EXPERIMENTAL TREATMENT OF ACUTE HEMORRHAGE WITH POLYVINYLPYRROLIDONE SOLUTIONS

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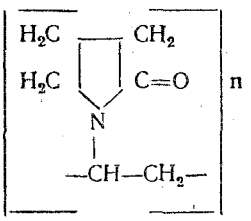
Apart from blood transfusion, a number of plasma extenders are used in the treatment of acute hemorrhage, such as specially treated heterogeneous proteins and colloidal solutions of synthetic products having similar physicochemical properties to blood plasma.

Of such synthetic products much interest has been taken in polyvinylpyrrolidone. This substance was synthesised by Reppe[5]from ammonia and formaldehyde, and has the following structure:



Polyvinylpyrrolidone is a white powder, soluble in water, giving colloidal solutions. It is chemically inert, and resists sterilization, long storage, and transportation.

It has, with isotonic salt solution, been widely applied in various countries as a plasma substitute, being known in Germany as Periston, in England as Plasmosan, in the USA as Plasdone or Polyvinylpyrrolidone Macrose, in France as Subtosane, in Italy as Plasmovinil, and in Finland as Replasin. These preparations are not altogether identical, since the conditions of synthesis and production differ in different countries. A considerable volume of literature devoted to both the experimental and the clinical study of this product has been published[1-4, 6-9].

The present paper is devoted to a description of the study of the Soviet preparation of polyvinylpyrrolidone, synthesized in the Institute of Organic Chemistry, Academy of Sciences USSR and in the Central Institute for Blood Transfusion, by M. F. Shostakovskii, P. F. Vasilyev, F. P. Sidelkovskaya, E. S. Morgunova, and M. G. Zelenskaya. We studied a 3.5% solution of polyvinylpyrrolidone, of a molecular weight of about 40,000, in Ringer's solution; its viscosity was about 3, and its colloidal osmotic pressure was equal to about 340 mm of water. The experiments were done on cats (dogs have a species intolerance to polyvinylpyrrolidone).

Altogether about 40 experiments were performed. We first established that the preparation was well tolerated by the animals, and that it did not cause any histological changes in their internal organs.

In order to exclude the possibility that polyvinylpyrrolidone exerts a direct toxic action on the heart, we performed some experiments on an isolated Pavlov-Starling heart preparation, in which blood perfusing the heart

was partly replaced by polyvinylpyrrolidone, in two stages (Fig. 1).

The first replacement was followed by retardation of heartbeat , rise in arterial pressure, and fall in right auricular pressure; these changes are evidence of improved circulation.

The minute volume of the heart remained unchanged. Similar, although somewhat less marked effects, were observed after the second stage of blood replacement, in which over half of the circulating blood had been replaced by polyvinylpyrrolidone, and the hemoglobin content had fallen from its initial value of 55% to 18%.

The minute volume of the heart was now slightly increased. No differences were observed in the electrocardiograms taken after the first and second replacements and at the end of the experiments, other than those due to retardation of heart rate. It follows that polyvinylpyrrolidone does not have any pathological effect on cardiac function, and even has some stimulating effect on the heart.

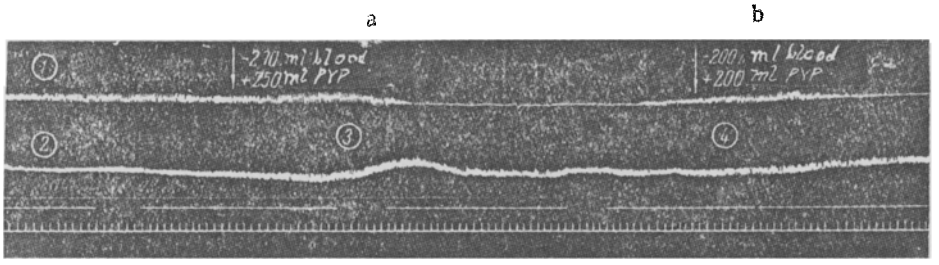


Fig. 1. Kymograph tracing showing the effect of partial replacement of blood by polyvinylpyrrolidone (PVP) solution on a Pavlov-Starling heart preparation. Explanation of tracings (from above down): pressure in right auricle, arterial pressure, zero line, time base. The arrows indicate the time of replacement of blood by PVP solution. 1) height of venous column 42 cm., arterial pressure 45 mm., volume of circulating blood 700 ml; 2) heart rate 108 beats per minute, minute volume 300 ml., hemoglobin 55%; 3) corresponding figures: 90 per min., 300 ml., 29%; 4) 96 per min., 324 ml., 18%.

