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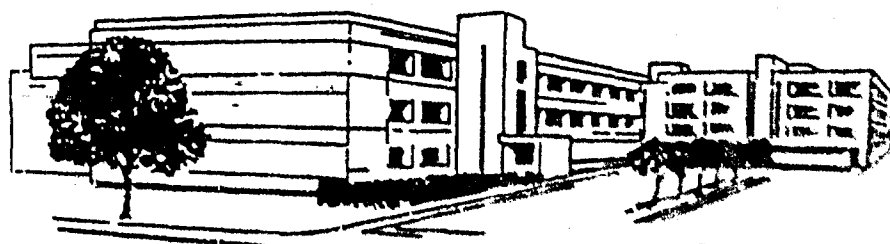
**The Effects of 7.5% NaCl/6% Dextran-70 On
Coagulation and Platelet Function In
Humans and Rabbits**

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Division of Military Trauma Research

November 1989

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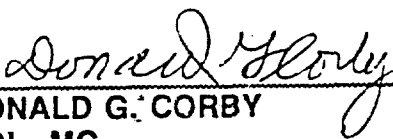
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A solution of 7.5% NaCl/6% Dextran-70 (HSD) has been recently introduced to give hemodynamic improvement in the treatment of hemorrhagic hypotension. Continued controversy, however, regarding reports that dextran interferes with blood coagulation, prompted us to investigate the effects of this HSD solution on select aspects of coagulation. In studies with human blood, HSD was mixed in vitro in a ratio of 1:5 or 1:10 with citrated plasma from healthy adult volunteers, and prothrombin (PT) and activated partial thromboplastin (APTT) time, as well as platelet function determined. HSD incubation significantly prolonged PT and decreased platelet aggregation. Further evaluation indicated that the hypertonic saline, but not the dextran component of HSD, accounted for these effects. In contrast, APTT was not affected by any solution. In other studies, euvoletic and hemorrhaged rabbits were infused with 4				
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ml/kg body weight HSD, and PT and APTT determined at various times ranging from 10 min to 3 days after infusion. HSD infusion did not affect PT or APTT in either group. Taken together, these data suggest that HSD, at concentrations expected in resuscitated patients, does not adversely affect blood coagulation.

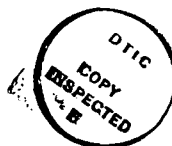
ABSTRACT

A solution of 7.5% NaCl and 6% Dextran-70 (HSD) administered intravenously gives short-term hemodynamic improvement in the treatment of hemorrhagic hypotension. Since dextrans have been reported to interfere with blood coagulation, the effects of HSD on the prothrombin time (PT), the activated partial thromboplastin time (APTT), platelet aggregation, and platelet concentration were studied. HSD mixed with human plasma in ratios of 1:5 and 1:10 caused a dose-dependent prolongation of the PT, but had no effect on the APTT, when compared with the corresponding saline controls. In separate mixing studies, the hypertonic saline but not the dextran component of HSD was associated with the PT prolongation. HSD decreased human platelet aggregation at the 1:5 dilution and the lower aggregation was associated with the hypertonic saline but not the dextran. In euvoletic and hemorrhaged rabbits administered 4 ml/kg of intravenous HSD the PT and APTT were unchanged. The platelet concentrations decreased slightly but remained within normal limits. The data from these studies indicate that in its intended use, HSD is expected to have minimal effect on blood coagulation.

Keywords: prothrombin time;

Partial thrombin time; platelets; (KT)

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The effects of 7.5% NaCl/6% Dextran-70 on coagulation and platelet function in humans and rabbits -- Hess et al.

