Disordered blood coagulation in burned children receiving high molecular weight dextran

TREVOR THOMAS, ARTHUR MORRIS, AND MICHAEL S. ROSE

From the Departments of Haematology and Plastic Surgery, Guy's Hospital, London

SYNOPSIS Coagulation studies were performed on nine children with burns. Four of these children received treatment which included intravenous dextran; all four showed abnormalities of coagulation and two of them developed a bleeding state. No abnormalities of haemostasis were detected in the remaining five children who had comparable degrees of burns but whose treatment did not include intravenous dextran.

Our attention was first drawn to a disturbance of coagulation following burns in a 2-year-old child (Table, case 1). He began to bleed profusely from the sites of injury two days after suffering a scald involving 25% of his body surface (Fig. 1). During the 48 hours following the burn fluid was administered intravenously in the form of dextran (Dextraven¹ 110 and 150) and half-strength Hartman's solution, as calculated from the fluid regime described in the addendum. The results of coagulation studies are shown in the Table (case 1). A diagnosis of disseminated intravascular coagulation was considered likely. At the time of the bleeding, swabs taken from the burned area showed no bacterial growth. As septicaemia is a recognized cause of disseminated intravascular coagulation, blood cultures were taken but no significant microbial growth occurred.

Heparin therapy was started by continuous intravenous infusion (100 units/kg/six hours). The subsequent changes are shown in Figure 2. These results are evidence that the disorder of coagulation was corrected. The bleeding stopped within 12 hours of starting heparin and the patient returned home 10 days later without requiring a skin graft. We afterwards observed that the onset of heparin therapy had coincided with the withdrawal of dextran.

Generalized spontaneous bleeding is extremely unusual as a complication of burns, except as a result of secondary infection. No reference is made to such events in current editions of standard textbooks (Sevitt, 1957; Biggs and MacFarlane, 1962; Hardisty and Ingram, 1965) or in recent symposia (Annals of the New York Academy of Sciences, 1968) or reviews

Fig. 1. Bleeding from sites of injury.

Fig. 2. Changes after heparin.

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(Pitney, 1971). The changes in coagulation factors and platelets have been studied after cutaneous burns in human subjects (MacDonald, Levenson, Davidson, Tagnon, and Taylor, 1944) and in experimental animals (Dodd-Wilson, Taylor, and Nicholson, 1965; Mazak, Vanasek, and Mateja, 1965). Shortly after an extensive burn clotting systems are accelerated (Sevitt, 1957). In subjects who die within hours or a few days of severe burns, disseminated microthrombi are frequently found. These findings may be the counterpart of a consumption coagulopathy. Nevertheless bleeding is an unusual problem in clinical experience.

In view of these observations we believe that the clinical and laboratory findings which follow may be of some interest.

Coagulation Studies in Other Burned Children

Because of the unexpected bleeding in an otherwise uncomplicated case of burns, clotting studies were performed in eight children with burns who were admitted to Guy's Hospital. Abnormalities of clotting were found in three of these children (cases 2, 3, and 5) all of whom had received dextran: case 3 bled considerably for a number of days from the site of a femoral vein puncture. No abnormalities of clotting were found in the remaining five patients,

none of whom had received dextran (cases 4, 6, 7, 8, and 9). Details are shown in the Table.

Case 4, with 13% burns, was given neither dextran nor plasma, and cases 6-9, with burns between 14% and 30%, received plasma and no dextran. In case 5, samples were tested before, during, and after the administration of dextran, and the sequence of events is illustrated in Figure 3.

In-vitro Effect of Dextran on Coagulation and Platelets

Standard coagulation tests (Hardisty and Ingram, 1965) were employed to characterize the effects *in vitro* of dextran upon the clotting system.

METHODS

Doubling dilutions of 6% dextran (Dextraven 110) were prepared in 5% dextrose. Each dilution was mixed with an equal part of pooled normal plasma. The diluted mixtures were tested for prothrombin time, kaolin-cephalin time, and thrombin time.

