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SIGNIFICANCE OF CRYSTALLOIDS IN MEDICAL FIELD

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Abstract:
Crystalloids are solutions made from low molecular weight salts or sugars that can pass between the intravascular and interstitial compartments. They are the most widely utilised intravenous solutions in hospitals, with the majority of surgical in-patients and many medical patients receiving at least one intravenous crystalloid infusion during their hospital admission. They were first used, in the form of intravenous salt solutions, in the early 19th century for the treatment of dehydration due to cholera, and were then first administered to surgical patients in the late 19th century. They are utilized for both fluid and electrolyte maintenance and replacement. Crystalloids are often perceived to be innocuous, low-risk intravenous solutions.,

Keywords:
Crystalloid, Infusion, intravenous, dehydration, electrolyte.

Introduction:

Crystalloids are medications which contain fluids and electrolytes to help maintain the body's fluid balance. They have been widely used in medicine for more than 100 years due to their low cost, wide availability and effectiveness in intravenous hydration and fluid resuscitation. Historically, the early and "*aggressive*" administration of crystalloids in adults and children has been supported for patients in shock. This practice has led to early recognition of critically ill patients and changes in mortality in high and low-income countries. However, it has been recently recognized that crystalloids are not innocuous. They have been questioned in terms of excess volume (quantitative) and their composition (qualitative). Excessive fluid administration and very positive balances have been associated with worse outcomes in critically ill patients. In addition, the composition of some crystalloids, like 0.9% saline solution, has been questioned due to their acid pH (5.0) and excessive chloride (40% more than plasma). Studies from more than 100 years ago as well as some recent ones have warned of the complications associated with their use The association between the use of 0.9% NS and acute kidney injury and microcirculation changes has alerted researchers and clinicians to consider alternatives for crystalloids in patients with circulatory abnormalities. A range of different crystalloid solutions are available, mainly containing sodium chloride and/or dextrose in a range of different concentrations, the most commonly used solutions being detailed in Table 1.

Hartmann's and Ringer's lactate solutions are also available, both of which contain lactate as a bicarbonate precursor. These were developed to be more similar to plasma in their composition. Some solutions are also available with additional potassium, so that maintenance or replacement of potassium can also be achieved via the one infusion. Most solutions are also available in a range of different volumes, according to individual patient fluid requirements.

Most crystalloid solutions are compatible with a range of intravenous drugs and sodium chloride 0.9% and dextrose 5% are often used as diluents and carrier solutions for their administration. Individual compatibility details should always be confirmed before administration. However, it is not recommended to administer blood products via the same intravenous line as Hartmann's or dextrose 5% due to concerns over clotting and haemolysis.

Crystalloids can be used as both replacement and maintenance fluids. Meta-analyses and systematic reviews have shown that crystalloids are effective in fluid resuscitation in septic and critically ill patients. If used appropriately according to individual maintenance fluid requirements, crystalloid solutions can effectively maintain fluid and electrolyte balance.[4]

However, it should be noted that crystalloids are not indicated for volume replacement in all clinical settings. According to recommendations of the Surviving Sepsis Campaign Guidelines and the European Society of Intensive

