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“Use and Benefits of Balanced Fluid Solutions”

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Fluid management is case of matter in clinical practice since intravenous (IV) solution have been introduced.

It is indispensable for the clinicians to refer to the normal role of water and electrolytes in the human body, in order to establish the best fluid to administer.

Body water accounts for approximately 60% of body weight; it is distributed in the extracellular (ECS) and intracellular spaces (ICS). The ICS contains nearly 55% of the water, and the ECS 45%. All body compartments are functional compartments that continually exchange within themselves fluid and electrolytes.

Main human body electrolytes are: sodium, potassium, calcium, magnesium, chloride and bicarbonate. Sodium is the main cation in the ECS and the main determinant of ECS volume. Potassium is the major cation in the ICS. It plays a key role in kidney function. Calcium is involved in many pattern of regulation of proteins functions. Magnesium is the physiological antagonist of calcium. It is crucial in neuromuscular stimulation. Chloride is the most important anion of the ECS and together with sodium, it determines the ECS volume. Bicarbonate is the main buffer-system of the blood and thus has a crucial role in maintaining acid-base balance.

The body electrolytes and proteins are responsible of many properties of biological fluids such as osmolarity, osmotic pressure, colloid-osmotic pressure and tonicity. These properties regulates body fluids movement among the body compartments. In particular: according to osmotic pressure, water diffusion will take place from low to high electrolytic concentration; while according to colloid-osmotic pressure water will pass from a compartment with low to one of high protein concentration.

In many clinical setting fluid and electrolytes physiology may be altered. In clinical practice we can distinguish two main settings: hypovolemia when a loss of fluid reach in proteins occurs; and dehydration when a loss of fluid poor in proteins occurs.

Evidence suggests that fluid management must be adapted to the specific body water loss. The intravenous solutions used should be different in quantity and in quality administered in case of hypovolemia or dehydration.

Respect with the quantity of infused fluid, literature evidenced the advantage of Goal-directed therapy (GDT). GDT is a complex strategy for fluid infusions aimed at optimizing tissue perfusion and oxygenation, guided by hemodynamic variables. Through hemodynamic monitoring GDT allows the physician to administer fluids and/or use other therapies, such as inotropes or vasoactive drugs, only to patients who need them in order to assure the oxygen delivery necessary for the particular patient's metabolic requirement. As a result, hemodynamic management is personalized: fluid are administered only in fluid responder patients, in whom increasing preload improve cardiac output.

One of the most important questions about fluid management is what kind of fluid to use. Many studies have tried to answer the question in a 50- year ongoing debate. At the state of the art, many fluids are available; they have been evolved in order to respect and to restore (in case of alteration), the physiological equilibrium of water and electrolytes in the body.

A balanced plasma - adapted solution is a solution qualitatively and quantitatively similar to plasma. It contains sodium, chloride, potassium, magnesium and calcium in the same amount of plasma and has metabolizable anions. Except for the risk of fluid overload, the infusion of this solution maintains and restores body physiology, reducing the incidence of side effects related to fluid management.

In respect to other solutions, a balanced plasma - adapted solution has a lower chloride content: clinical studies have revealed that chloride excess causes a specific splanchnic and renal vasoconstriction, interferes with cellular exchanges and reduces the glomerular filtration rate (GFR), with sodium and water retention. Hyperchloremia is often associated with metabolic acidosis and may cause a further reduction in GFR. It has been shown that balanced and plasma - adapted solutions help to avoid hyperchloremic acidosis, while assuring the same volume effect of unbalanced solutions and potentially reducing morbidity and mortality.

Currently available worldwide solutions do not contain the physiological buffer base bicarbonate because it cannot be incorporated in polyelectrolyte solutions, since precipitation of carbonates

would occur. For this reason any fluid infusion may cause “dilutional” acidosis, i.e. dilution of bicarbonate concentration, while the CO₂ partial pressure (buffer acid) remains constant. This alteration may have catastrophic consequences, especially in critically ill patients with pre-existing acidosis.

Replacing bicarbonate with metabolizable anions reduces the risk of dilutional acidosis. Metabolizable anions are organic anions that may be transformed in bicarbonate by tissues. The main metabolizable anions are gluconate, malate, lactate, citrate and acetate. In IV fluid composition, the most frequently used metabolizable ions are acetate, malate and lactate.