INTRODUCTION

For 40 years dextrans have been used as plasma volume expanders to manage hemorrhagic shock. Dextrans are attractive agents because of their sterility, colloid oncotic pressure, excellent storage characteristics, and relative freedom from complications of administration. Hemorrhagic complications after the administration of dextrans have been reported, but they appear to be uncommon (1-3). Several early studies with dextrans of average molecular weights (MW) >60,000 reported prolongation of bleeding and clotting times following infusion of large doses (2,4). Others reported that doses of 1000 ml of 6% Dextran-70 prolonged bleeding time, but did not affect clotting time nor platelet number (cf 2). In general, these effects of dextran appeared related to their average MW, with the larger dextrans (MW > 130,000) inducing the most effects on hemostasis (5,6). Thus, the literature suggests that, smaller amounts of dextrans with average MW < 100,000 do not induce alterations in hemostasis or exacerbate clinical bleeding (6).

Assessing the frequency of bleeding complications following dextran administration is difficult due to the diversity of underlying diseases and injuries, the rapid evolution of clinical shock with time, and the dilution of blood coagulation factors with any administered fluid (7). Unfortunately, there are no controlled trials of dextrans in the treatment of human hemorrhagic shock.

Dextrans have also been used to prevent post-surgical deep venous thrombosis (8-10). Most controlled trials of dextrans as antithrombotics did not show that dextran changed the incidence of bleeding complications when compared to untreated controls (8).

In other studies dextrans have been reported to affect the degree of fibrin cross-linking (11), the concentrations of Factor VIII (12), and the platelet aggregation response (13-15). The major clinical correlate of these laboratory effects is a prolonged bleeding time. The bleeding time changes were maximal 4-8 hours after dextran administration, but interestingly, did not correlate with peak plasma dextran concentrations (2,16).

A hypertonic saline (7.5%)/6% Dextran-70 (HSD) solution has recently been introduced as an improved resuscitation fluid for the management of hypovolemia. The use of HSD has reduced the volume of fluid necessary to resuscitate experimental animals from potentially lethal hemorrhage and has even been reported to improve survival in trauma patients when compared with patients resuscitated with Lactated Ringer's solution (17-19). It is hoped that reduced-volume resuscitation with HSD can be translated into greater availability and more rapid administration of fluid to trauma patients, with subsequent savings of life.

With these goals in mind, we examined the in vitro effect of HSD on human plasma coagulation and platelet aggregation and the effect of HSD administration in vivo, on coagulation and platelet number in both euvolemic and hemorrhaged rabbits. These in vivo studies specifically examined the effects of HSD on coagulation at doses employed to manage hemorrhagic shock, since the plasma volume expansion induced by dextran could dilute coagulation and clotting factors that may already be reduced by the hemorrhagic or hypovolemic state (7).

MATERIALS AND METHODS

Human Studies

Venous blood was obtained from 15 healthy adult volunteers, ranging in age from 20 to 63 years. Citrated plasma and platelet rich plasma were prepared by standard techniques. All test agents were obtained from Pharmacia AB (Uppsala, Sweden). The HSD (Lot: NC 54845), or its individual components, 7.5% NaCl (Lot: OD 59339) and 6% Dextran-70 (Lot: OD 59340), was mixed with citrated plasma in 1:10 and 1:5 (v/v) ratios. The 1:10 ratio mimics administration of 250 ml of HSD to a 70 kg individual with a 5 liter blood volume after a 50% hemorrhage. The 1:5 HSD-to-plasma ratio is the maximum expected in surviving patients. Normal saline (NS) was used as an equal volume control, as it is an alternate solution given in an emergency situation. Plasma coagulation was then measured by prothrombin time (PT) and activated partial thromboplastin time (APTT), as well as platelet aggregation. Tests for PT and APTT were run in triplicate.

PT was assayed by incubating a 0.2 ml aliquot of the citrated plasma and test solution mixture for 3 min at 37°C. Thromboplastin (0.1 ml; General Diagnostics, Morris Plains, NJ) was then added and the time for clot formation measured using a fibrometer (Helena Laboratories, Beaumont, TX).