Further study of the action of PVP was carried out on healthy animals, to which the solution was given intravenously, at a rate of 20 ml per kg body weight. In these experiments, as in those on hemorrhage, we observed arterial pressure and respiration (registered on a kymograph), functioning of the heart (electrocardiographic registration), and circulating blood volume (using the dye T1824-Evans blue).

Kymographic recordings showed that introduction of the PVP preparation was followed by increase in amplitude of the pulse and in blood pressure. During the following 2 hours blood pressure remained about 20 mm higher than initially, while the amplitude of the pulse fell somewhat.

No respiratory changes were observed either at the time of introduction of the PVP solution or during the subsequent 1-2 hours.

Introduction of PVP solution causes increase in the volume of circulating blood, which after 2 hours is equal to the amount injected.

The hemoglobin content fell immediately after introduction of PVP solution, and then rose slightly, to a level lower than the initial one, at which it remained over the period of two hours of observation. The hematocrit readings varied directly with the hemoglobin content.

Our experimental results thus show that transfusion with PVP solution has no pathological effect on the cardiovascular system, that its colloidal osmotic pressure is adequate, and that it remains in the blood stream, ensuring increase in circulatory volume. These data afford a basis for the solution of the question: can transfusion of PVP solution save the life of an animal which has lost so much blood that a rapidly fatal issue would be inevitable in the absence of effective treatment?

Amounts of 30-40 ml per kg of body weight* of blood were taken from the carotid or iliac artery of anesthetised cats; withdrawal of blood was continued until signs of acute circulatory failure appeared, and respiration

*According to published data and to our own observations the volume of circulating blood in cats varies from 60 to 75 ml., i.e., much less than in dogs.

became of the pre-agonal type. An amount of PVP solution equal to the volume of blood withdrawn was then introduced.

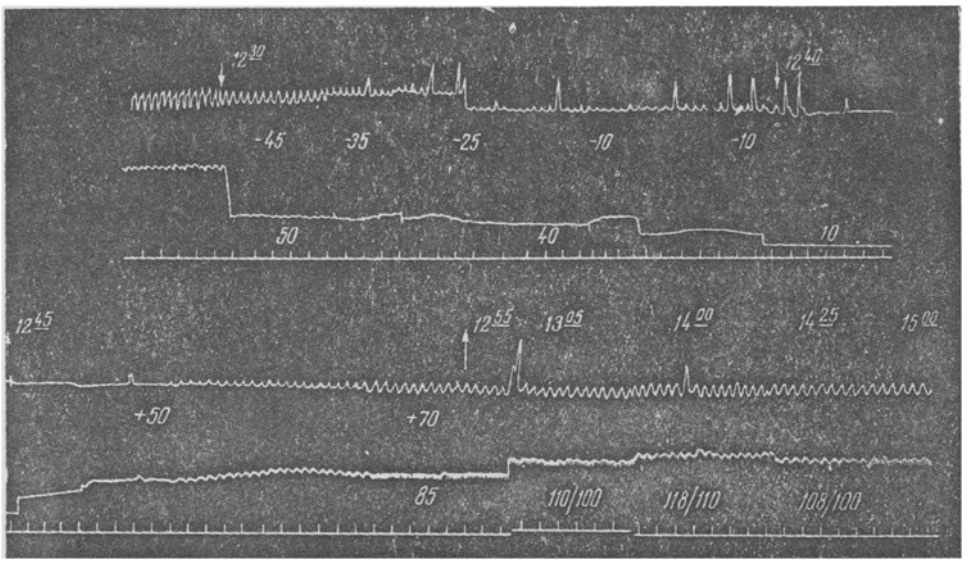


Fig. 2. Changes in respiration and arterial pressure following withdrawal of blood and its replacement by polyvinylpyrrolidone solution, in a 4 kg cat. Explanation of tracings: from above down, respiration, arterial pressure, time base; ↓ beginning and end of blood-letting, ↑ beginning and end of transfusion of PVP solution.

