Balanced Salt Solutions

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Outline

• Physiology of non-organic electrolytes
• Evolution aspects of electrolyte regulation
• Physiological processes regulating electrolytes
• Clinical data
  – Randomized trials
  – Observational studies
Balanced versus unbalanced salt solutions: What difference does it make?

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Terminology

• “Physiologically buffered”
  – Uses biological substances –eg acetate, lactate, HCO3-

• “Balanced” uses something besides Cl⁻ to balance +v charge

• Low Cl⁻ or Cl⁻ “sparing” solutions
Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

Censoring applied at hospital discharge or death. The x-axis is truncated at 40 days because the number of participants still in follow-up beyond 40 days is small.
Assessing Toxicity of Intravenous Crystalloids in Critically Ill Patients

John A. Kellum, MD; Andrew D. Shaw, MB, FRCA
Equal concentrations of solutes in and out

- Initial organisms likely had the same intracellular composition as their environment
- Substrates freely moved in and by-products out
- Moved down concentration gradients
Evolutionary aspects

• Strong non-organic (“atomic”) electrolytes are the major determinants of osmolality because they are not metabolized and therefore must be regulated by absorption or excretion.

• Because of the requirement of “electrical neutrality” (all positives must equal all negatives”) regulation of cation concentration is sufficient to regulate the osmolality of biological solutions

• Na⁺ is the logical choice for it is the second most abundant substance in sea water
Outside concentration greater than inside

Changes in the outside concentration will cause problems

- Eg evaporation, changes in depth, rapid increase in internal metabolites (osmols)
Outside concentration lower than inside

**Solution:**

Use $K^+$ on inside instead of $Na^+$
-also lower $Cl^-$
Evolutionary aspects

- Strong non-organic ("atomic") electrolytes are the major determinants of osmolality – not metabolized and therefore must be regulated by absorption or excretion.
Use $K^+$ on inside instead of $Na^+$
Also lower $Cl^-$

$K^+$ properties are very close to $Na^+$ and it is the 6\textsuperscript{th} most common substance in sea water - thus obvious choice for inside

- Inside osmolality can be controlled
- Can control volume
Strong Ions:

- Strong electrolytes are always completely dissociated in solution, $k_m > 4.0 \times 10^{-4}$ Eq/l

**POSITIVE**: $\text{Na}^+$, $\text{K}^+$, $\text{Ca}^{2+}$, $\text{Mg}^{2+}$

**NEGATIVE**: $\text{Cl}^-$, $\text{SO}_4^{2-}$, lactate, $\beta$-hydroxy butarate, formate, oxalate

e.g. NaCl does not exist in solution; there is only Na$^+$ and Cl$^-$
The major “players” in the SID of normal plasma are:

\[ \text{Na}^+ = 140 \quad \text{Cl}^- = 102 \]
Significance of Electrical Neutrality

- volume = $4.2 \times 10^{-6}$ l
- net +ve charge = $4.2 \times 10^{-13}$ Eq
- 1 eq = $4.0 \times 10^{-7}$ Coulomb
- Charge (volts) = $Q / 1.1 \times 10^{-10} r$

Radius = 1 mm

$1.0 \times 10^{-7}$ Eq/l of +ve > -ve

= 400,000 VOLTS!
Acid-Base balance considerations

• Why is it useful to have Cl\(^{-}\) less than Na\(^{+}\) in plasma and ECF?
  – Actually more Cl\(^{-}\) in sea-water than Na\(^{+}\)
  1. Room for other important negative charges
    • HCO\(_3\)\(^{-}\) is key component of PCO2/carbonic acid reaction and major metabolic product
    • Other weak acids (ie negative charge) include Albumin, Phosphate
  2. Greater positive than negative strong ions creates alkalemic solution (ie lower [H\(^{+}\)])
-ve > +ve
eg Cl\(^-\) > Na\(^+\)

-ve < +ve
eg Na\(^+\) > Cl\(^-\)

Alkaline solution
Smaller change in [H\(^+\)] for change in SID
H\(^+\) has the highest charge density of any atom for it only has a proton and no neutrons.
Importance of Cl$^-$ < Na$^+$

- Compartments of the body are alkaline
- Less change in H$^+$ for changes in strong ions
- More stable protein structures
Physiological regulation of $\text{Na}^+$ and $\text{Cl}^-$
Evolutionary Aspects

• “A biological engineer assigned the task of designing a kidney would not follow the pattern laid down in the kidney of man”
  