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Care Medicine, the use of albumin is advocated for fluid resuscitation in patients with severe sepsis, particularly if they require large amounts of fluid.[10,11]
Similarly, crystalloids might not always be the best choice for volume resuscitation in cases of cardiac surgery due to the potential for fluid overload.
The comparative 'cons' of crystalloids are due to their inherent pharmacological properties. As long as crystalloids are used in a considered manner, alongside colloids (if appropriate), then these pharmacological properties can be exploited for their clinical utility.
Potential for fluid and electrolyte overload
Crystalloids pass rapidly and freely across capillary membranes and equilibrate within the entire extracellular fluid space. Therefore, retention of a crystalloid within the intravascular space is poor. To replace a given volume of blood loss requires at least three times more crystalloid volume. As 75–80% of the infused crystalloid volume will remain in the extravascular space,[12] fluid replacement with crystalloids is associated with an increased level of tissue hydration and risk of oedema: specifically, increased extravascular lung water and peripheral tissue oedema. Peripheral tissue oedema can affect wound healing and is uncomfortable for the patient, potentially making mobilisation more difficult. Oedema adversely affects the transport of oxygen and nutrients to tissue cells, potentially impairing organ function. Fluid overload with crystalloids can result in an increase in the fluid content of vital organs, including a delay in the return of normal gastrointestinal motility. In elderly patients with reduced functional respiratory and cardiovascular function, this can also result in significant morbidity and mortality.[3] In such situations, fluids with a high volume effect, such as albumin, should be considered instead for volume resuscitation.
If large volumes of crystalloids with high chloride content, particularly sodium chloride 0.9%, are given in an attempt to restore the circulating volume, there is a risk of hypochloraemic acidosis. This, then, causes renal vasoconstriction and reduced glomerular filtration rate. In catabolic surgical patients, this is further compounded by increased urea production and the inflammatory response to surgery, resulting in a large proportion of sodium, chloride and water being retained within the interstitial space. Hence, there is a need for a balanced fluid replacement regimen, ensuring that an excessive quantity of neither fluid nor electrolytes are administered. Crystalloids are adequate for fluid resuscitation but lack additional beneficial properties provided by fluids such as albumin.
Potential for adverse respiratory effects
If an excessive amount of dextrose is administered, particularly in critically ill, ventilator-dependent patients, an enhanced production of carbon dioxide and lactate may result. In addition, dextrose should not be used in isolation to treat hypovolaemia, as it only provides free water and does not replace electrolytes.
Lack of additional biochemical properties
Crystalloids do not have any additional biochemical properties, with their action being only to provide fluid and, depending on the solution administered, electrolytes.

Thus, the ideal choice of crystalloids for fluid resuscitation is a matter of controversy today. In adults, several clinical trials have been conducted with a significant number of patients. A recent systematic review and meta-analysis found that there may be a small relative reduction in mortality when balanced solutions are used compared with 0.9% NS. Balanced solutions have been found to produce a relative reduction of 9%, or a 1% increase, in 90-day mortality. This figure suggests that, overall, it would seem reasonable to consider that using balanced solutions is associated with a reduction in mortality. Although this impact on mortality could be considered "relatively" small, we must remember that crystalloids may be one of the most used medications in medical practice. In this context, a small reduction could be significant when it is used so frequently as a resuscitation fluid.
Remembering the most important aspects of the origin of intravenous crystalloids can help us better understand the current questions. The process of developing, producing and storing these solutions has changed significantly over time. Likewise, their indications, volume and administration are increasingly tailored to the patients' needs. One more step toward this interesting path of precision medicine which, on this particular topic, can significantly impact the outcomes of critically ill patients. It may be that the use of both 0.9% NS and Ringer's lactate should be individualized. Taking specific patient aspects into account (comorbidities, electrolyte levels, and hemodynamic coherence, among others) could help in selecting a crystalloid with fewer adverse effects. In addition, it should be noted that crystalloid solutions with low dextrose concentration are available in some countries. This could be important, especially in

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infants with low liver glycogen reserves who may have simultaneous hypoglycemia or other associated disorders like hyponatremia. In this brief review, we seek to recall the process which has led people to use crystalloids in clinical practice, particularly for fluid resuscitation, and thus understand a bit better the origin of some of the controversies and complications associated with their use.

