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COMPARATIVE VALUE OF VARIOUS PARENTERAL FLUIDS * †

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CONSIDERATION of the comparative value of various parenteral fluids requires, in some measure, a review of the physiologic factors that enter into the maintenance of normal body fluid balance. The ebb and flow of body fluids follow a definite pattern which is determined by the needs of tissue in the normal individual, and by the physicochemical imbalance in the physiologically abnormal individual. The normal individual maintains proper fluid balance without assistance of parenteral administration. Only in the ailing or physiologically abnormal patient is it necessary to supplant the usual oral administration. In such instances the parenteral method is employed either because the enteral route is mechanically, physically or sensibly unsatisfactory, or because fluid replacement is so vitally necessary as to require rapid and immediate replacement of lost blood volume.

The circumstance of a suddenly depleted blood volume calls for hasty replenishment, and the quickest manner in which one may increase blood volume is to add fluid directly to the blood by infusion. This concept employed without regard for the factors that equilibrate the body fluids leads with certainty to the further derangement of a disturbed physiologic state. The introduction of fluid into the vascular system of itself is not sufficient, for unless such infusion carries with it the essential elements which have been depleted from the vascular economy, or agents which physiologically behave like the depleted elements, the salutary effect of the parenteral fluid administered will be transitory and not life sustaining. Occasion may demand that a less desirable medium be em-

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ployed, even though its effect is transitory until the selected fluid can be obtained. When such is the case it is essential that some cognizance be given to the dangers of continued or prolonged administration of such fluid.

Fluid may be lost from the body either as water, or combined with salts, body secretions, plasma, or blood. Further, fluid may be lost extrinsically or intrinsically. Fluid may be lost from the body to the outside, or into the extracellular spaces or body cavities where it is recognized as edema, ascites, or hemorrhage. In addition, fluid loss may be acute, as in acute hemorrhage, or chronic, as in progressive dehydration. The loss of fluid beyond that which is necessary to insure a healthy body economy is indicative of a deranged physiologic function. Continuance of this state eventually leads to complete disablement of the patient and ultimately to such complete disorganization of physiologic function that death supervenes.

Electrolytes

Water is the basic fluid which forms part of every living cell, and through which the chemical reactions of the body take place. Water is the solvent for the electrolytes which are vital to the maintenance of normal function of the cell, and is also the vehicle of transport for blood and lymph. Water is the substance which according to its per cent volume in the vascular system partially determines the viscosity of blood, and which in the intercellular spaces is the medium whereby nutrition is transported to tissue. The per cent volume for water in any tissue is dependent upon the quantity of water in the vascular system, the hydrostatic pressure, the presence of normal electrolytic balance, the presence of an intact endothelial system and the maintenance of a normal balance in the increment-excrement ratio of water. Interference with one or more of these factors breaks one or more links of interdependence upon which the tissue cell makes its normal demands.

Normally, the blood plasma volume has been estimated to be approximately 3,500 cc., or about 5 per cent of body weight, the interstitial fluid to be about 10,500 cc. or about 15 per cent of body weight, and intracellular fluid to be 50 per cent of body weight. Thus, the interstitial fluid exists, normally, as a buffer lake three times the volume of plasma, between the blood and the tissue cell. It contains essentially the same electrolytes, combined with organic acids and proteins, as does plasma. Intracellular fluid, however, differs considerably in its electrolytic content. The sodium ion which is present in high concentration in plasma finds its counterpart in the high concentration of potassium ion within the cell. The high concentration of chloride ion in the plasma is counterbalanced within the cell by a high concentration of phosphate and bicarbonate ion. The magnesium, calcium, and sulphate ions do not differ greatly in concentration between plasma and intracellular fluid.

