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Intravenous Fluids: Issues Warranting Concern

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We are issuing a clarion call for the development and availability of intravenous fluids with physiological compositions and more transparent and complete package labeling. Intravenous administrations of fluid are used in perioperative medicine to defend against derangements in

physiological state and to restore a normal state in a wide variety of clinical scenarios. These scenarios include their routine use during anesthesia and surgery in adult and pediatric patients, the treatment of critically ill patients with various pathologic conditions, e.g., bleeding, sepsis, and trauma, and the use of intravenous fluids as a vehicle for drugs. The physiological end-points targeted by the infusions include systemic blood volume, and in turn, cardiac output and tissue perfusion, metabolic function, electrolyte concentrations, and acid-base balance. Although colloids have the advantage of remaining predominantly intravascular, their use has been curtailed because of the risk of hemostasis and renal dysfunction. Currently crystalloids are used for nearly all conditions.

Crystalloid solutions have wide variations in chemical composition, which could theoretically impact their efficacy and adverse side effects, including those associated with volume load, (e.g., hypervolemia and tissue edema), and imbalances in electrolytes, (e.g., hyponatremia, hyperchloremia, hyperkalemia, and hypocalcemia). These side effects could have serious consequences especially when the infusions are large volume and over a long period of time. The solutions used for intravenous infusion contain biologically active chemicals and thus are categorized as drugs products by local agencies, such as the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). However, despite this designation, the packaging of the solutions is lacking in information about their chemical composition (e.g., osmolality and potential base excess (BE_{pot})), dose, indications, contraindications, and potential side-effects, information with obvious value in clinical decision making. The absence of this transparency has prompted wide-spread frustration among clinicians, as reflected in the international makeup of the authors of this editorial. We are recommending that labeling of the intravenous solutions be updated to reflect the physiologic consequences of the various crystalloid formulations, and that the teaching of protocols related to the infusion of these fluids be standardized and evidenced based.

The scientific evidence guiding fluid choice and dosing is limited. Indeed, the current guidelines are based on physiological experiments rather than comparative clinical trials. This lack of reliable relevant clinical data was recognized first by researchers in Europe in the early 2000s.[1,2]. However, little progress has been made since then. In 2018, Boer et al. emphasized this shortcoming in their review article in the *British Journal of Anaesthesia*[3]: “data from septic and critically ill patients are translated to the surgical patient without a clear rationale, irrespective of the differences in inflammatory state between these distinct populations; also, the impact of different fluid types in the perioperative setting and their impact on basic physiology is rarely taken into account”[3]. The current interest and wide international reach of the controversy related to intravenous fluid choice is evidenced by its discussion in three articles from Europe and the United States published in 2020.[4,5,6]

The rationale for new guidelines governing the use of an intravenous fluid should be based on its ability to maintain or restore the body's internal environment, the so-called "milieu interieur.' Normally this condition is maintained by intrinsic physiological mechanisms and is exemplified by a remarkable constancy for osmotic pressure and buffer base concentration within and between individuals. Indeed, a review of literature **values** demonstrates that osmotic pressure, or tonicity, varies by only 1.5 % (288 mosmol/kg H_2O, n = 263), and buffer bases (48 mmol/l), expressed as base excess, vary by only 2.2 % (BE ± 0 mmol/l, n = 90). [7,8,9,10]

Fluids best suited to promote an extracellular fluid (ECF) composition within narrow limits are physiologically composed, homogeneous fluids (i.e., those that are iso-tonic (osmolality), iso-hydric (base excess) and iso-ionic (sodium, potassium, chloride) solutions – not only in vitro (in the laboratory), but also in the patient after metabolization of the ingredients.[1, 7] Achieving wide spread application of this approach will require the adoption of standard definitions for osmolality and BE_{pot}.

It is critical that isotonic fluids have the same osmolality as fluids within the body, including blood plasma. Whereas the theoretical osmolarity of a fluid is calculated by summing up all osmotically active ingredients relative to 1 liter of volume (mosmol/l), the actual (real) osmolality (mosmol/kg H_2O) – rather than osmolarity – can be measured directly using freezing point depression, or calculated from osmolarity.[11] By pure chance, the actual (real) osmolality of plasma (288 mosmol/kg H_2O) is almost identical to the theoretical osmolarity of 291 mosmol/l calculated from its chemical composition, not 308 mOsm/L, as published by the AAP[12]. This coincidence is presumably responsible for some of the confusion in the medical literature.

The following examples show how the corresponding values for osmolarity and osmolality of various solutions can vary, sometimes substantially[11]: For example, normal (0.9 %) saline has an osmolarity of 308 mosmol/l, or an actual (real) osmolality of 286 mosmol/kg H_2O; lactated Ringer's (Hartmann's) solution is hypotonic (276 instead of 308 mosmol/l or 256 instead of 288 mosmol/kg H_2O); glucose (Dextrose) 5 % has an in vitro osmolality of 290 mosmol/kg H_2O (isotonic) and a theoretical osmolarity of 278 mosmol/l, but an in vivo osmolality of 0 mosmol/kg H_2O, corresponding to pure water. It is clear from these examples that a standardization of units (osmolarity vs osmolality) and clear package labeling is necessary to avoid inappropriate use of fluids, potentially leading to iatrogenic hypoosmolality and subsequent encephalopathy. The EMA recently issued a warning in this regard.[13] Notably, the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that special warnings and precautions be included in the Summaries of Product Characteristics for glucose-containing electrolyte solutions[13].