The cholera epidemic in 1830 was one of the most devastating pandemics of modern history. Originating in India in 1817, the disease spread rapidly around the world, reaching Europe in 1830. Cholera spread throughout France, Italy, Spain and the United Kingdom, killing more than 100,000 people. The disease was especially aggressive in London, where a lack of sanitation infrastructure and unsanitary living conditions contributed to the rapid dissemination of the disease. In 1832, the British physician Thomas Latta proposed that cholera could be treated with a water and salt solution administered by a route other than the oral or rectal route

Latta's solution was made up of sodium chloride, sodium bicarbonate and distilled water (Fig-1) gives a summary of the historical development of crystalloids and the main contributions of the researchers). It was administered intravenously, which was a novel strategy at that time. Although Latta's solution was effective for hydrating patients, it was also toxic at high doses, due to its fluid and electrolyte makeup. Latta conducted his first experiment on a middle-aged woman who had received all the treatments considered to be effective for cholera at that time. There was no response, and the woman died after receiving this solution intravenously. However, Latta continued his studies and conducted experiments in animals with different concentrations of sodium and chloride, originating the first mixture of water and sodium for intravenous use.

Fig- 1

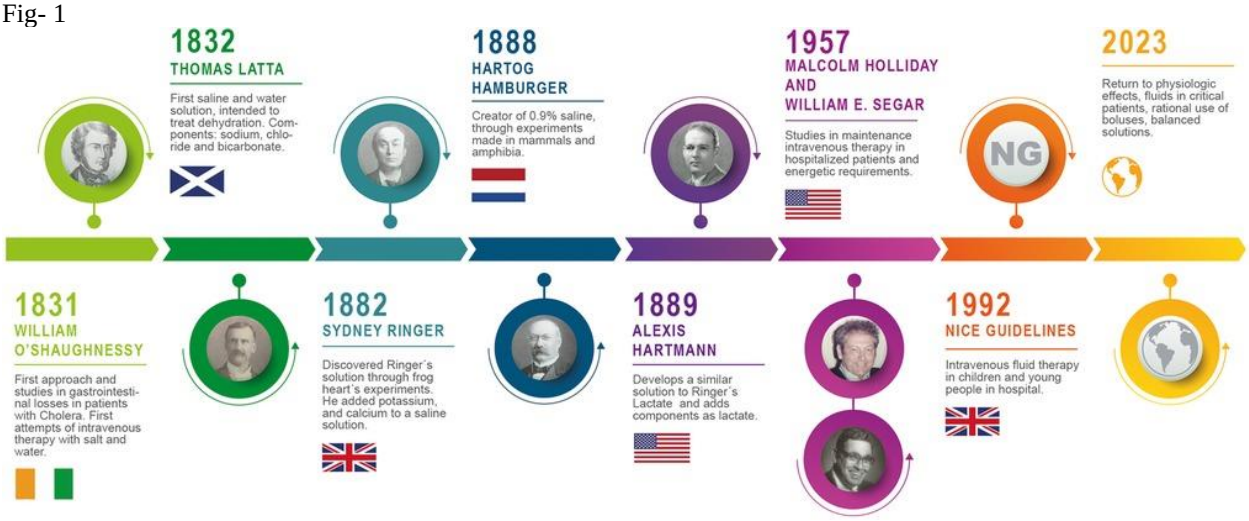

FIGURE 1. Timeline of the evolution of crystalloid solutions.

With the end of the cholera epidemic, saline solution could have been consigned to the history books. In 1896, the Dutch chemist Hartog Jacob Hamburger created a solution he termed "*physiological serum*" to study the hemolysis of red blood cells *in vitro*. He never intended to use this solution clinically . His experiments consisted of mixing solutions with different tonicities and evaluating the interaction of these solutions with erythrocytes from various species with regard to changes in concentration and temperature. Using the freezing point of amphibian and mammalian blood, Hamburger concluded that "*warm blood*" and 0.9% NaCl solution had similar freezing points. In addition, when erythrocytes had contact with this solution, it did not induce hemolysis, and therefore could be considered isotonic with warm-blooded mammals. Hamburger considered this solution to be "*normal*" or "*physiological*" since it did not cause hemolysis, as did hypotonic solutions. Experiments in amphibians showed that a solution with a 0.6% sodium concentration could be considered "indifferent" or "physiological" for frogs, because it did not cause hemolysis. Since that time, solutions with a sodium and water content which did not cause red blood cell lysis in amphibians or mammals were called "*physiological solutions*".