The essential difference between the electrolytes in the extracellular fluids and intracellular fluid is that the plasma is potentially more acid in character because of its high chloride ion concentration, as contrasted with the potentially basic quality of intracellular fluid which has an almost equivalently high concentration of phosphate and bicarbonate ions. In addition, sodium ion is found extracellular and potassium ion intracellular. The maintenance of a fairly constant concentration of sodium ion in the extracellular fluids is necessary for maintenance of osmotic pressure, for the loss of chloride ion alone is offset by a reciprocal increase in the bicarbonate ion and does not appreciably alter osmotic pressure. Under normal conditions the potassium and sodium ions do not permeate the cell membrane or vascular endothelium. When these ions are present outside of their confining membranes there is a quantitative shift of water in the same direction. Thus it is that in shock potassium ion is found in the interstitial fluid, and the cell is dehydrated while at the same time immersed in an interstitial bath. By the same token, an increased permeability to sodium ion in the vascular endothelium will result in vascular anhydremia with a shift of water into the interstitial lake. Under such condition the terminal vascular bed is encompassed within an interstitial edema. The greater the escape of these ions into the interstitial lake, the greater is the shift of water in the same direction. Peters (1) stated that the potassium ion which is normally a nonpermeable ion will diffuse through the cell membrane as a result of marked change in cellular metabolic activity. The shifting of fluids therefore is controlled by a normal ratio between intracellular and interstitial electrolytes.

BLOOD PROTEINS

Another factor of great importance in the maintenance of fluid balance is the osmotic effect of plasma proteins. The normal blood proteins exert an osmotic pressure of 30 mm. of mercury. As blood enters the capillaries, the hydrostatic effect of blood pressure is greater than the osmotic pressure of the blood proteins. At the arterial end of the capillaries the pressure is about 45 mm. of mercury. The 15 mm. mercury gradient causes water to leave the vascular bed for the interstitial lake. At the venous end of the capillaries the hydrostatic pressure is much lower. A negative gradient of about 20 mm. of mercury causes a shift of water from the interstitial fluid toward the vascular system. When there has been a great loss of plasma proteins, the first systemic effect is a marked reduction in blood volume. The resulting lessened venous return and decreased cardiac minute output produce a drop in blood pressure. The arterial pressure in the capillaries thus will be markedly reduced, and with the loss of plasma proteins, the normal osmotic relationship between the vascular bed and the interstitial fluid is disturbed.

As the effects of shock supervene, plasma proteins and electrolytes pass through the endothelium into the intercellular spaces, and through their osmotic properties, cause a shift of water in the same direction. Thus the osmotic pressure in the interstitial region becomes increasingly greater and produces a cumulative flow of water out of the vascular bed. At the same time, the vascular volume, being more and more depleted, leaves a constantly decreased blood volume return to the heart, with resulting blood pressure drop. Acute anoxemia is produced and the tissues suffer an acute anoxia of anemic and stagnant type. As the metabolism is progressively upset, a histotoxic anoxia develops. The cell membrane and the endothelium become more permeable, allowing the potassium ion to diffuse from the cell, as more electrolytes and plasma proteins pass from the vascular bed. The interstitial fluid increases in volume at the expense of the blood system and the tissue cells. If this abnormal shift of fluid is not checked, the tissues drown. The blood proteins, which had exerted an osmotic pressure of 30 mm. of mercury at the venous end of the capillaries in the normal individual, are so depleted as to produce insufficient effect to maintain water for blood dilution. Through this mechanism hemoconcentration takes place.

BODY EXCRETION

In the normal individual, water is lost from the body by way of the skin, lungs, kidney, and gastrointestinal tract. The loss through skin and lungs is termed insensible loss. The loss through the kidney and gastrointestinal tract is called sensible loss. Fifteen hundred cubic centimeters of water is needed for dilution for normal kidney function requiring excretion of approximately 35 Gm. of waste. In dehydration, nitrogen retention takes place and urinary excretion is diminished. This may continue to a point of severe renal damage and the urine may contain protein, red blood cells, and casts. Large losses of fluid and electrolytes may take place through the skin and give rise to electrolytic imbalance in the body. Nadler (2) stated that in profuse sweating as much as 2 Gm. of sodium chloride may be lost from the skin per hour. Sweat is derived from serum and each liter of sweat depletes the body of a liter of water. The concentration of salt in the secreted water is less than in the tissues, and a relatively excessive amount of salt is retained by the tissues. The salt cannot be retained without water to make it isotonic, and the excess is eliminated by the kidney. Approximately 1,500 cc. of water is vaporized from the skin and lungs for the regulation of body temperature, according to the calculations of Lashmet and Newburgh.