As is evident from the tracings of Fig. 2, arterial pressure fell to 10 mm as a result of bloodletting, and the systolic volume became so small that pulsation was no longer evident in the manometric tracing. Very severe respiratory disturbances are apparent; the respiratory rate showed marked alteration during withdrawal of blood, and respiration was practically absent at its completion. Transfusion of PVP solution was begun 5 minutes later, and this led to restoration of normal respiratory rhythm and amplitude. Blood pressure rose to 85 mm towards the end of the transfusion, and continued to rise after its completion. At the end of the experiment blood pressure remained steady, at a level necessary for survival, and respiration was rhythmical and of sufficient amplitude.

Electrocardiograms taken at the time of maximum blood loss showed the following deviations from the normal: almost total abolition of the R wave, weakening of the S wave, lowering of the ST interval below the isoelectric level, and tachycardia. Conduction was not affected. Transfusion of PVP solution restored heart function, and the electrocardiogram resembled the normal one.

The improvement in heart action is particularly well shown by the changes in the systolic index (according to Fogelson). This index was 83 at conclusion of bloodletting, but fell to 62 at the end of the transfusion, and to 49 two hours later. After transfusion the circulating blood volume was restored to 80-90% of the original value. (Fig. 3).

The changes in hemoglobin content and in hematocrit readings are evidence that the transfusion fluid remains within the vascular channels. The hemoglobin content falls considerably after bleeding and transfusion, then rises slightly, and remains at this level for the rest of the time of observation. The hematocrit varies parallel with the hemoglobin content.

Our experiments show that observation over 2 hours is sufficient to establish the principal properties of this plasma substitute as regards its hemodynamic action.

With less effective substitutes fall in blood pressure and in circulating blood volume are usually found 1-2 hours after the transfusion, and are due to loss of fluid from the vessels, as is shown by rise in the hemoglobin content and the hematocrit reading.

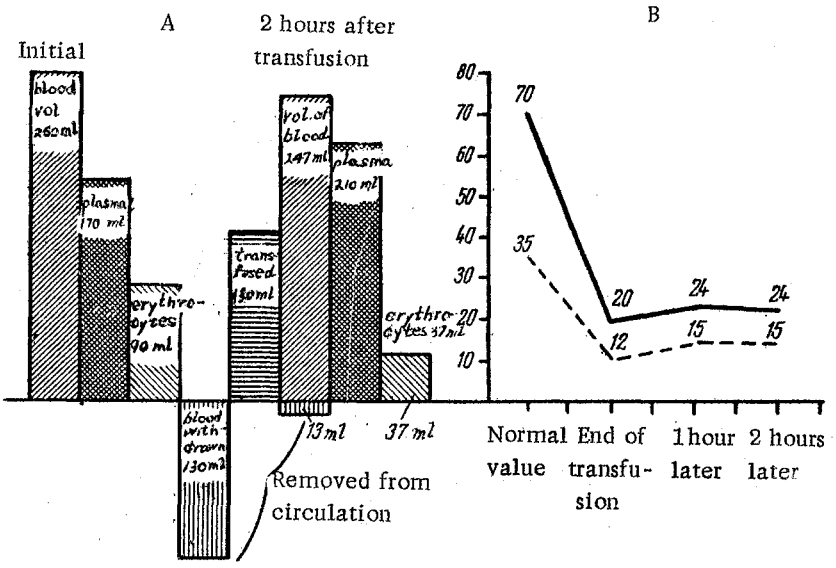


Fig. 3. Changes in the circulatory volume (A), and in the hemoglobin content and hematocrit reading (B), after withdrawal of blood and transfusion with PVP solution. The experiment was done on a 3.5 kg cat. The continuous line represents hemoglobin content, and the broken line hematocrit reading.

Our results thus show that polyvinylpyrrolidone solution is an effective agent for the treatment of acute, and otherwise fatal, hemorrhage.

How effective is PVP solution, in comparison with other plasma extenders? Although this problem was not part of our experimemental program, we did some control experiments with various solutions. Physiological saline does not give even a transient improvement with blood losses such as in our experiments. The French preparation Subtosane gave the same effect as our Soviet PVP, and is not superior to it. Poliglyukin (a preparation of dextran prepared in our Institute) has a rather stronger effect.

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