Around this same time, towards the end of the 19th century, the researcher Frances Alexis Carrel had begun to work on what could be the conservation of human tissue. As he was interested in vascular suturing and organ transplantation,

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he began to work on a solution that would sustain human tissue outside of the body. Based on Latta's experiments, he designed a sodium chloride solution with a content similar to plasma. With this solution, he was able to sustain human tissue to continue his transplant experiments. Years later, he received the Nobel Prize in Physiology. The editorial in Lancet on October 19, 1912, stated: "*And there is a new advance in blood vessel surgery which is, perhaps, even more surprising. Carrel has demonstrated that a portion of the artery can be kept in cold storage for several days or even weeks before the transplant and, even so, stay alive. No one who has followed these new surgical advances with interest can doubt that they have immense potential, and that the application of the methods learned in animals to human beings cannot take long…"*

The idea of using 0.9% NS in clinical practice resulted from experiments in dogs with intestinal obstruction. Hartwell and Hoguet applied subcutaneous of "*normal saline solution*" in their study of animals with intestinal obstruction). In 1913, Truch et al., based on these descriptions, proposed that fluids could be replaced after surgery in some patients through "*proctoclysis*." They compared almost 2,000 adults who received tap water vs. "normal" saline solution enemas. They warned of the risks of administering a solution with a high sodium and chloride content: "*we would be forcing an already weakened patient, in the space of 24 h, to receive the average amount of salt eaten as a condiment by a normal person in a month."*

Despite these descriptions of almost 100 years ago, 0.9% saline solution continues to be called "*physiological*," even though its composition does not resemble the composition of plasma. 0.9% saline solution has approximately 10% more sodium than plasma, 40% more chloride, an acid pH, a strong ion difference (SID) of zero. The SID is the total difference between strong anions and cations. It is simplified as the difference between sodium and chloride. Normal plasma is considered to have an SID between 38 and 42 mEq/L. This difference is associated with acidosis when large volumes of chloride are administered such as, for example, with the use of large amounts of 0.9% saline.

Figure 2

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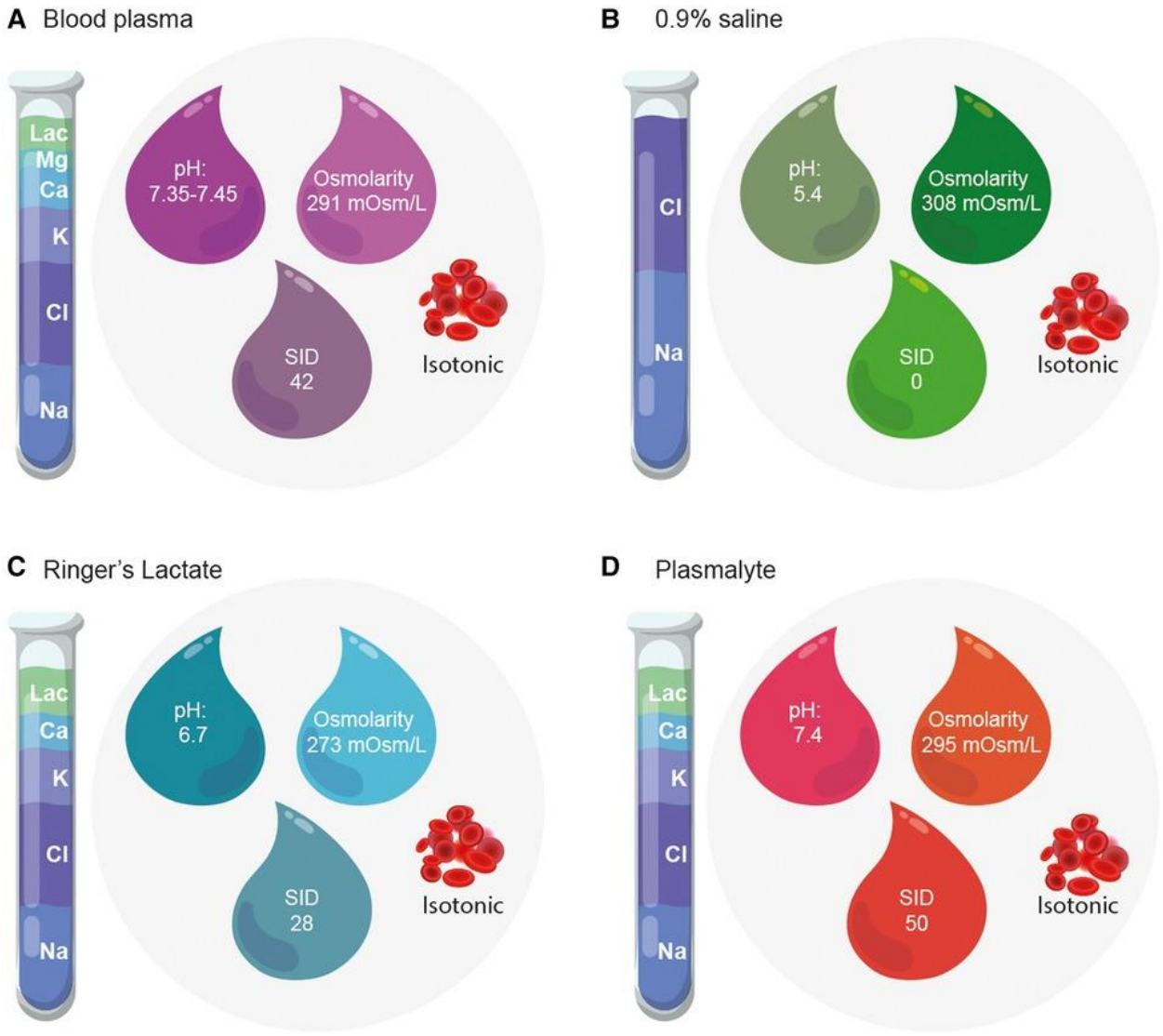

