

## Intravenous balanced solutions: from physiology to clinical evidence

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### Abstract

“Balanced” solutions are commonly defined as intravenous fluids having an electrolyte composition close to that of plasma. As such, they should minimally affect acid-base equilibrium, as compared to the commonly reported 0.9% NaCl-related hyperchloremic metabolic acidosis. Recently, the term “balanced” solution has been also employed to indicate intravenous fluids with low chloride content, being the concentration of this electrolyte the most altered in 0.9% NaCl as compared to plasma, and based upon a suggested detrimental alteration of renal function associated with hyperchloremia. Despite efforts made towards its identification, the ideal balanced solution, with minimal effects on acid-base status, low chloride content, and adequate tonicity, is not yet available. After the accumulation of pre-clinical and clinical physiologic data, in the last three years, several clinical trials, mostly observational and retrospective, have addressed the question of whether the use of balanced solutions has beneficial effects as compared to the standard of care, sometimes even suggesting an improvement in survival. Nonetheless, the first large randomized controlled trial comparing the effects of a balanced vs. unbalanced solutions on renal function in critically-ill patients (SPLIT trial, the 0.9% saline vs. Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy), just recently published, showed identical equipoise between the two treatments. In the present review, we offer a comprehensive and updated summary on this issue, firstly, by providing a full physiological background of balanced solutions; secondly, by summarizing their potential pathophysiologic effects; and lastly, by presenting the clinical evidence available to support their use at the present time.

**Key words:** balanced solutions, crystalloids, colloids, fluid therapy, acid-base equilibrium

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In recent years, research in critical and emergency care has experienced a great outburst of experimental and clinical studies regarding fluid therapy [1]. Besides the focus on hemodynamic targets to be achieved in critically ill patients, researchers have shifted their attention to the effects of different categories and types of fluids. Looking from afar at the never-ending debate on the potential benefit of colloids vs. crystalloids [2], we have moved towards the evidence that

even the type of both colloids and crystalloids may affect patient-centred clinical outcomes, including survival [3, 4].

Within this debate, while searching for the “ideal” intravenous solution, and facing the reality that the old habit of using the simplest crystalloid solution ever appeared on the market, i.e. 0.9% NaCl, may be harmful [5], novel crystalloid solutions have become available in our clinical practice, namely intravenous balanced solutions [6]. As we

will see, with the term “balanced fluids”, researchers, clinicians, and industry define intravenous solutions whose electrolyte composition is closer to the composition of plasma, as compared to previously available solutions. As such, balanced solutions should minimally affect acid-base equilibrium, as compared to the commonly reported 0.9% NaCl-related hyperchloremic metabolic acidosis [7]. More recently, researchers have started to employ the term “balanced” solution to also indicate intravenous solutions with a low content of chloride, being the concentration of this electrolyte the most altered in 0.9% NaCl as compared to plasma, and based upon a suggested detrimental alteration of renal function associated with hyperchloremia [8].

In the last three years, several clinical trials have supported the hypothesis that the use of intravenous balanced solutions, as generally defined, may have beneficial effects as compared to the standard of care. Moreover, the first large randomized controlled trial comparing the effects on renal function and hospital survival of an intravenous balanced solution vs. 0.9% NaCl in critically ill patients has been recently published (SPLIT trial — the 0.9% saline vs. Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy), showing no differences between the two treatments [9].

To further clarify the overall framework of this topic, we would like to offer a comprehensive review of this issue, firstly, by providing a full physiological background of balanced solutions; secondly, by summarizing their potential pathophysiological effects; and lastly, by presenting the clinical evidence available at the moment to support their use or not.

### WHAT DOES “BALANCED” SOLUTION MEAN?

Homeostasis of body’s water composition is a cornerstone of human physiology. As human beings, we normally match the daily output of water with oral water intake, and water homeostasis operates to maintain the effective circulating blood volume, as well as the overall content of water and electrolytes [10]. Fluid balance denotes a constraint of human homeostasis for which the amount of fluids lost from the body, in normal conditions, should equal the amount of fluid intake. Euvolemia defines the state of normal body fluid volume. While this process is regulated finely and efficiently in normal conditions, when an acute process alters such homeostasis, an intravenous administration of fluids may become necessary. This necessity, however, has two important implications in designing a fluid for intravenous administration. Firstly, the necessity for osmolarity and, therefore, the need for electrolytes dissolved in the solution, as we cannot administer intravenously a solution without an appropriate *tonicity* (as close as possible to plasma osmolarity). Secondly, the need, in specific clinical situations, for an oncotic pressure, or *oncoticity*, of the fluid and, therefore, for an oncotic molecule dissolved in the solution, ideally aimed

at maintaining the volume infused within the intravascular compartment.

Theoretically, an ideal balanced solution should have the entire content of all electrolytes equal to the electrolyte content of plasma. At the same time, each water solution must display (and actually does display) the characteristic of electrical-neutrality: the total amount of free positive charges dissolved in the solution (as cations) always equals the total amount of free negative charges dissolved in the solution (as anions) [11]. In the attempt to design an ideal balanced intravenous solution, these assumptions have revealed two aspects which are important to keep in mind. Firstly, all the intravenous solutions available (with the exception of 0.9% NaCl and pure dextrose-containing solutions) have included organic anions (such as acetate, lactate, malate, gluconate, etc.), as precursors of  $\text{HCO}_3^-$  in order to balance the total content of positive charges, i.e., organic components that are rapidly metabolized to  $\text{HCO}_3^-$  in a living system (Table 1) [7]. This specific characteristic is mainly related to the difficulty of including  $\text{HCO}_3^-$  directly in intravenous solution, as the normal process to obtain an intravenous solution including  $\text{HCO}_3^-$  (as in 8.4%  $\text{NaHCO}_3$ ) is quite complex. Secondly, precisely for the necessity of electrical-neutrality and in an attempt to avoid both hypotonicity and a high Strong Ion Difference (SID, thereby maintaining the  $\text{Na}^+ - \text{Cl}^-$  difference within 24–30  $\text{mEq L}^{-1}$ ), we have observed the development of balanced solutions with a relative supra-physiological concentration of  $\text{Cl}^-$  (Table 1).