The digestive fluids, saliva, gastric juice, bile, pancreatic juice, and succus entericus consist of water, electrolytes, and enzymes. They are fluids which are isotonic with the interstitial fluid and are derived from blood serum. They vary considerably in chemical composition. Gamble (3) estimates the twenty-four-hour digestive secretions as follows:

Saliva	1,500 cc.
Gastric secretions	2,500 cc.
Bile	500 cc.
Pancreatic juice	700 cc.
Secretion of intestinal mucosa	3,000 cc.
Total	8,200 cc.

Except in certain pathologic states, these fluids under normal conditions are secreted and reabsorbed. The persistent loss of one or more of these fluids, as a result of disease, will give rise to profound dehydration and electrolytic imbalance in a short time. Gastric juice is richer in chloride and poorer in base than is serum. Pancreatic contains less chloride and more bicarbonate than does serum. Persistent loss of pancreatic juice will deplete the body bicarbonates and cause an acidosis. Persistent loss of gastric juice will deplete the chlorides and encourage alkalosis. In disease process, in addition to the electrolytic imbalance, there is an associated loss of considerable quantities of water. Vomiting, gastric and duodenal fistulas, intestinal obstruction, short circuiting secretions to the outside as in biliary, pancreatic and intestinal fistulas, and diarrhea commonly cause dehydration and electrolytic imbalance. Continued dehydration causes ketosis to develop which further aggravates the status of the individual. The employment of sodium bicarbonate parenterally for counteracting acidosis and bicarbonate depletion is not essential because bicarbonate can be formed in the kidney. Peters and Van Slyke observed that bicarbonate can be produced in the kidney but that chloride deficiency must be combated by administration of chloride. NH_4HCO_3 (formed in kidney) plus NaCL → NH_4Cl (excreted in urine) plus $NaHCO_3$ (retained in body).

The blood volume is diminished by as much as 40 per cent to 50 per cent as a result of plasma loss in dehydration. A decrease in blood volume causes a compensatory vasoconstriction to develop, leading to diminished volume of blood flow, particularly in the extremities. The blood pressure is not appreciably lowered if dehydration is gradual.

SUPPLEMENTARY TREATMENT

There is clinical evidence that adrenal cortical extract plays a significant role in maintaining a normal relation of intracellular and extracellular electrolytes and upon the maintenance of endothelial impermeability to sodium ion. The parenteral administration of adrenal cortical extract may tend to maintain electrolyte balance in the presence of impending shock and the subsequent vicissitudes of water shift. Its use in conjunction with parenteral fluid therapy deserves consideration. The use of oxygen by inhalation to maintain capillary tone and tissue viability is also of value. The water soluble vitamins also, particularly vitamin C and citrin, have some effect upon capillary permeability.

PARENTERAL FLUIDS

1. Isotonic sodium chloride given parenterally is essential for the restoration of lost chloride. In acute hemorrhage the loss consists of both electrolyte and plasma proteins. Correction must be made to insure against further flooding of the interstitial lake which develops in such a circumstance. Loss of chloride through starvation or disease usually is associated with ketosis. Admixing 5 per cent glucose to the solution of sodium chloride combats ketosis effectively. Stewart (4) observed that physiologic saline given intraperitoneally produces a rich cellular peritoneal exudate which may be important in the production of adhesions. Concentrated sodium chloride given intravenously produces temporary increase in blood volume. This effect is not maintained because sodium chloride is rapidly excreted.

2. Ringer's solution is indicated whenever chlorides and fixed bases of sodium, potassium, calcium, and magnesium are lost. In dehydration, particularly resulting from excessive loss of gastric or intestinal secretion or severe infections, Ringer's solution given parenterally rapidly replaces the lost electrolytes. Ringer's solution can be given intravenously, subcutaneously or intraperitoneally in doses of 80 cc. to 100 cc. per kilogram of body weight. Its constituents are sodium chloride 0.6 per cent, potassium chloride 0.004 per cent, calcium chloride 0.002 per cent, and magnesium chloride 0.002 per cent.

3. Solution of sodium lactate is indicated in all types of severe acidosis except that associated with congenital heart disease and persistent cyanosis. If it is administered parenterally, rapid alkalinization is produced for effective treatment of urinary infections. Sodium lactate is seldom used alone in treatment of fluid loss. The average dose is 10 cc. molar solution diluted in 5 volumes of distilled water per kilogram of body weight.