The APTT was determined by incubating a 0.1 ml aliquot of the plasma-test solution mixture with 0.1 ml of PPT activator (General Diagnostics, Morris Plains, NJ) for 5 min at 37°C. CaCl_2 was added and the clotting time measured in the fibrometer.

Platelet aggregation was measured according to the standard platelet rich plasma (PRP) method of Born (20). PRP was processed from citrated whole blood by centrifugation at 150g for 10 min. Platelet concentrations were adjusted to 300,000/ μl using autologous platelet poor plasma. The PRP and appropriate dilution of test solution in a final volume of 0.45 ml, was added to a siliconized cuvette with a teflon coated stir bar. Standard aggregation agonists epinephrine (10 μM), ADP (0.2 mM), collagen (0.2 mg/ml), and ristocetin (1.5 mg/ml; Bio/Data Corp., Hatboro, PA) were added (0.05 ml) and the percent of platelet aggregation was measured in the optical channel of a Whole Blood Aggregometer (Model 540, Chrono-Log Corp., Haverstown, PA). Aggregation with each agonist in each mixture was measured once.

Animal Studies

Adult, female, New Zealand White Rabbits (Elkhorn Rabbitry, Watsonville, CA) weighing between 3 and 4 kg were divided into euvolemic (control; n=5) and hemorrhaged (n=5) groups. Rabbits were catheterized via the middle ear artery and in the hemorrhaged group, bled 8 ml/kg body weight over 15 min to produce a moderate hemorrhage. Rabbits were allowed to stabilize for 30 min, after which time HSD was infused intravenously into the marginal ear vein, a dose of 4 ml/kg body weight. Blood samples were withdrawn prior to and 0.5, 1, 2, 4, 24, 48, and 72 hours after HSD infusion. During the experimental period, rabbits were individually housed in stainless steel cages with free access to food and water. Citrated plasma was prepared by centrifugation and the PT and APTT determined as above except that reagents were purchased from Ortho Diagnostic Systems (Raritan, NJ). Platelet concentrations at each time point were determined by

standard methods in a System 9000 electronic Cell Counter (Baker Instruments, Allentown, PA).

Statistical Analysis

Data were analysed by 2-way or 3-way analysis of variance with treatment, mixing ratio, and, when applicable, replication, as the variables. The Newman-Kuels test was used to compare categorical differences in the means of the variables (21). Probabilities less than 0.05 were considered significant.

RESULTS

Coagulation

Incubation of HSD with human plasma prolonged PT in a dose dependent manner. At a concentration of 1:5 (v/v) PT was 22% higher than in plasma incubated with NS (Fig. 1). At an HSD concentration of 1:10, PT was prolonged about 13%. When HSD or NS was mixed with human plasma, APTT was prolonged about 3 sec with both diluents at the 1:5 dilution (Fig. 1). At the 1:10 dilution, APTT was not significantly different from the control (Fig. 1). Further investigation revealed that the effect of HSD on PT was due to the hypertonic saline component. PT was significantly prolonged in citrated plasma incubated with 7.5% saline in comparison to both NS and Dextran-70 (Table I).

At the times assayed, it was observed that in both control and hemorrhaged rabbits, neither PT nor APTT was significantly affected by HSD administration (Fig. 2a, b). If anything, the trend tended to be toward faster clotting times rather than prolonged times.

Platelets

Aggregation of human platelets was diminished by 1:5 mixing with HSD for all agonists (Fig. 3). Aggregation with epinephrine also was diminished by HSD at the 1:10 mixing ratio. HSD component mixing studies showed that the decrease was induced by the hypertonic saline and not the Dextran-70 component of HSD (Table II).

Platelet counts were slightly lower in hemorrhaged rabbits compared to their euvolemic counterparts, but the differences were not statistically significant. Although a decline in the platelet count followed the administration of HSD in both euvolemic and hemorrhaged

rabbits, platelet counts remained within the range of laboratory and published norms (data not shown).