In the history of developing novel intravenous solutions, based on the observation that 0.9% NaCl induces hyperchloremic metabolic acidosis, balanced solutions have been thought as the intravenous solutions causing minimal effects on acid-base equilibrium. In parallel, after the observation of the harmful effects of  $\text{Cl}^-$  content (with supra-physiologic  $\text{Cl}^-$ -containing solutions) and the associated hyperchloremia on renal function, balanced solutions have been conceived as general intravenous solution with a normal (or lower than normal)  $\text{Cl}^-$  content. Moreover, while these concepts were firstly applied for crystalloid solutions, they have been rapidly transferred to colloid solutions, with the use of “balanced” solutions with regard to the solvent in which the colloid molecules are dissolved.

As we will see in detail below, the two aspects characterizing balanced solutions (i.e., minimal effect on acid-base, and a physiological content of  $\text{Cl}^-$ ) cannot coexist nowadays, when also fulfilling the need for an osmolarity close to that of plasma. Therefore, there are two categories of intravenous “balanced” solutions available: 1) those with a minimal effect on acid-base equilibrium, having a SID close to a value of 24–29  $\text{mEq L}^{-1}$ ; and 2) those with a  $\text{Cl}^-$  content equal or lower than 110  $\text{mEq L}^{-1}$ . To the first category belong intravenous solutions such as Lactated Ringer’s, Acetated Ringer’s, Hart-

**Table 1.** Intravenous balanced solutions: qualitative and quantitative composition

|   | Crystalloids      |                   |                     |            |                  |                | Gelatins |         |          | Starches |           |          |
|---|-------------------|-------------------|---------------------|------------|------------------|----------------|----------|---------|----------|----------|-----------|----------|
|   | Lactated Ringer's | Acetated Ringer's | Hartmann's solution | PlasmaLyte | Sterofundin ISO* | ELO-MEL isoton | Ionolyte | Isoplex | Gelaspan | Hextend  | Tetraspan | Volulyte |
| Na <sup>+</sup> [mEq L <sup>-1</sup> ]    | 130               | 132               | 131                 | 140        | 145              | 140            | 137      | 145     | 151      | 143      | 140       | 137      |
| K <sup>+</sup> [mEq L <sup>-1</sup> ]     | 4                 | 4                 | 5                   | 5          | 4                | 5              | 4        | 4       | 4        | 3        | 4         | 4        |
| Ca <sup>2+</sup> [mEq L <sup>-1</sup> ]   | 3                 | 3                 | 4                   | –          | 5                | 5              | –        | –       | 2        | 5        | 5         | –        |
| Mg <sup>2+</sup> [mEq L <sup>-1</sup> ]   | –                 | –                 | –                   | 3          | 2                | 3              | 3        | 1.8     | 2        | 0.9      | 2         | 3        |
| Cl <sup>-</sup> [mEq L <sup>-1</sup> ]    | 109               | 110               | 111                 | 98         | 127              | 108            | 110      | 105     | 103      | 124      | 118       | 110      |
| Lactate [mEq L <sup>-1</sup> ]            | 28                | –                 | 29                  | –          | –                | –              | –        | 25      | –        | 28       | –         | –        |
| Acetate [mEq L <sup>-1</sup> ]            | –                 | 29                | –                   | 27         | 24               | 45             | 34       | –       | 24       | –        | 24        | 34       |
| Malate [mEq L <sup>-1</sup> ]             | –                 | –                 | –                   | –          | 5                | –              | –        | –       | –        | –        | 5         | –        |
| Gluconate [mEq L <sup>-1</sup> ]          | –                 | –                 | –                   | 23         | –                | –              | –        | –       | –        | –        | –         | –        |
| Dextrose [g L <sup>-1</sup> ]             | –                 | –                 | –                   | –          | –                | –              | –        | –       | –        | –        | –         | –        |
| Gelatin [g L <sup>-1</sup> ]              | –                 | –                 | –                   | –          | –                | –              | –        | 40      | 40       | –        | –         | –        |
| HES [g L <sup>-1</sup> ]                  | –                 | –                 | –                   | –          | –                | –              | –        | –       | –        | 60       | 60        | 60       |
| Dextran [g L <sup>-1</sup> ]              | –                 | –                 | –                   | –          | –                | –              | –        | –       | –        | –        | –         | –        |
| <i>In-vivo</i> SID [mEq L <sup>-1</sup> ] | 28                | 29                | 29                  | 50         | 29               | 45             | 34       | 46      | 56       | 28       | 29**      | 34       |
| Osmolarity [mOsm L <sup>-1</sup> ]        | 278               | 277               | 279                 | 294        | 309              | 302            | 286      | 284     | 284      | 307      | 297       | 287      |

*In-vivo* SID — all organic molecules contained in balanced solutions are strong anions. The resulting calculated SID (*in vitro*-SID) is equal to 0 mEq L<sup>-1</sup>. Once infused, the organic molecules are metabolized to CO<sub>2</sub> and water; the resulting *in vivo*-SID corresponds to the amount of organic anions metabolized; \* Sterofundin-ISO or Ringerfundin; \*\* Tetraspan *in vivo*-SID reported is the sum of organic anions; it is noteworthy that there is an inequality with SID calculated as the difference between inorganic cations and inorganic anions (29 mEq L<sup>-1</sup> vs 33 mEq L<sup>-1</sup>).

mann's solution, Sterofundin ISO, Hextend, and Tetraspan. To the second category belong intravenous solutions such as Lactated Ringer's, Acetated Ringer's, Hartmann's solution, Plasma-Lyte, Elo-Mel Isoton, Isoplex, and Gelaspan (Table 1). Indeed, no ideal balanced solution has become available so far. Among the entire balanced solutions available, either they belong to just one category (having an effect on acid-base equilibrium while having a normal Cl<sup>-</sup> content, and vice versa), or present some limitations, such as relative hypotonicity (in the case of Lactated Ringer's, Acetated Ringer's, or Hartmann's solution) [12].

