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Volume expansion and flow promotion in shock

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Summary

Volume replacement is the most important step in treating hypovolaemic shock.

Blood is needed when the oxygen carrying capacity threatens to fall below a critical level, but has the disadvantage of transmitting virus hepatitis. Anicteric hepatitis is about four times more frequent than the icteric form. Pasteurized plasma protein solution and albumin are free from the risk of transmitting hepatitis virus, and are good volume restorers.

Dextran 70 represents the best artificial colloid with additional anti-thrombotic properties. Dextran 40 is indicated in special situations to promote flow.

There is no proof that large amounts of Ringer solution are superior for treating hypovolaemic shock in man compared with colloids and electrolytes.

Introduction

It is generally agreed that *early* volume replacement represents the most important single step in treating *hypovolaemic* shock. For treating *normovolaemic* forms of shock volume expansion and thus possibly flow promotion is considered to be an important therapeutic step by many clinicians. With great simplification one might say that it is not so important *what* one gives, if one just gives *enough* and *in time*. This is probably true, if one thinks in terms of immediate survival only. However, if we consider the final outcome we should consider all possible pharmacological and side-effects of a given therapeutic regimen. Therefore, we should keep in mind the following facts regarding different forms of volume therapy:

Blood

(a) The greatest danger of a blood transfusion lies in the risk of transmitting viral hepatitis. As Grindon, Holland & Schmidt (1967) recently stated: 'A reasonable conclusion is that, of 1000 patients who receive 1 unit of blood, approximately 100 patients will develop hepatitis, ten will become jaundiced, and one will die of this disease'.

(b) In severe haemorrhagic shock, blood transfusion is the most effective therapy. Erythrocytes produce a volume-effect which corresponds to the amount transfused. There are, however, good reasons to believe that in certain patients [the percentage is not accurately known—it is presumed to be about 20% (Gruber & Bergentz, 1967)] the main portion of the plasma component leaves the vascular system within about 1 hr. This phenomenon, known as 'homologous blood syndrome', probably has immunological causes and has nothing to do with the known blood groups.

For description of different Dextrans see Table on p. 490.

Plasma

(a) Since the incidence of hepatitis after administration of fresh plasma, stored pooled plasma or dried plasma is about the same as after blood transfusion these preparations should not be used for treatment of shock (Gruber, 1968).

(b) Pasteurized plasma protein solution and albumin do not carry the risk of transmitting viral hepatitis and give a reliable volume effect (Gruber, 1968). Their main disadvantages are that they are available in limited amounts only and are very expensive. Furthermore, they do not contain globulins.

Dextran 70 (Macrodex)

A solution of Dextran 70 in 0·9% NaCl is the best artificial colloid for volume replacement available today. It does influence the clotting mechanism in dosages of more than 1·5 g/kg body weight/24 hr in man. However, this is not of practical importance since larger amounts are not usually given, because the limiting factor in administering erythrocyte-free solutions is the amount of circulating haemoglobin. Dextran 70 and 40 are not antigenic in man. However, anaphylactoid reactions do occur, but they are less frequent than after blood or plasma administration. In addition to being reliable volume substitutes both Dextran 70 and 40 do have a definite antithrombotic effect (for reviews see Bygdeman, 1968a, b; Gruber, 1968; Dhall, Bennett & Matheson, 1968).

Gelatin

For the following reasons gelatin preparations cannot be recommended as blood substitutes:

(a) Their physico-chemical properties are not precisely known.

(b) The main portion of a gelatin solution is excreted in the urine within a few hours. Nothing definite is known about plasma concentration and breakdown of gelatin which remains in the body, since specific methods of demonstration are lacking.

(c) Gelatin infusions raise the sedimentation rate (ESR) at lower concentration and molecular weight compared to Dextran (Dextran 70 does not influence ESR, Dextran 40 lowers it).

(d) Gelatins cause cell aggregation in lower concentration and with lower molecular weight than Dextran (Dextran 70 does not influence aggregation, Dextran 40 counteracts it).

(e) There are no data concerning the influence of gelatin preparations on blood viscosity at shear rates which occur in the capillary bed in humans.

(f) The volume-effect of gelatin solutions in hypovolaemic individuals does not quite correspond to the amount infused initially and then declines rapidly. The volume-effect lies approximately between the levels observed after infusion of equal amounts of electrolyte solution or plasma.

(g) The ability of gelatin to improve cardiac output has not been fully investigated. The data available show that the effect does not equal that of plasma. There are no data concerning a specific flow-improving effect of gelatin solutions.

(h) Only a few experimental results obtained with older 5% preparations permit the assumption of a therapeutic effect comparable to that obtained with plasma in the treatment of severe shock. For the preparations available today there are no usable results of shock studies in dogs and other large animals, nor do the shock models used in rabbits allow conclusions with regard to the therapeutic effectiveness in hypovolaemic patients. There are no clear, verifiable data concerning the *clinical* utility of gelatin preparations in treatment of serious shock states.