DISCUSSION

Dextrans were administered to 200,000 patients in the 1940s and 1950s before it was recognized that there were subtle changes in hemostasis associated with their use (1). In experimental animals or humans dextrans have subsequently been shown to prolong the bleeding time and clotting time, to bind to fibrinogen, to interfere with fibrin cross-linking, to reduce the concentrations of factors V, VII and VIII in plasma, and to inhibit platelet aggregation and platelet factor III activity (1-3,8,22). The magnitude of these changes is a function of the dose and molecular weight of the dextrans infused and the time after infusion (1-3,8). For dextrans of less than 100,000 molecular weight, infusions of less than 1.5 g/kg do not significantly affect hemostasis (23). Nevertheless, there is reticence to use an antithrombotic drug for treating hemorrhage.

In the present study, the clinical screening tests of hemostasis, the PT, APTT, and platelet count and aggregation were determined following in vitro incubation with HSD in human plasma and following HSD infusion in both euvoletic and hemorrhaged rabbits. The rabbit studies were designed to mimic the use of HSD in the management of hypovolemia. Measuring both PT and APTT allowed the monitoring of both the intrinsic and extrinsic pathways of coagulation. Although each system can operate independently, they interact through factor X to assure proper hemostasis. Therefore, evaluating both systems allows a more complete evaluation of the overall coagulation response. In fact, it is this interaction between the two systems that has been suggested to account for maintenance of the clotting mechanism despite a possible impairment of thrombin formation by dextran (8,24).

In the present study, although PT appeared to be prolonged in a dose dependent manner in the in vitro human studies, no such effect was observed in rabbits. Further evaluation indicated that the hypertonic saline component of HSD could account for this effect since PT was prolonged in separate mixing studies of hypertonic saline with human plasma. It has been shown that

following i.v. HSD administration, sodium concentrations rise quickly and return to normal within a few minutes after infusion. This indicates that the Na is distributed quickly throughout body compartments (17). Since our first blood sample for coagulation studies after HSD infusion in rabbits was at 30 min, plasma Na levels had returned to pre-HSD infusion levels. Thus, the data from the in vivo studies suggest that any possible effect of hypertonic saline on PT would only be transient. In addition, dextran concentrations in plasma peak early (25) and as previously reported (cf 2), do not correspond to any effect on blood coagulation.

The antithrombotic properties of dextran are well established and may be expressed despite no observed abnormality in coagulation or bleeding time (8,14). Although this observation may reflect the effects of HSD on coagulation and platelet function, they also reflect effects of HSD on the hemodynamic and rheological properties of blood (8). In the present study HSD and its hypertonic saline component decreased platelet aggregation to all agonists at the 1:5 dilution, and for the most sensitive agonist, epinephrine, to a lesser degree at 1:10. Again, this appears to be an effect of the high salt concentration as neither normal saline nor Dextran-70 had any effect at either dilution. At present, the mechanisms responsible for the effect of HSD or hypertonic saline on platelet function are unknown. Weiss (14) found that ADP release from platelets was not observed until dextran concentrations exceeded 50 mg/ml PRP. This concentration is approximately 4 times higher than the highest dextran concentrations used in the present study, but as we observed, the defect in platelet aggregation could be accounted for by the hypertonic saline component of HSD. Although previous investigations did not suggest an effect of dextran on surface receptors or more specifically, glycoproteins II and III (8,26) of platelets, it remains to be established whether the hypertonic saline associated with HSD could induce a transient conforming change in the platelet membrane possibly by affecting intracellular cation balance, or other related mechanism. Nevertheless, it is important to note that effects of dextran on platelet aggregation occur hours after dextran infusion and probably involve a number of mechanisms (14). These delayed effects of dextran were beyond the scope of this study.

In both euvolemic and hemorrhaged rabbits, i.v. infusion of HSD resulted in a transient decrease in the platelet count, but the values remained within the normal range. This observation most likely reflects the hemodilution induced by dextran infusion (27) and is consistent with previous reports following Dextran-70 infusion in rabbits (28). Taken together, the rabbit data suggest that the hypertonic saline and Dextran-70 components of HSD do not interact in a synergistic way to impair hemostasis, and that HSD does not cause a major impairment of hemostasis at the studied dose.