### STEWART'S APPROACH AND THE MECHANISMS REGULATING ACID-BASE DURING FLUID INFUSION

In the attempt to elucidate clearly the effects of intravenous solutions on acid-base status, it may be helpful to summarize the principles of Stewart's approach to acid-base equilibrium, taking into account both the hydro-electrolytic and acid-base balance.

In his physicochemical approach to acid-base and electrolyte equilibrium [13, 14], Peter Stewart began with describing the components of biologic fluids:

- water*, the solvent, which has a high molality (~55.5 mol kg<sup>-1</sup>), and is very weakly dissociated;
- strong electrolytes* (such as Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>), which are always entirely dissociated in biologic solution, and can be considered as chemically non-reacting;
- weak, non-volatile acids* (mainly albumin and phosphates), which are defined as substances only partially dissociated in aqueous solution, according to their dissociation constant;
- carbon dioxide (CO<sub>2</sub>) system* — dissolved molecular CO<sub>2</sub> in equilibrium with carbonic acid (H<sub>2</sub>CO<sub>3</sub>) and its dissociation products.

Moreover, Stewart pointed out three constraints under which the system, i.e. an aqueous solution including strong electrolytes, non-volatile weak anions and CO<sub>2</sub>, has to operate:

- electrical neutrality* — in every aqueous solution, the sum of positive charges must always equal the sum of negative charges;
- dissociation equilibria* — the dissociation equilibrium of incompletely dissociated substances must always be satisfied;

**Table 2.** Acid-base derangements according to Stewart's approach

| Independent variable                     | Variation | Acid-base effect      |
|--|-----------|-----------------------|
| PCO <sub>2</sub> [mm Hg]                 | ↑         | Respiratory acidosis  |
|  | ↓         | Respiratory alkalosis |
| SID [mEq L <sup>-1</sup> ]               | ↑         | Metabolic alkalosis   |
|  | ↓         | Metabolic acidosis    |
| A <sub>TOT</sub> [mmol L <sup>-1</sup> ] | ↑         | Metabolic acidosis    |
|  | ↓         | Metabolic alkalosis   |

PCO<sub>2</sub> — carbon dioxide partial pressure; SID — strong ion difference; A<sub>TOT</sub> — total non-volatile weak acids

- 3) *conservation of mass* — the total concentration of an incompletely dissociated substance must always be accounted for as the sum of the concentrations of its dissociated and un-dissociated forms.

Subsequently, Stewart set up a system of different equations describing how the variables at play reacted to each other, and how the hydrogen ion (H<sup>+</sup>) concentration (i.e., pH) varied according to these changes. The *dependent* variables were defined as H<sup>+</sup>, OH<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, CO<sub>3</sub><sup>2-</sup>, weak acid, and weak ions (A<sup>-</sup>). After mathematically solving the system, he identified three variables with the ability to influence, *independently*, the pH of biologic fluids (Table 2):

- 1) *the partial pressure of carbon dioxide* (PCO<sub>2</sub>);
- 2) *the concentration of non-volatile weak acids* (A<sub>TOT</sub>), mainly albumin and phosphates;
- 3) *the Strong Ion Difference* (SID), defined as the difference between the sum of strong cations (mainly Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) and the sum of strong anions (mainly Cl<sup>-</sup>, lactate, and other possible unmeasured anions), according to the following formulas:
  - a)  $SID = (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + \text{other strong anions})$ ;
  - b) *Abbreviated SID* = (Na<sup>+</sup> + K<sup>+</sup>) - (Cl<sup>-</sup>)

The influence of the independent variables can be predicted by solving six simultaneous equations:

- 1)  $[H^+] \times [OH^-] = Kw'$  (ionic product of water derived from water dissociation equilibrium, with Kw' being temperature-dependent, and including the dissociation constant Kw of water dissociation equilibrium)
- 2)  $[H^+] \times [A^-] = K_A \times [HA]$  (non-volatile weak acid dissociation equilibrium)
- 3)  $[HA] + [A^-] = [A_{TOT}]$  (conservation of mass for non volatile weak acids)
- 4)  $[H^+] \times [HCO_3^-] = K_c \times PCO_2$  (carbonic acid dissociation equilibrium)
- 5)  $[H^+] \times [CO_3^{2-}] = K_c \times [HCO_3^-]$  (bicarbonate ion dissociation equilibrium)
- 6)  $[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$  (electrical neutrality)

The above-mentioned mechanisms regulating acid base equilibrium clearly suggest that intravenous solutions may have an effect on plasma pH with a specific electrolyte composition, which determines the Strong Ion Difference of the infusion fluid (SID<sub>inf</sub>), after the metabolism, *in vivo*, of the organic anion included. after the metabolism of the organic anion included. Moreover, depending on their type (albumin and gelatins), fluids can also contain weak acids [7]. Therefore, according to the total amount infused, the SID<sub>inf</sub> and the content of weak acids, intravenous fluids can alter both SID and A<sub>TOT</sub> of plasma, with consequent effects on plasma pH. As a general rule, during fluid administration, plasma SID and A<sub>TOT</sub> will tend toward the SID<sub>inf</sub> and A<sub>TOT</sub> of the administered fluid. However, as shown in Table 2, modifications of these two variables have different effects on plasma pH. The fluid that does not alter plasma pH, at constant PCO<sub>2</sub>, regardless of the total amount infused and the degree of plasma dilution, should therefore balance the variations of these two independent variables [15].