A partial thromboplastin time, without kaolin, was used as a test of activation of the contact factors. Blood was taken from normal donors and the tests were carried out in siliconized apparatus. A series of doubling dilutions of 6% dextran were prepared in 5% dextrose. Equal parts of each dilution were added to the normal plasma. Partial thromboplastin times

Case No.	Age	Sex	Per-centage Area Burnt	Bleeding	Intra-venous Fluid	Prothrombin Time ^a			Kaolin-cephalin Time ^a			Thrombin Time ^a			Fibrinogen Titre ^a			Platelet Count × 10 ³ ^a			Progress of Patient
						1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
1	2	M	25	Yes	P + D ¹	17	13		70	35		8	9		16	64		17	125		Recovered; no graft
2	4½	F	20	No	D	15	13		120	45		8	7.5		32	128		100	100		Recovered; split skin grafts
3	2	F	40	Yes	D	20	25		64	100		7.5	11		64	16		140	45		Died of respiratory burns
4	9/12	M	13	No	—	14			30			14									Recovered; no grafts
5	9	F	17	No	D	13	14	14	30	68	55	13	7	9	128	64	64	130	45	150	Recovered; no grafts
6	8/12	M	15	No	P	13	13		33	33		12	10		64			201	252		Recovered; split skin grafts
7	8/12	M	16	No	P	14	14		28	37		12	16		128	64		324	151		Recovered; no skin grafts
8	3	M	30	No	P	13	14		31	36		11	13		128			189	343		Recovered; split skin grafts
9	2	M	14	No	P	13	14		27	39		11	11								Recovered; no skin grafts
Control figures						13-14			32-37			11-14			64-			200-400			

Table Clinical and laboratory details of children with cutaneous burns

¹D = dextran, P = plasma.

^a1, 2, 3 denotes: 1, sample taken before intravenous therapy commenced; 2, sample taken during intravenous therapy; 3, sample taken 24 hours after conclusion of intravenous therapy.

Fig. 3. Sequence of events in case 5 after dextran.

were then measured in these mixtures. Control measurements were made upon plasma-dextrose mixtures.

The aggregating effects of dextran on platelets were studied by mixing platelet-rich plasma in equal parts with dilutions of dextran in dextrose. Samples were incubated for 30 minutes at 37°C. They were then examined microscopically.

Results

The addition of dextran was found to have no effect on the prothrombin or kaolin-cephalin times. However the addition of a 50% dextran solution was responsible for shortening the thrombin time from 12 seconds to 8 seconds.

The addition of dextran to plasma did not shorten the partial thromboplast time.

Dilutions between 12.5 and 50% of the 6% dextran solution caused aggregation of platelets after 30 minutes at 37°C whereas aggregation was not observed after incubation with dextrose.

Discussion

Dextran preparations are widely employed in the early treatment of severe burns with fluids. A

limited enquiry from burns units in the vicinity of London has made it clear that bleeding problems in subjects receiving dextran have not been encountered. But although the laboratory findings described above could have been a consequence of the burns (MacDonald *et al*, 1944; Johansson, 1961 and 1964; Arturson and Wallenius, 1964; Hawtof, 1966) it seems more likely that the administration of dextran produced the coagulation abnormalities and the fall in platelets. Certainly, at least, the concentration of dextran employed in the *in vitro* test systems corresponded closely to the *in vivo* dextran concentrations which were present during and shortly after colloid replacement treatment (see addendum).

The effects of dextran upon platelets and clotting factors are partly determined by its molecular size (Nilssen and Eiken, 1964). Our observations are similar to those of Dhall, Harper, McKenzie, and Matheson (1966) who demonstrated that dextrans ranging in molecular weight from 10 000 to 500 000 caused aggregation of human platelets *in vivo*. Berman (1964) showed that dextran inhibits platelet aggregation *in vivo* at sites of injury in the hamster cheek pouch. Others have shown that dextran infusion into healthy human subjects reduces platelet adhesiveness (Bygdeman and Eliasson, 1966; Bennett, Dhall, McKenzie, and Matheson, 1966). Possibly these discordant findings can be explained by the sequestration *in vivo* of clumped platelets after dextran infusion, leaving a residual circulating population of platelets with uncharacteristic activity. However, Bennett *et al* (1966) did not note any substantial change in the venous platelet count of their subjects within 24 hours of dextran infusion.