While the reticence to administer a known antithrombotic to patients in hemorrhagic shock is understandable, it must be weighed against the alternatives. Excellent alternatives to HSD for resuscitation are usually available in modern hospitals, but not at sites of casualty care such as freeway accidents or battlefields, the intended sites for use of HSD. The present study suggests that these clinical trials will not be confounded by serious problems of dextran impaired hemostasis.

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10 -- Hess et al.

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Figure Legend

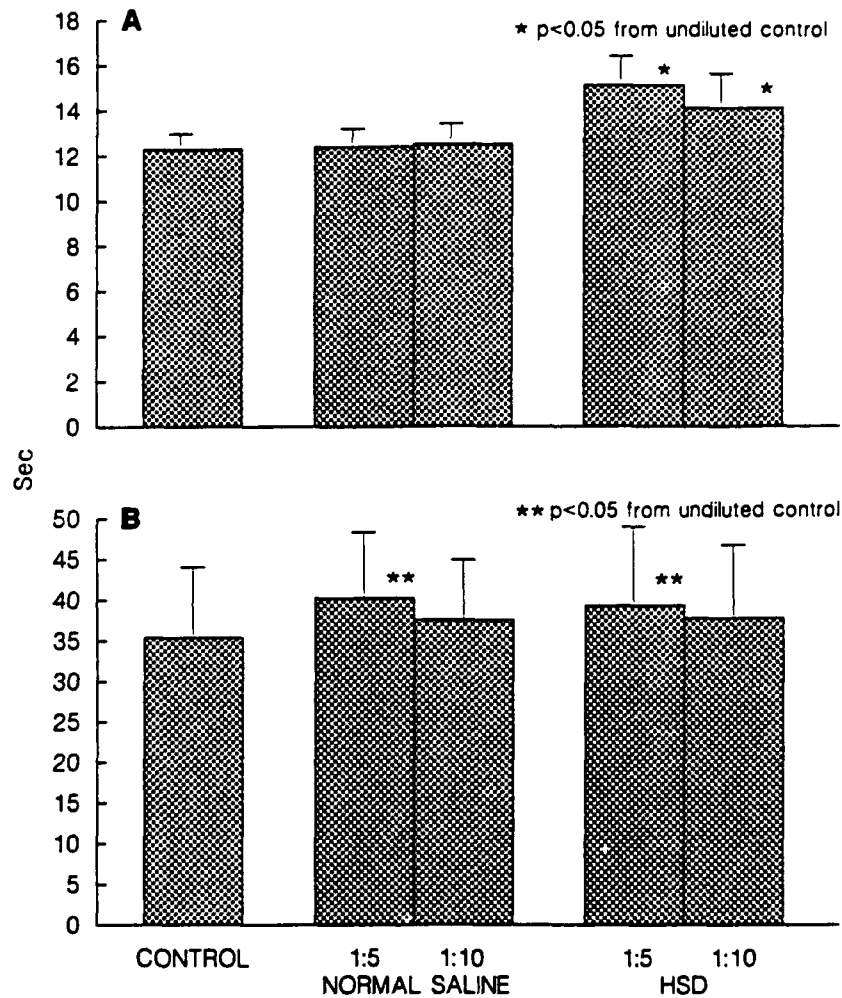


Figure 1: Effect of HSD on A) prothrombin time (PT) and B) activated partial thromboplastin time (APTT) following incubation with human citrated plasma. Data expressed as mean $\pm$ SD for 15 determinations.