For crystalloid solutions, i.e. intravenous fluids not containing weak acids (albumin or phosphates), the following general rule has been identified based upon *in vitro* and *in vivo* studies [11, 15]:

- 1) If SID<sub>inf</sub> is greater than the baseline concentration of plasma HCO<sub>3</sub><sup>-</sup>, then pH will tend toward alkalosis during the intravenous infusion;
- 2) If SID<sub>inf</sub> is lower than the baseline concentration of HCO<sub>3</sub><sup>-</sup>, then pH will tend toward acidosis during the intravenous infusion;
- 3) If SID<sub>inf</sub> equals the baseline concentration of HCO<sub>3</sub><sup>-</sup>, then pH will not change, regardless of the extent of the dilution.

With this regard, we can state that a "balanced" crystalloid solution should be a crystalloid solution that has an *in-vivo* SID, i.e., after the metabolism of organic anions, very similar to the patient HCO<sub>3</sub><sup>-</sup> concentration. It is noteworthy that this rule should apply also for non-ionic colloids, i.e. solutions that contain colloidal macromolecules that are electrically uncharged (such as starches and dextrans). On the other hand, ionic colloids, i.e., solutions that contain colloidal macromolecules that are electrically charged (such as gelatins and albumins) should have a greater SID<sub>inf</sub>, in order to balance the acidifying effect of the administered weak acid. If the A<sub>TOT</sub> of the infused colloidal solution is equal to plasma A<sub>TOT</sub>, then SID<sub>inf</sub> should ideally be equal to plasma SID in order to leave plasma pH unchanged regardless of the amount of infused fluid.

The theoretical understanding of the effects of intravenous solutions on acid-base equilibrium has two important consequences. Firstly, the effect on acid-base of a specific intravenous solution may vary in different patients, hav-

ing different  $\text{HCO}_3^-$  concentrations. Secondly, no available solution may be considered as totally balanced, and may be considered as the “ideal” balanced solution. In fact, since normal  $\text{HCO}_3^-$  concentration is about  $24 \text{ mEq L}^{-1}$ , and electrical neutrality must be satisfied, either we aim at not affecting acid-base at the cost of an increased  $\text{Cl}^-$  content in order to have a  $\text{SID}_{\text{inf}}$  close to  $24 \text{ mEq/L}$ , or we aim at having a physiological  $\text{Cl}^-$  concentration at the cost of a greater  $\text{SID}_{\text{inf}}$ .

## ELECTROLYTE CONTENT AND BALANCED SOLUTIONS

Another important aspect related to the concept of “balanced” solutions concerns the content of specific electrolytes other than  $\text{Na}^+$  and  $\text{Cl}^-$ , in particular of magnesium, calcium and potassium ( $\text{K}^+$ ).

### MAGNESIUM

Hypomagnesemia, i.e. a plasmatic concentration of magnesium below  $1.5 \text{ mg dL}^{-1}$ , is a relatively common finding in both critically ill patients and patients admitted to ICU [16]. As with other abnormalities in plasmatic electrolyte concentration, severe hypomagnesemia may be associated with a higher incidence of cardiac arrhythmias and alterations in electrocardiographic findings, as well as alterations of the cerebral nervous system. Interestingly, experimental data have reported a reduction in glomerular filtration rate (GFR) and of renal blood flow (RBF) in relation with a concentration of magnesium lower than normal values, and a restoration of GFR and RBF after magnesium administration [17]. Recently, both hypomagnesemia and ionized hypomagnesemia have been reported as being associated with a worse prognosis, especially for a non-recovery renal function after development of acute kidney injury (AKI) [18], as well as longer ICU stay and greater mortality [19]. Therefore, when dealing with fluid replacement and the necessity of intravenous fluid replacement, it may be reasonable to employ intravenous fluids also including magnesium, in order to prevent hypomagnesemia. This is the rationale upon which the novel generation of “balanced” solutions (such as the crystalloid solutions Plasma-Lyte or Sterofundin ISO) have been developed with the inclusion of magnesium, as compared to the old generation (Lactated Ringer’s, Acetated Ringer’s or Hartmann’s solution) (see Table 1). Although no studies have ever investigated the effects of balanced solutions on the incidence of hypomagnesemia, and magnesium can be easily supplemented intravenously, in clinical conditions in which a large volume replacement is required, this aspect may be an important issue in favour of the use of a novel balanced solution, as compared to all other types of fluids.

### CALCIUM

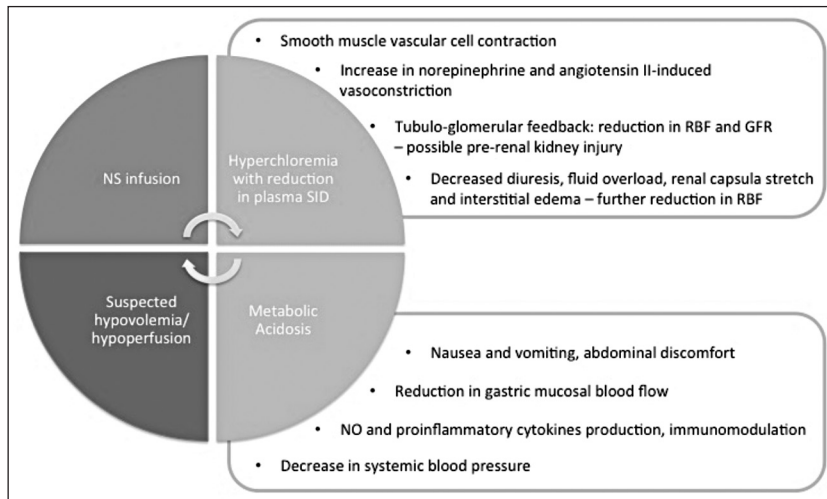
Hypocalcemia, especially if measured as total  $\text{Ca}^{2+}$  content, may be considered the most common abnormality in plasma electrolyte concentration observed in acutely ill patients [16], achieving a prevalence as high as 90% of critically ill patients [20]. Besides the possible causes, the possible symptoms and clinical consequences are well known: alterations in muscle contractility, of peripheral and central nervous system function, cardiac arrhythmias and others. Replacement of plasma  $\text{Ca}^{2+}$  content is obtained generally with the intravenous administration of either  $\text{Ca}^{2+}$ -gluconate or  $\text{Ca}^{2+}$ -chloride. Nonetheless, it may be reasonable to include also  $\text{Ca}^{2+}$  in an ideal “balanced” solution, especially in the necessity of large volume replacement therapies. However, we need also to consider the possible limitation of having a  $\text{Ca}^{2+}$ -containing intravenous solution, as related to the risk of  $\text{Ca}^{2+}$  precipitation when infused through the same vascular access of either blood components (precipitation of  $\text{Ca}^{2+}$  as  $\text{Ca}^{2+}$ -citrate) or bicarbonate (as  $\text{Ca}^{2+}$ -carbonate). This is the rationale underlying the development of  $\text{Ca}^{2+}$ -free intravenous balanced solutions (Table 1).