FIGURE 2. Composition of blood plasma and crystalloid solutions. The composition of crystalloids and blood plasma differ in terms of electrolyte concentration, pH, osmolarity and strong ion difference. (**A**) Composition of Blood plasma. (**B**) Composition of 0.9% saline. (**C**) Composition of Ringer's Lactate. (**D**) Composition of Plasmalyte-148 ©.

Only Hamburger's experiments indicate that this crystalloid does not cause red blood cell hemolysis. It remains a mystery how it came to be a general-purpose *in-vivo* intravenous liquid. Perhaps it was due to the ease, convenience and low cost of mixing common salt with water. With the current evidence, the use of unbalanced solutions is once again being questioned. Animal and human models have found that the composition of 0.9% NS has been associated with a greater inflammatory response, immunological disorders, endothelial activation and glycocalyx degradation, among other problems. All of which have a clinical impact in the greater frequency of hyperchloremic metabolic acidosis, kidney failure, and mortality associated with its use.

Sidney Ringer was a 19th century British physiologist known for his studies on metabolism and cellular function. One of Ringer's most famous experiments was his study on the chemical composition of extracellular fluid and its influence on muscle contraction. His studies were mainly done in amphibians. His experiments consisted of instilling distilled

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water with inorganic salts into frog hearts and evaluating aspects like contractility. After his assistant made a mistake in one of the experiments, tap water was used instead of distilled water. Ringer was surprised to see the cardiac behavior in frogs and their ability to survive. Thus, he described the importance of extracellular water and electrolytes in the cardiac work of living beings. This experiment laid the foundation for the modern understanding of homeostasis and cell regulation. In his observations, he emphasized the need for appropriate proportions of potassium, calcium and chloride for protoplasmic activity. Therefore, he proposed a mixture of water and electrolytes which he called "*Ringer's solution.*" He considered that this solution and its electrolyte proportions could temporarily "*replace"* blood and provide a physiological medium for its adequate functioning.