4. Ringer's lactate solution is made by addition of 10 cc. of molar sodium lactate solution to 450 cc. of Ringer's solution. The acidosis or alkalosis of metabolic origin is effectively relieved by parenteral administration. Ringer's lactate solution is suitable in the treatment of any form of dehydration. It can be mixed with 10 per cent dextrose. The average dose is 80 cc. to 100 cc. per kilogram of body weight.

5. Sodium bicarbonate solution is used to replace fluid and combat acidosis. A 1.5 per cent solution is approximately isotonic. It is employed commonly by subcutaneous route.

6. Dextrose solutions are indicated in the presence of ketosis, disturbed carbohydrate metabolism, and acute infections. Isotonic solutions supply glucose for metabolism but do not aid in correcting dehydration. Dextrose solutions do not replace lost electrolytes. Concentrated solutions of glucose given intravenously are used to combat edema, but the effect is transitory. Absorption from intraperitoneal administration of 5 per cent glucose may be uncertain and may carry

the possible sequel of intractable abdominal distention. Given intravenously to replace blood loss from acute hemorrhage, glucose is taken into the interstitial spaces to increase edema further. Solutions of glucose are frequently used in conjunction with Ringer's lactate solution to combat dehydration.

7. Acacia in sterile solution of 6 per cent to 30 per cent has been employed to produce the osmotic effect of a colloid when blood volume has been suddenly reduced by hemorrhage or shock. Acacia in concentration of 6 per cent with saline exerts an osmotic effect similar to that of blood proteins. As a supportive parenteral fluid it is more suitable than are the diffusible crystalloids because it tends to remain within the vascular system. Acacia, however, is excreted poorly from the body and is retained mostly in the reticulo-endothelial system of the liver. Anaphylactic reactions, toxic reactions and interference with liver function have resulted from its use.

8. Human serum albumin accounts for approximately 85 per cent of the osmotic pressure of plasma proteins. It has been estimated that 1 Gm. of albumin will attract 15 cc. of water. Used in solution of 25 per cent, 25 Gm. (100 cc. of solution) will produce approximately the equivalent osmotic effect of 400 cc. of normal human plasma. Intravenous injection of pure human albumin leads to rapid hemodilution and restoration of blood volume. The increase in blood volume is at the expense of intercellular fluid. Accessible in small volume it is readily transportable. Human serum albumin serves as an excellent supportive agent. In the severely dehydrated patient, albumin must be administered with an infusion of electrolytes because of its hypertonicity.

9. Bovine plasma and bovine albumin as blood substitutes are being investigated. The incidence of reactions with bovine plasma has been high when it has been employed as a blood substitute. The use of this agent for parenteral purpose requires further study.

10. Isinglass, which is a gelatine derived from fish bladders, has been used in concentrated solution as a supportive parenteral fluid in experimental animals. Isinglass has colloidal properties and restores blood pressure to normal shortly after administration to dogs in shock.

11. Pectin, derived from the white layer beneath the skin of citrus fruits, promises to be a source of a readily available and easily extracted colloid. In 0.75 per cent solution, pectin has been demonstrated by Hartman, Schelling, Brush and Warren (5) to combat effectively shock from acute blood loss in man. Pectin contains no protein and the likelihood of reactions is remote. Solution of pectin administered to 125 human beings in shock increased blood volume and systolic and diastolic blood pressure. Pectin solutions to be most effective must be water clear, have a viscosity of 2 to 4 at 38 C., an osmotic pressure of 45 mm. to 75 mm. of mercury, and a molecular weight between 60,000 and 70,000.

12. At the Mayo Clinic, human plasma, six times concentrated, has been used for purposes of dehydration in the treatment of acute cerebral

edema. Concentrated human plasma is being investigated as a therapeutic agent.

13. Crystalline hemoglobin (pure) has been given in parenteral fluid as a supportive colloid. Hemoglobin exerts a great osmotic pressure, and there is some evidence that it does carry oxygen outside of the corpuscle. Its use as a parenteral blood substitute is under investigation.