### POTASSIUM

Hypokalemia is a further life-threatening electrolyte abnormality often observed in critically ill patients [16]. Moreover, it is often associated with abnormalities of the content of other electrolytes. Symptoms include both alterations of muscle contractility, and alterations in cardiac rhythm. Although the common route of  $\text{K}^+$  replacement is oral administration, intravenous administration may be required in severe cases. All the available intravenous balanced solutions present a concentration of  $\text{K}^+$  within normal ranges, which does not necessarily cope with the normal daily intake  $\text{K}^+$  requirement [21]. This feature has been erroneously considered a reason for preferring the use of 0.9% NaCl as the only intravenous solution potentially applicable in the case of patients with acute or chronic renal failure. As we will discuss below, several trials in this clinical context have clearly demonstrated that this concern is mistaken.

## THE IMPORTANCE OF CHLORIDE CONTENT AND ITS PATHOPHYSIOLOGIC EFFECTS

Chloride is the main anion of the extracellular fluid, and although its concentration in plasma is not as tightly regulated as that of  $\text{Na}^+$  and  $\text{K}^+$ , it has a central role in acid-base equilibrium [22, 23]. Because of such physiological features,  $\text{Cl}^-$  is also the main anion of any crystalloid solution given intravenously for fluid resuscitation and volume maintenance [7]. Nonetheless, over the years, it has become evident that the  $\text{Cl}^-$  content of intravenous fluids, especially at supra-physiologic levels, may have relevant clinical consequences [24].



**Figure 1.** Pathophysiology and clinical consequences of hyperchloremic acidosis

The circle represents a clinical scenario in which normal saline (NS) is administered as resuscitation fluid (upper left), hyperchloremia ensues as a result and reduces the plasma strong ion difference (SID, upper right) which in turn causes metabolic acidosis (lower right). If the clinician interprets the acid-base derangement as a consequence of an hypovolemic state with tissue hypoperfusion (lower left), which represents the most frequent cause of metabolic acidosis in critically-ill patients, therapy will consist of fluid resuscitation (upper left), potentially maintaining the vicious cycle.

The green and yellow inserts summarize the detrimental effects of hyperchloremia (green) and metabolic acidosis (yellow), respectively. It is noteworthy that some pathophysiological effects of hyperchloremic metabolic acidosis (e.g. reduction in renal blood flow and glomerular filtration rate, decreased diuresis with fluid overload, decrease in systemic blood pressure) can worsen the clinical picture, potentially misleading the clinician into administering more chloride-rich fluids for a (presumed) hypovolemic/hypoperfusive state.

Normal saline, still one of the most employed intravenous crystalloid solutions, presents a high, non-physiological content of  $\text{Cl}^-$  (and  $\text{Na}^+$ ), and has long been known to induce, as a side-effect of its liberal administration, hyperchloremic metabolic acidosis [25, 26]. Even if it is often considered self-limiting and benign in nature, 0.9% NaCl-induced metabolic acidosis will be added to any other possible causes of acidosis, especially in critically ill patients, thereby potentially complicating or worsening the clinical picture (as during the treatment of diabetic ketoacidosis, as an example) [27, 28]. Moreover, the induction of hyperchloremic metabolic acidosis in relation to 0.9% NaCl may also mislead clinicians into looking for, and maybe erroneously treating, a “classic” cause of metabolic acidosis in an otherwise healthy patient [29]. In this last scenario, if the clinician erroneously attributes metabolic acidosis to tissue hypoperfusion (probably the most common cause of metabolic acidosis in critically ill patients), a vicious cycle may derive, in which the treatment for the misdiagnosed acid-base disturbance with further fluid administration will worsen hyperchloremia and acidosis (Fig. 1).

Over the years, more concern has been raised over other unwanted side effects of 0.9% NaCl intravenous administration as compared to balanced solutions [8, 30], as different mechanisms underlying a potential  $\text{Cl}^-$  toxicity have been postulated. Several reports have observed that  $\text{Cl}^-$  mediates vascular smooth muscle cell  $\text{Ca}^{2+}$ -dependent contrac-

tion [31], may modify vascular responses to vasoconstrictor agents in the kidney [32] and may affect plasma renin activity and systemic blood pressure [33]. Moreover, a very well-known physiologic mechanism underlying the regulation of  $\text{Na}^+$  and water balance in the renal system, i.e. the tubule-glomerular feedback (TGF), has been shown to be dependent on  $\text{Cl}^-$  delivery, rather than  $\text{Na}^+$  delivery, to the distal tubule and its uptake by the macula densa [34]. This mechanism physiologically maintains GFR fairly constant and relatively independent from systemic blood pressure oscillations, prevents excessive salt and water loss when the proximal tubule is not able to reabsorb the filtrate (e.g. osmotic diuresis), and reacts more efficiently in conditions of salt depletion [35]. However, the very same mechanism is believed to operate during liberal administration of  $\text{Cl}^-$ -rich fluids. Studies on healthy individuals receiving an intravenous load of crystalloids support this hypothesis: administration of 0.9% NaCl, as compared to balanced solutions, was associated with a lower diuresis and natriuresis [24, 36], and a lower renal artery blood flow velocity and cortical renal perfusion [37]. As occurs in other notable cases, evolution has selected a very efficient mechanism to safeguard homeostasis from the most common and life threatening situations (in this case, water and salt deprivation), whereas our treatment is challenging the human body with the opposite situation, i.e. water and salt overload, leading to an inadequate (maladaptive) physiological response. In fact,