Acetate and malate are contained in plasma in very low concentrations. They may be metabolizable in all tissues, especially in muscles, liver, and heart. Acetate is an early onset alkalizing anion (it acts in 15 minutes), while malate has a slower action than that acetate.

The most used metabolizable anion has been lactate, that is normally produced in human body. In fact, it is the main product of anaerobic glycolysis. It is metabolizable only by the liver. Its use has been cause of debate in clinical practice and literature, especially for patients with pre-existing lactic acidosis. Lactic acidosis is a manifestation of disproportionate tissue lactate formation in relation to potentially impaired hepatic lactate metabolism. Lactate levels are a major criteria in routine evaluation of the critically ill patients: changes in lactate concentration can provide an early and objective evaluation of patient responsiveness to therapy. Furthermore, plasma lactate levels in the first 24-48 hours has a high predictive power for mortality in patients with various forms of shocks including cardiac, hemorrhagic, and septic shock. In such situations, the administration of lactate containing fluids may exacerbate the already existing lactic acidosis and interfere with lactate monitoring for diagnostic purpose.

Balanced, plasma-adapted solutions reduce the risk of lactic acidosis and base excess (BE) alterations.

The debate about the ideal IV fluids is still open. The solutions available in the market are: crystalloids, colloids, and other fluids, such as dextrose solutions and mannitol solutions.

Crystalloids are low-molecular weight salts, dissolved in water. After the infusion approximately 30% of infused crystalloids stay within the intravascular space for only 30 minutes. The remainder is distributed in the interstitial space.

Using crystalloid clinical problems may be: disturbances of the acid-base and of electrolytic balance and cellular tone alterations. There are more differences between plasma and crystalloids, the more

side effects in crystalloids use. Many generation of crystalloids have been developed in order to making them balanced and plasma adapted, reducing adverse effect.

The latest generation crystalloids has a ionic composition which is very close to plasma, a lower chloride content than normal saline, and higher chloride content than ringer solutions and metabolizable ions (acetate and malate). As a result, these are isotonic, balanced, and plasma adapted solutions that reduce the risk of chloride excess and dilution acidosis, with a decreased influence on lactate monitoring, lactic acidosis and BE amount.

Colloids are high molecular weight molecules that do not dissolve completely in water, nor do they pass freely through the capillary membrane. An isotonic colloid is distributed only within the intravascular space with an efficiency in expanding plasma volume of quite 100%.

Using colloid clinical problems may be: acid-base unbalance, due to the electrolytic composition of the solution; bleeding disorders due to the properties of colloidal molecules; and renal dysfunction due to colloidal and solution properties.

Colloids may be classified in different group: dextrans, gelatines and hydroxyethyl strach (HES). These groups differ for the nature of colloidal molecules with a progressive improvement of therapeutic effects and reduction of side effects.

At the state of the art, the group with the best therapeutic profile is represented by HES. During the time in this group there has been an evolution: the characteristics of colloidal molecules have been modified in order to obtain a better relationship among therapeutic and adverse effect. This goal has been reached with third and fourth generation HES.

Third generation HES are the most diffused in european practice. Their therapeutic profile is better than gelatins, especially respect with possible renal damages.

Fourth generation HES present a better profile than third. In particular, they have reduced side effects on kidney with a lower risk of hyperchloremic and dilution acidosis.

Third and fourth generation HES are very similar for colloidal molecules, but they are different for their electrolytic composition: fourth generation HES are formulated in an isotonic, balanced and plasma adapted solution, while third generation are formulated in normal saline solution.

At the state of the art, the matter about crystalloids versus colloids has been overcome: the medical literature has largely demonstrated the difference in the pharmacokinetics and pharmacodynamics of these two classes of plasma substitutes. Consequently, crystalloids should no longer be considered as an alternative to colloids and viceversa.

In recent literature there is strong evidence concerning the use of balanced, isotonic crystalloids with balanced isotonic colloids. They must be considered as the two faces of the same coin, and their use as part of an integrative fluid management in different clinical settings.

In major abdominal surgery, balanced solutions have been associated with a reduction of systemic inflammatory response, generally responsible for an increase in oxygen demand, and in postoperative multi-organ failure that severely affects the prognosis of surgical patients. They are also related to a reduction of interstitial edema and of splanchnic and renal flux alteration: Consequently, their use improves healing of wound and anastomosis, and reduces recovery time of abdominal organ function, with a positive impact on outcomes. Furthermore balanced solutions reduce coagulation alteration and bleeding risk, respect with unbalanced solutions.