Large amounts of electrolyte solutions

(a) Animal and human studies show that the blood volume can barely be maintained for a few hours after replacement of the blood lost with two to three times as much isotonic electrolyte solution.

(b) There is no reason to believe that a disproportionately large reduction of the interstitial space occurs in hypovolaemic shock (Anderson *et al.*, 1967; Reid, Digerness & Kirklin, 1967; Roth, Lax & Maloney, 1967; Schloerb *et al.*, 1967; Shizgal, Lopez & Gutelius, 1967; Vineyard & Osborne, 1967; Boba, 1968).

(c) In animal experiments, early replacement of lost blood with *large* amounts of electrolyte solutions without colloids in haemorrhagic but not in endotoxic (Rush & Sparks, 1967) shock produces results as good as those obtained with blood, plasma-derivatives or artificial colloids. There is no proof that this type of therapy is superior; there are no results of careful comparative studies in humans.

(d) There seems to be little danger of oedema with infusion of large amounts of electrolyte solutions when cardiac and renal functions are intact; however, there are no precise data about this risk in shock patients who have heart and kidney disease.

(e) Additional use of *hypertonic* solutions (regardless of the substance dissolved) along with blood transfusion has a favourable haemodynamic effect (Messmer, 1967). Nothing is known about the therapeutic value in humans; in animal experiments the results are contradictory.

Flow promotion

Flow promotion and volume expansion are very much related to each other and cannot be dealt with separately. But although we can measure volume pretty accurately suitable quantitative methods for direct measurements of capillary flow are lacking. Therefore a critical evaluation of this whole problem is difficult. In addition in treating shock we are not so much interested in flow *per se*, but would rather like to know more about the circulation's ability to deliver adequate amounts of oxygen to the tissues. In spite of these technical difficulties a certain number of facts are known.

Flow improvement is dependent on the following effects of a volume-substitute:

Volume-expanding effect

Four per cent pasteurized plasma protein solution, 5% albumin and 6% Dextran 70 have a volume-expanding effect roughly equal to the amount infused, whereas 15–20% albumin or 10% Dextran 40 (Rheomacrodex) are plasma *expanders* in the true sense of the word.

Colloid osmotic effect

Concentrated albumin solutions and 10% Dextran 40 are strongly *colloid* (= *oncotic*) *hypertonic solutions* and, therefore, absorb water from the interstitial space into the capillaries. Thus, they might passively dilate capillaries (Guyton, 1963; Hint, 1964; Hopkinson *et al.*, 1968).

Effect on the rheological properties of blood

The rheological properties of blood are mainly influenced by erythrocyte aggregation and viscosity.

(a) *Blood cell aggregation.* The importance of this phenomenon is not fully clarified. Again methodological difficulties are responsible. However, it has been shown that erythrocyte aggregation increases blood viscosity *in vitro* at low shear rates (Gelen, 1962). Recent studies demonstrate that trauma does

produce sludge (Long & Corley, 1967; Matsumoto, Hardaway & McClain, 1967; Matsumoto *et al.*, 1968) and that erythrocyte-aggregates can block part of the capillary system (Bigelow, 1964). There is no doubt that infusion of Dextran with a molecular weight below 50,000 counteracts aggregation (Thorsen & Hint, 1950; Long & Corley, 1967).

(b) *Blood viscosity.* The viscosity of whole blood is mainly dependent on: haematocrit, rheological properties and the plasma viscosity. These relations are exemplified in Table 1 (data from Rand *et al.*, 1964).

TABLE 1. Viscosity (cP) at 37°C for normal human plasma and blood measured at various levels of haematocrit and shear-rate (rate of flow) (Rand *et al.*, 1964)

Shear-rate (sec^{-1})	Plasma	Haematocrit		
		20%	40%	60%
212	1·4	2·5	3·8	6·5
106	1·5	2·6	4·4	7·2
42	1·5	2·8	5·3	8·8
21	1·6	2·9	5·8	10·9

It is evident that blood flow can be greatly improved if the haematocrit is decreased, rheological properties are improved and plasma viscosity is not changed (Groth, 1966a, b; Bollinger *et al.*, 1968). Infusion of Rheomacrodex fulfils these criteria (Fig. 1). Thus it has been shown repeatedly that Dextran 40 decreases blood viscosity in man (Groth, 1966a, b; Yao & Shoemaker, 1966; Bollinger *et al.*, 1968). On the other hand, it is known that blood infusion in shock may increase viscosity (Schenk *et al.*, 1964) and might be detrimental (Replogle & Merrill, 1967; Kho & Shoemaker, 1968).

The rheological properties of blood are influenced by several other factors like the internal viscosity of blood cells and the frictional forces between the capillary wall and the blood cells. However, their relative importance is difficult to assess (Rosato, Miller & Hebel, 1968).