following this reasoning, a possible further detrimental consequence of the relatively slower diuretic response to the infusion of  $\text{Cl}^-$ -rich crystalloids may be fluid overload [38]. Increased extracellular volume [29, 37] can in fact cause an increase in central venous pressure and renal venous engorgement, which reduce trans-renal pressure gradient and flow, as well as interstitial oedema which increases renal interstitial pressure due to the relatively non-expandable kidney capsula [39]. Moreover, increased central venous pressure is commonly associated with increased intra-abdominal pressure, a situation that in turn can lead to fluid accumulation in relation to the reduction in venous return and cardiac output [40]. All these mechanisms can cause kidney hypoperfusion and damage.

The kidney is not the only organ on which a potentially detrimental effect of  $\text{Cl}^-$ -rich fluid administration has been studied. Healthy volunteers challenged with an intravenous administration of a bolus of 0.9% NaCl have complained of abdominal discomfort [41]. Similarly, in elderly patients receiving intraoperatively a fluid replacement with 0.9% NaCl, a decrease in gastric mucosal perfusion, assessed by gastric tonometry, has been reported [42]. These reports raise the concern that  $\text{Cl}^-$ -mediated vasoconstriction and the associated reduction in blood flow is operating also at the splanchnic level, even though the role of  $\text{Cl}^-$  and hyperchloremia *per se*, as compared to the role of acidosis, cannot be clearly separated based upon these studies [43, 44].

Finally, an effect of hyperchloremic acidosis on the function of the immune system has been postulated based upon experimental studies in septic animals, in which an intravenous administration of HCl aimed at achieving a specific targeted pH increased plasma nitric oxide levels and pro-inflammatory cytokines [45, 46]. Moreover, a study on septic rats resuscitated with intravenous administration of either 0.9% NaCl or a balanced solution (Plasma-Lyte), showed the development of hyperchloremic metabolic acidosis, as associated with an increased IL-6 levels, incident acute kidney injury (AKI) and a higher mortality rate in those receiving 0.9% NaCl [30]. Although the association between hyperchloremia and immune system dysfunction is far from proof of causality, it is worth mentioning that in a retrospective analysis of a large hospital claims database, patients receiving only 0.9% NaCl perioperatively showed a higher probability of developing a major postoperative infection, as compared to patients receiving only Plasma-Lyte [29].

## RENAL TRANSPLANTATION AND INTRAVENOUS FLUIDS

The choice of intravenous fluids in patients with renal failure (either acute or chronic) is particularly challenging, as these patients have, by definition, an impaired renal handling of water and main electrolytes. Renal transplantation is

the typical clinical situation in which considerable amounts of intravenous fluids are administered normally to patients with end-stage renal disease. Indeed, despite some controversies [47], patients undergoing renal transplantation still receive, in many centres, large amounts of intravenous fluids (up to  $30 \text{ mL kg}^{-1} \text{ h}^{-1}$ ), in the attempt to increase their intravascular volume and therefore improve graft function [48]. A survey recently performed in the United States pointed out that 0.9% NaCl, and 0.9% NaCl-based intravenous solutions, were the most commonly employed intravenous solutions during renal transplantation. The major reason for this choice was the selection of a  $\text{K}^+$ -free solution [49], in the attempt to avoid hyperkalemia in patients with reduced potassium excretion capabilities.

However, as discussed above, the intravenous administration of large amounts of 0.9% NaCl, having a  $\text{SID}_{\text{inf}}$  equal to zero, induces always hyperchloremic metabolic acidosis, thereby potentially leading *per se* to the development of hyperkalemia, and may affect renal function, in relation to the detrimental effects of hyperchloremia. A few randomized controlled studies have compared, in patients undergoing renal transplantation, the intravenous administration of 0.9% NaCl with the intravenous administration of different balanced solutions, all of which containing  $\text{K}^+$  within plasmatic ranges (Table 3) [50–53]. While no significant difference in graft function was observed, all studies clearly documented a higher incidence of hyperchloremia and acidosis in patients receiving 0.9% NaCl as compared to patients receiving intravenous balanced solutions. It is noteworthy that no difference was observed regarding plasmatic concentrations of  $\text{K}^+$  and events of hyperkalemia between the two groups.

Taken together, these data strongly support the avoidance of 0.9% NaCl and other possible intravenous fluids causing metabolic acidosis in patients with acute or chronic renal failure, as well as during renal transplantation, and provide the first solid data on the safety of employing  $\text{K}^+$ -containing balanced solutions for volume replacement and maintenance in this specific clinical setting.

## CLINICAL EVIDENCE

Despite the strong physiological rationale and the accumulation of data suggesting possible harms for the use of 0.9% NaCl for several years, the first large randomized controlled trial investigating a possible long-term and clinically relevant benefit of a balanced solution over an unbalanced solution for fluid resuscitation or volume maintenance, has been concluded just very recently [9]. Indeed, several clinical trials, even designed as prospective and randomized studies [54, 55], had been conducted aimed at comparing several physiological effects of the two categories of intravenous solutions, whereas the