Literature suggests, when possible, the use of GDT with balanced solutions because they reduce the incidence of perioperative complications and the length of hospital stay, particularly in high risk surgical patients.

In cardiac surgery a fully balanced therapy has been related to a reduction of the inflammatory response with better tissue oxygen delivery and diffusion; a reduced risk of capillary leakage and pulmonary edema. This is very important in patient exposed to micro and macrocirculation alterations. Moreover, balanced solutions reduce the risk of bleeding and the need of blood products, even when used for by-pass priming. Finally, they reduce the risk of sodium and fluid overload that may be deleterious for cardiopatic patients; and the risk of renal failure that is one of the first cause of morbidity and mortality after cardiac surgery.

Recent studies have focused on balanced HES use in orthopedic surgery patients, suggesting that they could be used throughout the peri-operative period with fewer side effects than non-balanced HES. Moreover, in major orthopedic surgery, many studies have shown that GDT with balanced solutions is a valid approach, with a reduction in hospital stay and postsurgical complications.

In neurosurgery the use of balanced, plasma adapted solutions helps to avoid cerebral edema and other cerebral damages. In fact, in the neurosurgery patient the infusion of a hypotonic crystalloid reduces plasma osmolarity with cerebral edema and intracranial pressure increasing. Patients in whom osmolarity is lower than 240 mOsmol/L have a mortality rate of 50%. In clinical practice it is often forgotten that ringer solutions are hypotonic solutions that should be avoided in neurosurgical settings.

On the other side, hypertonic solutions cause plasma osmolarity increasing, with cellular dehydration and death. Neurosurgery patients mortality is clearly associated with hyperosmolarity ,

especially in head trauma. Taking in count sodium and chloride content, normal saline is lightly hypertonic and it should be used with care in neurosurgical patients.

In these patients, an isovolemic state is acquired by the infusion of iso-osmolar, balanced fluids. Hypertonic solutions should be used in cases of intracranial hypertension, when refractory to conventional therapy occurs.

In sepsis the role of balanced solution in reducing inflammation and capillary leakage has been demonstrated. Furthermore, in septic patients balanced solutions reduce the incidence of metabolic acidosis and base excess alterations. Since 1990, clinical trials have demonstrated that BE on the is indeed the best prognostic indicator for mortality, complication rate and transfusion needs. Moreover, in animal models, the reduction of BE alteration relates with a reduction of IL-6, one of the major pro-inflammatory cytokines enrolled in sepsis. Considering their advantages, the use of balanced colloids and crystalloids is recommended in septic patients.

The literature supports the use of balanced, and plasma-adapted solutions in children to avoid dilution and hyperchloremic acidosis and to reduce the risk of peri-operative hyponatremia, especially when a large amount of fluid is needed. Their use decreases the negative effects involving renal and cardiac function, particularly in children with kidney disease or those who have undergone cardiac surgery. In children the use of balanced solutions in the peri-operative period is recommended for their obvious positive effect.

Literature is lacking about the use of balanced, plasma-adapted solutions in thoracic surgery, burns and trauma patients. Evidences found about their beneficial effects in major surgery and in critically ill patients suggest their use even in these cases.

The evidences support that the combined use of last generation balanced crystalloid and fourth generation balanced HES:

- maintains acid-base and electrolytic balance, reducing the alteration of splanchnic and renal flux due to hyperchloremic and dilution acidosis, ameliorating base excess and containing sodium overload and other electrolytes modification;
- reduces the risk of cerebral edema and cells apoptosis, maintaining cellular tone;
- reduces the risk of renal dysfunction;
- contains fluid effects on coagulation and platelets alteration;
- has an anti-inflammatory effects with possible benefit on patients with SIRS and capillary leakage.

To conclude: balanced plasma-adapted solutions have fewer side effects than either older-generation colloids or crystalloids, thus shortening the hospital stay. Their cost-effectiveness ratio suggests their use will improve patient outcome while conserving economic resources at the same time.

Summary

Hypotonic fluids should be avoided because of the risk of cerebral oedema; hypertonic solutions should be used only as long as plasma osmolarity is less than 320 mOsmol/kg. Isotonic solutions should be used as a matter of principle, especially in pre-existing hyperosmolar state. In order to reduce the risk of iatrogenic disorders in electrolytic plasma concentration and acidbase balance, it is suitable to use balanced plasma - adapted solutions.

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