Bergentz, Eiken, and Nilssen (1961) found that infusion of high-molecular weight dextran into dogs caused thrombocytopenia, fibrinogenopenia, and depletion of other coagulation proteins. Heparin prevented all of these effects apart from the thrombocytopenia. If these effects of dextran represented a true consumption coagulopathy, heparin would be expected to prevent thrombocytopenia. Furthermore the rate at which the platelet count returned to normal in case 1 after heparin therapy is unusually rapid for this syndrome.

We found no evidence that dextran either inhibited or activated coagulation *in vitro*. However, we found a striking shortening of the 'thrombin time' both in the plasma of patients transfused with dextran and in normal plasma mixed with dextran. This 'fibrinoplastic' effect has been previously described by Laurell (1951) and Jacobaeus (1955).

Working with dogs, Nilssen and Eiken (1964) showed that the molecular weight of the dextran was the main factor in determining the degree to which coagulation was impaired. They argued that the

administration of high molecular weight dextran causes a consumption coagulopathy. We are inclined to explain our findings as the result of independent effects of dextran upon coagulation factors and platelets. It is intriguing that dextran is responsible for a shortened thrombin time both *in vivo* and *in vitro*, and correspondingly accelerates the final steps in clot formation, whereas its other effects *in vivo* are inclined to produce impaired clotting. Whatever the sequence of events, it is clear that a reduction in coagulation and a fall in platelets frequently accompanies the administration of high-molecular weight dextrans.

Dextrans are widely used in the early treatment of burns and overt failure of haemostasis is a most unusual complication. Possibly in such clinical circumstances dextrans have a beneficial effect in preventing microvascular occlusion which would represent more of a hazard than impaired coagulation. There appears to be little reason to suggest preferential use of plasma since clinically overt bleeding disorders are so unusual during dextran treatment and resolve rapidly if the dextran is withdrawn. Nevertheless it is worth emphasizing that laboratory evidence characteristic of a defibrination syndrome may accompany or follow the administration of dextran. Two of the four children who had received intravenous dextran developed clinical bleeding and two did not. It is not clear precisely what determined which children bled. The cause, nature, and extent of the burn was similar in all four children, as was the order of disturbance affecting haemostasis. In burned subjects receiving dextran who develop clinical bleeding, coupled with evidence of a generalized disorder of coagulation and a fall in the platelet count, withdrawal of dextran may be the most appropriate therapeutic step.

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Addendum

FLUID REGIME

The amount of fluid required in the first 48 hours is estimated by comparing the percentage of body surface burned with the volume of fluid (the percentage of total fluid volume expressed in litres, assuming body weight in kg = litres) in the following table.

Percentage of Body Surface Burned	Percentage of Fluid Replacement
10-15	5-7
15-20	10-15
20-30	15-20
30-50	20-30
Over 50	30

ADMINISTRATION

This volume is given as half colloid (dextran or plasma) and half electrolyte (half-strength Hartman's solution) in three periods:

Period I ..	One third in eight hours
Period II ..	One third in 16 hours
Period III ..	One third in 24 hours

TREATMENT OF CASE 1

Body weight, 15 kg; percentage of body surface burned 25; fluid replacement = 20% of 15 litres to which add basal requirements 1 000 ml per 24

hours. Colloid infusion in period I 500 ml plasma, in period II 800 ml Dextran 150¹, and in period III 1000 ml Dextran 110.

¹Dextran 150 was used only in case 1. In the other subjects only Dextran 110 was employed.

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