* P<0.05 from undiluted control
 ** P<0.05 from undiluted control

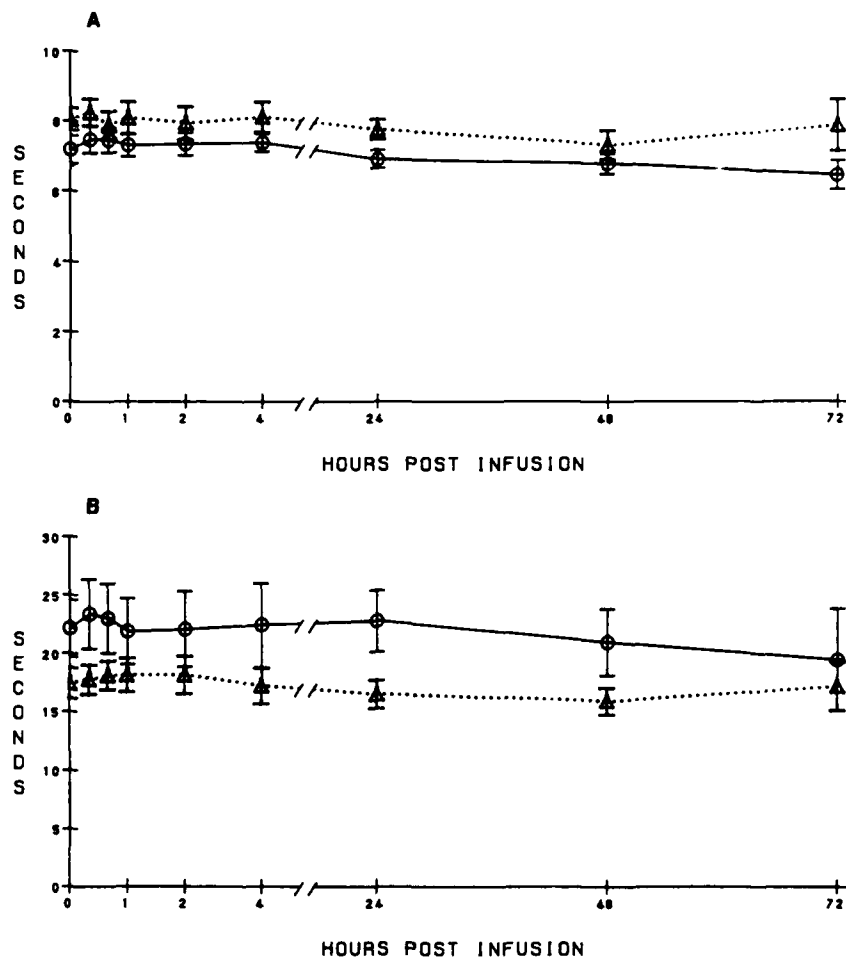


Figure 2: Effect of HSD infusion on A) PT and B) APTT in euvoletic (n=5) solid line and hemorrhaged (n=5), dotted line rabbits. Data expressed as Mean $\pm$ SE.

