				
Prehospital fluids, L	1.25 (1)	1.28 (1.1)	1.32 (1)	1.18 (0.9)
Total fluids first 24 h, L	15.7 (15.1)	15.9 (14.2)	14.8 (14.3)	16.2 (18.7)

Demographic data are presented as mean (±SD) and biochemical/coagulation markers as mean (±SEM) for continuous variables or as number (percentage) for categorical values.

*_Coagulopathy_ defined as INR of 1.3 or greater, PT of 14 or longer, and/or platelet count less than 100×10^9/L at the 3-h blood draw.

†Statistical significance ($P < 0.05$) between hypertonic fluids (HS or HSD) versus NS treatment groups, by Student _t_ test.

Table 2

Admission values for coagulation and fibrinolysis biomarkers in patients by resuscitation treatment

		Resuscitation groups		
Marker	**Healthy controls (n = 20)**	**HS (n = 9)**	**HSD (n = 8)**	**NS (n = 17)**
Coagulation				
TAT [1–4 ng/mL]	2.7 (0.5)	27.2 (1.9)*	14.6 (2.1)*†	39.6 (3.1)*
TF [ND]	139.2 (12.5)	109.6 (14.2)	70.3 (10.4)*†	192.6 (29)
TFPI [7.5–41.2 ng/mL]	16.2 (1.8)	24.6 (3.1)	28.8 (3.7)*	22.1 (2.5)
TM [2.7–5.4 ng/mL]	4.6 (0.7)	4.8 (0.6)	5.2 (0.9)	6.5 (1.2)
Fibrinolysis				
tPA [3–12 ng/mL]	5.2 (1.6)	19.7 (2.5)*	25.2 (3.1)*†	15.4 (1.9)*
PAI-1 [4–40 ng/mL]	7.3 (2.2)	38.7 (4.1)*	19.6 (3.4)*†	46.3 (6.5)*
TAFI [40%–250%]	110.1 (7.5)	95.2 (10.2)	80.5 (11.4)*†	104.6 (6.3)
D-dimer [0–400 ng/mL]	227 (25.4)	8,023 (1,205)*†	10,786 (1,359)*†‡	6,375 (997)*

Data are presented as mean (±SEM). Reference ranges are indicated in square brackets.
Statistical differences

*$P < 0.05$ vs. age-matched controls;

†$P < 0.05$ vs. time-matched NS-treated patients;

‡$P < 0.05$ vs. time-matched HS-treated patients, by ANOVA.
ND indicates not determined.

Table 3
Summary of the directional changes for each biomarker

Admission values	Shock groups versus healthy controls	Highest levels (shock groups)	Changes across time (first 24 h)
TAT	5-15× higher	NS > HS > HSD	
TF		NS > HS > HSD	Increased NS group
TM			Increased all groups
TFPI		HSD > HS > NS	Increase HSD/NS
D-dimer	60–80 × higher	HSD > HS > NS	Mostly unchanged
tPA	3–5 × higher	HSD > HS > NS	
PAI-1	2–6 × higher	NS > HS > HSD	
TAFI	Consistently lower	NS > HS > HSD	Sustained decrease all groups