Ringer's solution contained a liter of distilled water, sodium chloride, 0.33 g (mEq) and calcium. This solution had a higher pH than 0.9% NS and less chloride. Subsequently, around 1932, the American pediatrician and biochemist Alexis Hartmann modified Ringer's solution. He added sodium lactate in order to reduce the acidosis found in infants with diarrhea, dehydration and oliguria. Since then, Ringer's lactate has been considered to have a composition more like that of human plasma. However, although its use in large quantities has been questioned due to its potassium and lactate content, it has not been shown to have serious side effects that would require its suspension in patients with kidney injury or liver dysfunction). In fact, in a clinical trial in adults following kidney transplantation, Ringer's lactate was associated with less acidosis and hyperkalemia. In addition, it has been used as a solution for diluting human albumin (reducing a 20% concentration to 4%), proving to be safe and isotonic, possibly related to negative charges in the gelatin molecules contributing to plasma osmolality. However, this solution should not be used in children with head trauma because it has been associated with worse outcomes and even increased mortality.

Other balanced solutions have been developed recently. The use of intravenous fluids for maintenance therapy or fluid resuscitation in children in critical care is a universal practice. Multiple electrolytes solutions that are more similar to plasma in all its components are increasingly wanted. This is the case of Plasma-Lyte 148® (PL-148). This is a crystalloid which was patented in 1982 by Baxter International Inc®. They were seeking a solution which would have the physicochemical properties of plasma and could truly be considered "physiological." It contains 140 mmol/L of sodium, 5 mmol/L of potassium, 1.5 mmol/L of magnesium, 98 mmol/L of chloride, 27 mmol/L of acetate and 23 mmol/L of gluconate). Its composition gives it a pH of 7.4, which is adjusted with sodium hydroxide. The term "148" comes from the sum of its cations (sodium, potassium and magnesium). PL-148 is safe for diluting medications commonly used in intensive care (morphine, fentanyl, ketamine, salbutamol, aminophylline, and clonidine are stable for 24 h when mixed with Plasma-Lyte 148® and Plasma-Lyte 148® + 5% Glucose for administration at equivalent concentrations). Clinical trials in children have shown that PL-148 is safe and effective when compared with other crystalloids Its greatest benefits may be related to its physiological chloride content and better pH than other solutions, with a similar cost to other crystalloids in most countries where it is available.

Osmolality is the concentration of particles dissolved in a liquid. In medical science, osmolality is used to determine certain serious conditions like diabetes, dehydration and shock . Plasma osmolality ranges from 280 to 296 mOsmol/kg. The concentration of substances like chloride, sodium, potassium, glucose and urea are calculated. The solvent volume remains the same regardless of changes in pressure or temperature. The common method for measuring osmolality is through osmometry. The osmotic activity of crystalloids and intravenous fluids is best described by calculating the *in vivo* osmolality (mOsm/kg) of the solution.

It is important not to confuse osmolality with osmolarity. Osmolarity is the concentration of a solute. It corresponds to the number of osmoles of solute particles per unit volume of solution. The osmotic pressure of a solution determines the solvent's diffusion through a semi-permeable membrane separating solutions with different osmotic concentrations. Neither should this concept be confused with tonicity. Tonicity is part of the solution's total osmolarity. It is the force exerted by the particles which do not freely pass through the membrane. Therefore, tonicity can be described as the "*relative concentration*" of the solution. Thus, the term "osmolarity" is the total concentration of diffusible and non-diffusible solutes. Tonicity is the total amount of only non-diffusible solutes.

In vitro 0.9% NS is slightly hypertonic, with an osmolality of 308 mOsmol/kg (154 mOsml/kg of Na^+, 154 mOsml/kg of Cl^-). However, as these electrolytes are only partially active, *in vivo* 0.9% NS has a calculated osmolality of 287 mOsmol/kg. That is, it is considered isotonic due to its osmolality. Often, the term "isotonic" is confused with "physiological." The first refers to its osmolality, the second to its composition. 0.9% NS is isotonic, but its composition is not physiological. *In vivo* Ringer's lactate has an osmolality of approximately 274 mOsmol/kg (slightly

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hypotonic) and PL-148 has an osmolality of 270–290 mOsmol/kg. To avoid confusion between tonicity and composition, it is preferable to classify crystalloids as balanced or unbalanced.