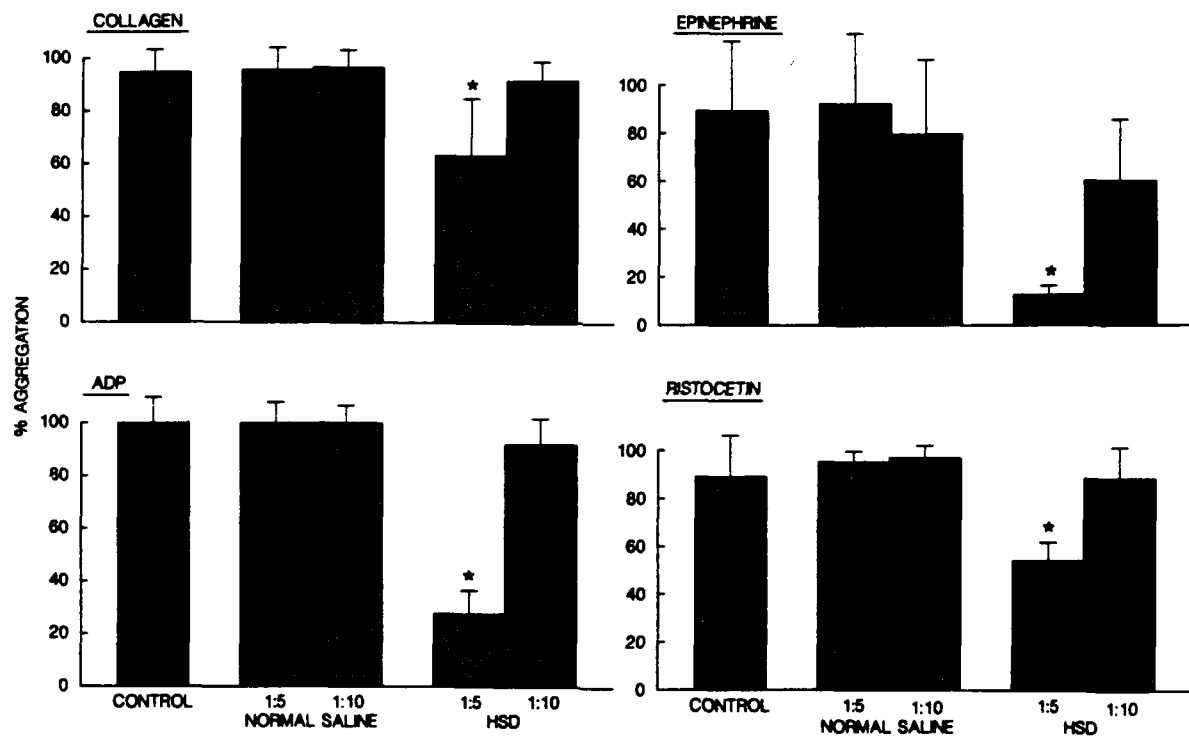


Figure 3: Effect of HSD on platelet aggregation in human platelet rich plasma. Data expressed as mean $\pm$ SD for 15 determinations.

* $P < 0.05$ from undiluted control

Table I

Effects of HSD Components (6% Dextran-70 and 7.5% NaCl)
on Prothrombin Time of Human Plasma¹

<u>Treatment</u>	<u>Prothrombin Time (Sec)</u>
Normal Saline	14.8 ± 1.5 ^a
Dextran-70 (1:5 dilution)	15.0 ± 1.3 ^a
7.5% NaCl (1:5 dilution)	22.8 ± 4.3 ^b
Dextran-70 (1:10 dilution)	14.5 ± 1.4 ^a
7.5% NaCl (1:10 dilution)	17.0 ± 2.4 ^{a,b}

¹ Data expressed as mean ± SD for duplicate determinations from 8 patients.

Values with different superscripts are significantly different (p<0.05)

Table II
Effect of 6% Dextran-70 and 7.5% NaCl on Platelet Aggregation in Human Platelet Rich Plasma¹

<u>Treatment</u>	<u>Dilution</u>	<u>Epinephrine</u>	<u>Agonist ADP</u>	<u>Collagen</u>	<u>Ristocetin</u>
None	---	84.0±19.7	91.2±9.8	84.2±10.6	92.0±7.0
Normal Saline	1:5	92.0±11.6	94.5±11.4	83.7±5.1	88.5±5.2
	1:10	87.5±15.4	93.0±11.4	81.2±16.4 ²	87.2±11.6
Dextran-70	1:5	96.2±15.1	98.5±11.1	76.2±8.3	88.8±10.4
	1:10	93.6±11.6	94.0±8.9	80.0±15.8	88.4±11.8
7.5% NaCl	1:5	22.2±15.4*	39.2±13.1*	56.0±27.9*	66.0±13.3*
	1:10	93.6±12.7	97.8±13.5	92.0±8.8	94.2±9.8

¹ Data expressed as mean ± SD of percent aggregation for single determinations from 5 patients.

² n = 4

* P<0.05 from control and other treatments.

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