Table 3. Clinical trials on the use of fluids during renal transplantation

| First author [reference] | Study type   | N   | Living donor [n, %] | Groups         | Intra-operative fluid volume | Duration of procedure [minutes] | Mean $\Delta K$ [mEq L <sup>-1</sup> ] | Mean $\Delta pH$                       | Mean $\Delta Cl$ [mEq L <sup>-1</sup> ] | Mean POD 3 serum creatinine [mg dL <sup>-1</sup> ] |
|--------------------------|--------------|-----|---------------------|----------------|------------------------------|---------------------------------|--|--|---|--|
| O'Malley [50]            | Double blind | 51  | 48 (94%)            | NS<br>LR       | 5.85 L                       | 336*                            | NS = +0.3<br>LR = +0.1                 | NS = -0.11<br>LR = +0.01               | NS = n/a<br>LR = n/a                    | NS = 2.3<br>LR = 2.1                               |
| Khajavi [51]             | Double blind | 52  | 52 (100%)           | NS<br>LR       | 60 mL kg <sup>-1</sup>       | n/a                             | NS = +0.5<br>LR = -0.5                 | NS = -0.06<br>LR = -0.005              | NS = n/a<br>LR = n/a                    | NS = 1.9<br>LR = 2.1                               |
| Hadimioglu [52]          | Double blind | 90  | 90 (100%)           | NS<br>LR<br>PL | 2.80 L                       | 119§                            | NS = -0.3<br>LR = -0.3<br>PL = -0.3    | NS = -0.08<br>LR = -0.02<br>PL = +0.02 | NS = +21.2<br>LR = +3.3<br>PL = +1.7    | NS = 2.1<br>LR = 1.8<br>PL = 1.9                   |
| Potura [53]              | Open label   | 150 | 0 (0%)              | NS<br>EI       | 1.75 L                       | 74§                             | NS = +0.8<br>EI = +0.6                 | NS = n/a<br>EI = n/a                   | NS = n/a<br>EI = n/a                    | NS = 5.8<br>EI = 6.2                               |

NS — normal saline (0.9% NaCl); LR — Lactated Ringer's; EI — ELO-MEL isoton; POD — post-operative day; \* operating room time; § surgical time

scientific community still needed an understanding of whether such physiological effects (i.e. on acid-base equilibrium, on renal function and other organs) translated into a survival difference (Table 4). As we will see below, although the SPLIT trial has made an important step ahead within this issue [9], many questions are still open regarding the possible efficacy (or neutral clinical effect) of intravenous balanced solutions.

An important aspect related to the apparent lack of solid evidence supporting the use of specific types of crystalloids (or colloids) may rely on an unclear focus of the research conducted so far, which actually has led to clinical trials approaching this issue from different perspectives, summarized here.

### UNBALANCED INTRAVENOUS SOLUTIONS IN RELATION TO OUTCOME

Firstly, is 0.9% NaCl intravenous solution more dangerous than intravenous balanced solutions? In a large retrospective analysis of a hospital claims database, Shaw *AD et al.* examined patients undergoing major abdominal surgery and receiving only 0.9% NaCl, and compared them to patients receiving only Ca<sup>2+</sup>-free balanced solutions on the day of surgery [29]. Indeed, patients receiving 0.9% NaCl showed a higher incidence of postoperative infections, a greater incidence of the use of renal replacement therapy and a higher unadjusted mortality rate, as compared to those receiving intravenous balanced solutions. It is noteworthy that when the analysis was adjusted for possible confounding covariates, no difference in mortality rates was observed between the two groups. Moreover, the same group of researchers investigated the same hypothesis, in a large cohort of patients receiving crystalloids during the first 48 hours after the development of systemic inflammatory response syndrome (SIRS) [56]. After the application of a propensity-matched cohort methodology, patients in the 0.9% NaCl group showed greater in-hospital mortality, length of hospital stay and frequency of readmission at 90 days than patients in the Ca<sup>2+</sup>-free balanced group, even after adjustments for Acute Physiology Score and baseline covariates.

### INTRAVENOUS CHLORIDE LOAD IN RELATION TO OUTCOME

Secondly, is the total Cl<sup>-</sup> load intravenously administered to patients associated with outcome? Yunos *et al.*, in the first large prospective before-and-after study, compared a Cl<sup>-</sup>-restrictive strategy, which was applied to fluid therapy of all consecutive ICU admissions over 6 months, to the Cl<sup>-</sup>-permissive strategy over the same 6 months period of the previous year [8]. After the introduction of the Cl<sup>-</sup>-restrictive intravenous fluid strategy, the use of 0.9% NaCl and gelatins



**Table 4.** Clinical trials comparing balanced solutions and 0.9% NaCl including mortality as primary or secondary outcome

| First author [reference] | Design                                 | N     | Fluids compared  | Outcomes  |
|--------------------------|--|-------|--|---|
| Yunos [8]                | Observational, prospective, open label | 1533  | Chloride-rich fluids (0.9% NaCl, 4% succinylated gelatin solution, 4% albumin in sodium chloride) vs. chloride-poor balanced solutions (Hartmann's solution, Plasma-Lyte 148, poor chloride 20% Albumex) | Serum creatinine, AKI, need for RRT, in-hospital and ICU LOS, survival  |
| Mahajan [54]             | RCT, double-blind                      | 22    | 0.9% NaCl vs. Lactated Ringer's  | Acid-base, electrolytes, fluids, in-hospital LOS and in-hospital mortality  |
| Shaw [29]                | Observational, retrospective           | 3704  | 0.9% NaCl vs. Plasma-Lyte (A or 148)   | Respiratory failure, cardiac complications, infections, gastrointestinal dysfunction, acute renal failure, electrolytes, acid-base, re-hospitalization, mortality |
| Young JB [55]            | RCT, double-blind                      | 65    | 0.9% NaCl vs. Plasma-Lyte A  | Acid-base, electrolytes, coagulation rate, fluids, urinary output, organ failure, in-hospital and ICU LOS, in-hospital mortality                                  |
| Shaw [57]                | Observational, retrospective           | 3116  | 0.9% NaCl vs. calcium-free balanced solutions (Plasma-Lyte or Normosol)*   | Mortality, in-hospital complications, electrolytes, acid-base, in-hospital LOS, readmission   |
| Raghunathan [58]         | Observational, retrospective           | 6730  | 0.9% NaCl vs. 0.9% NaCl and balanced solutions (mainly Lactated Ringer's)  | In-hospital mortality, acute renal failure, ICU and hospital LOS  |
| Raghunathan [59]         | Observational, retrospective           | 60734 | 0.9% NaCl vs 0.9% NaCl and balanced solutions (mainly Lactated Ringer's) vs 0.9% NaCl and colloids (mainly albumin) vs. 0.9% NaCl and balanced solutions and colloids                                    | In-hospital mortality, hospital LOS, costs  |
| Young PJ [9]             | RCT, double-crossover, double blind    | 2092  | 0.9% NaCl vs. Plasma-Lyte 148  | AKI, need for RRT, mechanical ventilation, in-hospital and ICU LOS, mortality   |