  Robert F Pitt: Physiology of the Kidney and body fluids

• Kidney is “regulatory” not an “excretory” organ
Kidney is a curious organ

- Excretes 1 to 2 L/day, 10-15 Gm of urea nitrogen, few grams of NaCl, and a few other products

To do so ---

Filters 180 L of plasma, 23,900 meq Na\(^+\) and 19,742 of Cl\(^-\) and plus other valuable constituents and then reabsorbs most of them (99.6% of Na\(^+\))!!
Renal excretion of CaCl$_2$ load

Normal

Chronic Nephritis

Gamble 1945 (in Pitts 1968)
Clinical evidence of significance

• “there is little evidence that in the 50 years of normal saline usage, there has been significant morbidity from the use of this fluid” Yunos et al CC 2010

But how can you tell since this is the standard fluid!!
Cocharan Review 2013

[Intervention Review]

Perioperative buffered versus non-buffered fluid administration for surgery in adults

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Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

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David Story, MD
Lisa Ho, MClinPharm
Michael Bailey, PhD

Context  Administration of traditional chloride-liberal intravenous fluids may precipitate acute kidney injury (AKI).

Objective  To assess the association of a chloride-restrictive (vs chloride-liberal) intravenous fluid strategy with AKI in critically ill patients.

Design, Setting, and Patients  Prospective, open-label, sequential period pilot study of 760 patients admitted consecutively to the intensive care unit (ICU) during the control period (February 18 to August 17, 2008) compared with 773 patients admitted during the intervention period (February 18 to August 17, 2009) at a...
Yunos approach

- Single centre
- Prospective sequential open label observational study
- 6 month control (760), 6 months with phasing out chloride rich solutions, further 6 month observational period (773)
- (1/2 pt were from OR where Cl- was not controlled)
Yunos et al AKI (2 & 3)

Reduced Cl⁻

No. at risk

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<th>Year</th>
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<th>2009</th>
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<td>772</td>
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Log-rank $P = .001$
Hyperchloremia After Noncardiac Surgery Is Independently Associated with Increased Morbidity and Mortality: A Propensity-Matched Cohort Study

Stuart A. McCluskey, PhD, MD,* Keyvan Karkouti, MSc, MD,*† Duminda Wijeysundera, PhD, MD,* Leonid Minkovich, PhD, MD,* Gordon Tait, PhD,* and W. Scott Beattie, PhD, MD*
McCluskey et al 2013

- Retrospective data base study over 5 years
- Non-cardiac surgery
- Compared those with hyperchloremia (≥ 110 mmol/L) to those without on post op day 1 to 5
- Adjusts with propensity analysis
Is increased Cl\textsuperscript{-} just a marker?
If matched for propensity why is one group higher?
Pt in very positive fluid balance has more Cl\textsuperscript{-}
Is it concentration or total amount of Cl\textsuperscript{-}?
Large data base study with propensity scoring
110,325 excl - received Ca^{2+} solutions

**Major Abdo Sx**

467,131

**Plasmalyte**
during hospitalization
9905

Balanced fluid on procedure date
8285

Only balanced fluid
926

balanced fluid cohort
926

**0.9% saline during**
hospitalization
346,901

0.9% saline on procedure date
262904

Only 0.9% saline
30994

0.9% saline
2778

(3:1 propensity matched)
Post-operative infection rate ($P=0.006$)

3:1 Matched Cohort
- Plasma-Lyte (N=926)
- NaCl 0.9% (N=2778)

Plasma-Lyte
(N=51)

NaCl 0.9%
(N=229)
Only 2.7% received only the balanced solution and only 0.3% met study criteria. Thus there were likely unrecognized selection criteria. Social status appeared to be one

Shaw et al
Summary

• When giving salt solutions consider total body distribution
• High Chloride has potential toxic effects on tissues – eg kidney, bowel
• Clinical significance not known- will require very large trials (5000+)
  – No good randomized data
  – Supportive observational data
  – Supportive animal data
Equal concentrations of solutes in and out

\[ \text{Na}^+ , \text{K}^+ \]
Equal concentrations of solutes in and out

Na$^+$  K$^+$  Na$^+$

K$^+$
Osmolarity determines the amount of water in the body

- In the *extracellular* space the major particles are \([\text{Na}^+ \text{]} \& [\text{Cl}^+]\)
- In the *intracellular* space the major particles are \([\text{K}^+], [\text{Mg}^+], [\text{PO}_4^{2-}] \& \text{Protein}\)

*We don’t expand volume with water but with salt solutions and salt balance is key*