There are sufficient data available to state that Rheomacrodex does improve flow (Kavee, Lichtenstein & Laufman, 1967). The mechanism of action is complex and is the combined result of volume expansion, colloid osmotic effect, haemodilution, the disaggregating and perhaps also the anti-thrombotic effect.

If *haemodilution* from a rheological standpoint seems reasonable we must always keep in mind the corresponding decrease in oxygen-carrying capacity (Gump, Butler & Kinney, 1968). However, since blood viscosity is an almost exponential function of the haematocrit, haemodilution must have a much greater effect on blood flow than on oxygen-carrying capacity which is a linear function of the haematocrit (Table 1).

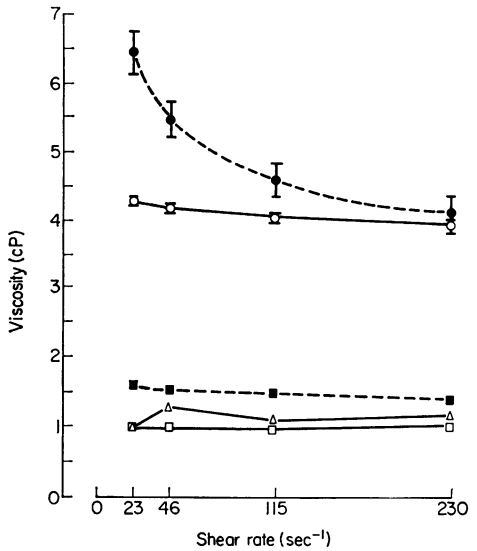

FIG. 1. Rheomacrodex (○), as supplied in 10% solution, is fairly viscous. At low shear rates its viscosity is less than that of normal human blood (●). The main fact is that the viscosity of the Rheomacrodex solution in the bottle is quite irrelevant to its *in vivo* effects, because the circulating Dextran is diluted. Rheomacrodex 10% is a hyperoncotic solution. Almost immediately after infusion it draws water from the extravascular space. Therefore, the circulating Dextran concentration in clinical use is around 1% and rarely exceeds 2%. The viscosity of a 1% (□) and even a 2% (△) Rheomacrodex solution is well below that of normal human plasma (■) so that a viscosity-lowering effect is to be expected. (Adapted from Groth (1966a, b) and according to personal communication from O. Tangen, Uppsala.)

There is some experimental and clinical evidence to show this when haemodilution is carried out with albumin or Dextran 40. However, this might not be true if colloid-free solutions are used (Gump *et al.*, 1968). Groth & Löfström (1966) have measured tissue oxygen tension after administration of Rheomacrodex, 10% albumin, blood and Dextran 70. They have shown that the beneficial effects of Rheomacrodex and albumin could not be due to dilution alone, since they were not achieved by infusion of Dextran 70 leading to a comparable reduction in haematocrit. Evonuk & Sullivan (1967) have shown that oxygen consumption in dogs increases after administration of 1 g/kg body weight of Rheomacrodex, and recently this has been demonstrated to be true in patients with traumatic, though not with septic, shock (Kho & Shoemaker, 1968). These findings are confirmed by observations of Hinshaw *et al.* (1960), Hunt *et al.* (1967), Korolkov & Koziner (1967a, b), Schmidt & Bökenkamp (1967) and Whitmore (1967). Certainly more data are needed, especially regarding regional differences (Race, Cooper & Rosenbaum, 1968). However, they might

explain the beneficial action of Rheomacrodex seen in different shock states—*experimental*: haemorrhagic (Lepley *et al.*, 1963; Johnston, Pearson & Murphy, 1964; McPherson & Haller, 1964; Schenk *et al.*, 1964; Greenfield & Blalock, 1964; Schumer, 1967; Takaori & Safar, 1967), endotoxic (Lillehei *et al.*, 1964; O'Neill & Foster, 1964; Wiznitzer & Rozin, 1965), exotoxic (Atik *et al.*, 1967) and cardiogenic (Bloch *et al.*, 1965); and *clinical* (Bergentz *et al.*, 1961; Baker *et al.*, 1964; Carey *et al.*, 1965a, b; Cohn & Luria, 1965; Gunnar *et al.*, 1967; Loeb *et al.*, 1967).

It is difficult to prove whether the effect of Dextran 40 is a specific one (Engstedt *et al.*, 1967), since the three main pharmacological actions of plasma volume expansion, flow improvement and the antithrombotic effect are all related and their relative importance is not fully understood. So far no studies are known which demonstrate an antithrombotic effect of albumin, though disturbances of the clotting mechanism and thrombo-embolic complications probably do play a role in shock pathogenesis (Cook & Webb, 1968).

Conclusions

It is fair to say that specific means for improving flow do not need to be taken if adequate prompt volume replacement is guaranteed. However, significant rheological alterations do occur in long-standing shock with massive tissue injury as is common in surgery. The occurrence of microthrombo-embolism further complicates this situation and limits oxygen delivery. It is in these situations where the use of flow-promoting agents seems to be justified.

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