The Pragmatic Pediatric Trial of Balanced vs. Normal Saline Fluid in Sepsis (PRoMPT BOLUS) is currently being conducted. This clinical trial compares fluid resuscitation using balanced vs. unbalanced solutions in children with sepsis. With a large sample size (slightly more than 5,000 patients), this study will provide high-quality evidence of the possible differential effects of these crystalloids. For now, with the available observational data and trials in children, the clinical trials in adults and the weak historical support for the use of 0.9% NS, it would seem reasonable to consider balanced solutions to generally be the best available option for fluid resuscitation in patients who require it . However, each case should be evaluated individually. All the factors which may affect patient outcomes should be considered when ordering crystalloids, to ensure they are a safe approach. This is one more step toward precision medicine in fluid resuscitation. For example, patients with head trauma or hyponatremia should receive 0.9% NS as the crystalloid of choice for fluid resuscitation, because balanced solutions have been associated with worse outcomes. For children with septic shock, the adult and pediatric sepsis consensuses recommend the use of balanced solutions as the liquids of choice Crystalloid solutions have lower acquisition costs compared with colloids.[5] In addition, a cost-effectiveness analysis performed in 1991 regarding the use of colloids and crystalloids in fluid resuscitation also illustrated that the cost of each life saved using crystalloids was $45.13 compared to $1493.60 with colloids.[6]

Crystalloid solutions are stable at room temperature, and so can easily be stored in a range of clinical settings, both in the hospital and in more challenging environments, such as field hospitals in combat settings, emergency ambulances or remote medical outposts. A long shelf life facilitates responsive stock management.

Crystalloid solutions are readily obtained within clinical settings, with the majority of clinical areas within an acute care environment maintaining stock of a range of appropriate crystalloids.

There is a low incidence of adverse reactions associated with crystalloid solutions. The main problems associated with the use of crystalloids are not immunologically-mediated reactions but are due to the prolonged administration of supraphysiological amounts of sodium and chloride, which can result in hyperchloraemic acidosis and a reduced glomerular filtration rate. Utilising a more physiologically balanced intravenous fluid regimen appropriate to the individual’s biochemistry and fluid balance can reduce the sodium and chloride load. A meta-analysis demonstrated that, compared with hydroxyethyl starches, patients who received crystalloids or albumin were less likely to require renal replacement therapies and transfusion with red blood cells and experienced fewer overall adverse events.

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Conclusions

Conclusions

Crystalloids are inexpensive, readily available intravenous solutions for the replacement and maintenance of fluid requirements. However, they should be prescribed in a considered approach tailored to individual patients’ fluid requirements and clinical condition to avoid excessive fluid and electrolyte administration and subsequent effects on morbidity and mortality. A balanced fluid regimen should be administered incorporating a combination of different crystalloids and colloids, if indicated. Individual solution choices should reflect the current evidence-base. Education of the entire multi-disciplinary team regarding the appropriate use of crystalloids within a balanced fluid regimen is essential to ensure that practice is consistent and informed by consensus guidelines.The indiscriminate use of crystalloid boluses is being questioned in terms of their quantity and quality of composition. Intravenous fluids were established in clinical practice and licensed for use without robust investigation of their efficacy or safety.

0.9% NS has a historical basis which suggests that its development was aimed at *in vitro* experiments rather than use in humans. The term “*physiological solution*” should be considered inappropriate for this solution due to its composition. Balanced solutions have a composition more similar to plasma, and recent evidence suggests that they may have fewer side effects. The decision to perform fluid resuscitation should include an appropriate choice of the type of crystalloid to be used, with an individualized approach, considering the potential risks and complications associated with their use. The precision medicine based strategy for fluid resuscitation should be the fundamental principle of treatment for all patients, considering the best crystalloid (balanced or unbalanced) according to each particular case.

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