LOS — length of stay; AKI — Acute Kidney Injury; RRT — Renal Replacement Therapy; \* Both groups were allowed to receive other fluid types (0.9% NaCl, Lactated Ringer's, 0.45% NaCl)

decreased significantly, and, consequently, the amount of  $\text{Cl}^-$  administered to patients also decreased significantly. In association with the modification of the fluid strategy, the authors observed a reduction in the incidence of AKI, as assessed according to the Risk, Injury, Failure, Loss and End-stage kidney injury (RIFLE) criteria, especially in the injury and risk classes (14% vs. 8.4%,  $P < 0.001$ ), as well as a reduction in the use of renal replacement therapies (10% vs. 6.3%,  $P = 0.005$ ), even after adjustments for covariates. Following the same hypothesis, although through a retrospective analysis of a large cohort of patients with SIRS, Shaw *et al.* observed a direct correlation of both the total amount of  $\text{Cl}^-$  intravenously received and the associated increase in serum  $\text{Cl}^-$  concentration during fluid resuscitation with an increased risk of death [57]. Such an association appeared to be independent of the total amount of fluids administered.

#### **BALANCED INTRAVENOUS SOLUTIONS IN RELATION TO SAFETY AND SURVIVAL**

Thirdly, are intravenous balanced solutions safer overall and do they provide a survival advantage as compared to intravenous unbalanced solutions, especially in patients with sepsis, in whom early fluid therapy is a crucial part of

the clinical treatment? This issue has been addressed by the same group of investigators in two large retrospective studies performed on the same large clinical database in two different cohorts of patients with sepsis [58, 59]. In the first one, the authors showed a decrease in in-hospital mortality for any increase in the fraction of balanced solutions over the total amount of fluids intravenously received for the initial resuscitation (2 days), irrespective of the total amount of fluids received [58]. In the second study, the administration of intravenous balanced solutions in association with 0.9% NaCl appeared to be associated with a lower in-hospital mortality and a similar length of stay and costs per day as compared to the exclusive administration of 0.9% NaCl [59].

#### **THE SPLIT TRIAL**

In October 2015, the SPLIT trial (the 0.9% saline vs. Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy), the first large randomized controlled trial comparing the clinical effects of two different types of crystalloids, was finally published, after the conclusion of patient enrolment in October 2014 [9]. In this double-blind, cluster randomized, double-crossover trial, conducted in 4 ICUs in New Zealand, 2,278 ICU patients in need of crystalloid fluid therapy were

enrolled to receive either 0.9% NaCl or Plasma-Lyte 148, as a balanced solution, according to an alternating block of 7-weeks for each specific ICU. The study was designed to evaluate, as the primary outcome, the proportion of patients with AKI during the first 90 days after enrolment, and to assess several clinically relevant endpoints as secondary outcomes. In contrast to the hypothesis, the authors observed an identical proportion of patients developing AKI in the two groups of treatments (9.6% in the balanced solutions group vs. 9.2% in the 0.9% NaCl group), as well as a similar use of renal replacement therapy and in-hospital mortality.

Although the trial was conducted and analyzed with a rigorous methodology and represents a very important step ahead in the field, it presents some limitations, an aspect which leaves important questions unanswered. In particular, the study population included was composed, in its vast majority, of post-operative patients, after elective surgery (especially cardiovascular procedures), with small incidence of co-morbidities, a low severity (as assessed by the Acute Physiology and Chronic Health Evaluation [APACHE] II score [60]), and including small percentages of high-risk patients (less than 5% for patients with sepsis). Consequently, most of the patients in both groups received very small amounts of intravenous study fluids (2L as median values, during the study period), limiting, therefore, their exposure to the treatment under investigation. Moreover, no data on the effects of the two treatments on plasma Cl<sup>-</sup> concentration have been measured, making therefore impossible to assess the potential determinant of the deterioration of renal function during fluid therapy. As the authors concluded, these findings, whereas showing neutral effects of the two strategies in post-operative patients, leave unsolved the potential effects of intravenous balanced solutions in high-risk populations, more exposed to fluid therapy and at risk of AKI.

## CONCLUSIONS

Both the introduction in clinical practice of intravenous balanced crystalloids solutions and the findings collected on their use in comparison with the traditional administration of 0.9% NaCl, have brought a new awareness in the field of fluid therapy. As even the type of solutions may affect patient-centred clinical outcome, including survival, such fluids should be considered as “drugs” [1]. The type of fluid, the dose, the rate of administration, the timing and the duration of the treatment are all equally important. Intravenous balanced solutions have potentially several physiologically relevant advantages, although the actual translation of such rationale into clinically relevant outcomes is still unclear. Moreover, the “ideal” intravenous balanced solution including all the characteristics necessary for such definition (least

effect on acid-base, and electrolyte content equal to that of plasma), has instead of have not yet become available. The SPLIT trial, the first large randomized controlled trial prospectively comparing the effects of a balanced solution (Plasma-Lyte 148) with those of 0.9% NaCl in critically ill patients showed, unexpectedly, precise equipoise between the two treatments, although presenting important limitations [9]. Whether or not the use of intravenous balanced solutions is beneficial in high-risk patient categories (sepsis, trauma, burns), when exposed to larger amounts of fluids or when at higher risk of AKI, still needs to be investigated. Moreover, further research on the potential mechanisms underlying the clinical effects observed on specific types of crystalloid solutions is warranted.

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