14. Human ascitic fluid, derived from patients suffering from ascites, cardiac failure, or portal cirrhosis can be used as a blood substitute. Obtained in quantities of 12 to 15 liters every two weeks and removed with aseptic precaution, ascitic fluid can be stored in sterile flasks at temperatures of 0 C. to 5 C. for periods of five months or longer. Addition of sodium citrate to ascitic fluid is necessary to prevent clotting. In composition ascitic fluid very closely resembles blood plasma but contains about one-half the concentration of proteins. Ascitic fluid is not of practical use because of limited availability.

15. Cadaver blood and placental blood have been used for parenteral administration. Limited availability and possibility of contamination make these agents impractical.

16. Human plasma has proved one of the most reliable agents for combating acute blood loss and shock. The immediate requirement of the patient in shock is a fluid which has suitable osmotic properties to prevent loss of vascular fluid into the tissues. Blood dilution must be produced to overcome the progressive hemoconcentration which develops. Administered for the immediate support of the patient, it can be followed, if necessary, by transfusion of whole blood. Preserved red blood cells may be given by transfusion to replace their loss. Plasma supplies, in addition, complement and immune bodies which are of immunologic value. In the frozen or dry state plasma can be stored safely for long periods of time. It is readily transported and does not have undue bulk. Pooled plasma which has been stored for a few days causes fewer reactions than freshly drawn plasma.

17. Whole blood transfusion, either direct or indirect, supplies all the necessary elements to replace acute blood loss. Preserved chilled blood has been found to produce minimal reaction and can be administered safely if not stored longer than eight days. Type 0 blood is, generally, suitable for all individuals in acute emergency conditions. Repeated transfusions may require investigation of the patient's Rh factor. Selection of the proper Rh blood prevents untoward reactions.

ROUTE OF ADMINISTRATION

The most common route of administration for parenteral fluid, for prompt effect, is venoclysis. Intramuscular, intraperitoneal and subcutaneous routes occasionally are employed. In 1940 Tocantins described the introduction of fluids into the general circulation via the bone marrow. He observed that parenteral fluids so given were absorbed as readily as if given by vein. Bone marrow is the more advantageous route when veins are inaccessible because of generalized edema, widespread burns, or circulatory collapse. Doud and Tysell (6) reported an infusion of 16,825 cc. of whole blood and 29,250 cc. of fluids by the intravenous and intramedullary route in a patient suffering from uncontrollable hemorrhage of ulcerative colitis. In this instance the sternal needle was left in situ, on one occasion, for nine days and on another occasion, for five days.

CONCLUSIONS

1. Crystalloids are effective for replacing lost electrolytes and for combating metabolic disease. Because of ready diffusibility, crystalloids generally are not satisfactory as supportive agents in hemorrhage or shock.

2. Acacia, because of its toxic effects, is not entirely satisfactory as a parenteral supportive fluid even though it possesses suitable colloidal properties.

3. Bovine plasma, bovine albumin, isinglass, crystalline hemoglobin, human ascitic fluid, cadaver blood, and placental blood, either because of limited availability or uncertain properties, cannot be considered practical agents for general parenteral use.

4. Pectin, because of its plasma-like osmotic properties, easy availability, and nonantigenic qualities, has promise of being a suitable supportive agent for parenteral use.

5. Human serum albumin and human plasma are agents of unquestionable value as parenteral supportive fluids. Ease of storage and transport and the stability of these agents make them highly valuable as blood substitutes.

6. Whole blood remains the best agent for treatment of acute blood loss or shock.

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1944 ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

According to an announcement in the *Journal of the American Medical Association* 123: 644 (Nov. 6) 1943, it will not be possible to obtain adequate hotel facilities for the 1944 Annual Session of that body in St. Louis. The Board of Trustees have decided that it will now be held in Chicago, June 12 to June 16.

Our readers are encouraged to make application for space on the program of the Section on Anesthesiology for this meeting. March 15, 1944 is the deadline for such offers to participate in the program to be in the hands of the Secretary of the Section, Dr. John S. Lundy, Rochester, Minnesota.

The sessions of the Section on Anesthesiology will be held in the north hall of the Stevens Hotel. The scientific exhibits, of which E. A. Rovenstine, M.D., New York, N. Y., is the representative, will be in the Palmer House. Technical exhibits will be shown in the Stevens Hotel.