Potential Base Excess (in mmol/l) is a useful parameter to predict the influence of an infusion solution on the acid-base equilibrium of the patient. This parameter indicates the amount of bicarbonate that can potentially be consumed or released in the body after infusion[1] of fluids

and is recommended for labeling of solutions by manufacturers in Europe, especially in Germany and Austria[11]. The following examples illustrate the advantages of using the BE_{pot}. Saline 0.9 %, which lacks the bicarbonate concentration present in plasma (24 mmol/l), accordingly has an acidifying effect (BE_{pot} -24 mmol/l) after infusion, and thus may cause hyperchloremic acidosis. In contrast, an "acetate-buffered" crystalloid solution[11] containing 45 mmol/l of acetate results in a BE_{pot} of +21 mmol/l (acetate 45 minus bicarbonate 24 mmol/l) and is, therefore, an alkalizing solution. This action results because the infused acetate is rapidly metabolized in muscle and other tissues leading to an indirect release of equimolar amounts of bicarbonate. For this reason and others,[11] we prefer acetate over lactate solution. Furthermore, we recommend that the label "buffered"[14] "or acetate-buffered"[14] for infusion solutions should be replaced by either "acetate-containing" or "physiologically composed balanced isotonic" solution, since acetate per se has no inherent buffering capability.[11]

In conclusion, we recommend strongly that the medical community take Lönnqvist´s appeal ("time for a solution")[2] seriously, and urge medical companies and manufacturers to provide solutions that are physiologically composed and balanced (Table 1) and which include clear and detailed guidance for their safe and effective use. We believe that these relatively simple steps will have a substantial clinical benefit in reducing morbidity, and potentially saving lives.

References

1. Zander R: Infusion fluids: Why should they be balanced solutions? EJHP Practice 2006; 12: 60 - 2
2. Lönnqvist PA: Inappropriate perioperative fluid management in children: time for a solution?! Paediatr Anaesth 2007; 17: 203 - 5
3. Boer C, Bossers SM, Koning NJ: Choice of fluid type: physiological concepts and perioperative indications. Br J Anaesth 2018; 120: 384 – 96
4. Maheshwari K, Turan A, Makarova N, Ma C, Was E, Ruetzler K, Barsoum S, Kuhel AG, Ritchey MR, Higuera-Rueda C, Kopyeva T, Stocchi L, Essber H, Cohen B, Suleiman I, Bajracharya GR, Chelnick D, Mascha EJ, Kurz A, Sessler DI: Saline versus lactated Ringer's solution: The Saline or Lactated Ringer's (SOLAR) Trial. Anesthesiology 2020; 132: 614 - 24
5. Story DA: Intravenous fluids: Which Recipe? Anesthesiology 2020; 132: 609 – 11
6. Kasatkin A, Urakov A, Nigmatullina A, Kopytov M: Balanced Crystalloid versus 0.9 % Sodium Chloride: What we overlook in our research. Anesthesiology 2020 Nov 9. doi: 10.1097/ALN.0000000000003614. Epub ahead of print. PMID: 33166381
7. Zander R: Fluid Management – Second expanded (corrected) edition 2020. Paperback, ISBN: 978-3-347-12851-4

8. Fazekas AS, Funk GC, Klobassa DS, Rüther H, Ziegler I, Zander R, Semmelrock HJ: Evaluation of 36 formulas for calculating plasma osmolality. Intensive Care Med 2013; 39: 302 – 8
9. Lentner C: Physical chemistry, blood, somatometric data; in: Geigy Scientific Tables, Vol. 3, Lentner C (ed.), Ciba-Geigy Limited, Basle, 1984, p 73, ISBN: 0914168525 9780914168522
10. Zander R, Lang W: Letter to the editor: Base Excess and strong ion difference: Clinical limitations related to inaccuracy. Anesthesiology 2004; 100: 459 – 60
11. Sümpelmann R, Becke K, Zander R, Witt L: Perioperative fluid management in children: can we sum it all up now? Curr Opin Anaesthesiol 2019; 32: 384 – 91
12. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K, Basu RK, Conway EE Jr, Fehr JJ, Hawkins C, Kaplan RL, Rowe EV, Waseem M, Moritz ML, SUBCOMMITTEE ON FLUID AND ELECTROLYTE THERAPY: Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics. 2018; 142: e20183083
13. European Medicines Agency (EMA): Annual Report 2017; https://www.ema.europa.eu/en/news/ema-2017-annual-report-published
14. Potura E, Lindner G, Biesenbach P, Funk G-C, Reiterer C, Kabon B, Schwarz C, Druml W, Fleischmann E: An acetate-buffered balanced crystalloid versus 0.9 % saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial. Anesth Analg 2015; 120: 123 – 9

Table 1: Recommended Compositional Information for Label of Intravenous Solutions
iso-tonic (osmolality in mosmol/kg H_2O *instead* of osmolarity in mosmol/l)
iso-hydric (potential base excess (BE_{pot}), mmol/l, *instead* of pH or titration acidity)
iso-ionic (sodium, potassium, chloride in mmol/l *instead* of g/l)
acetate *instead* of lactate in mmol/l