Controversy Regarding Use of Buffered Versus Non-buffered Fluids

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OUTLINE

• Background

• Describe the composition of crystalloid fluids

• Evaluate evidence from animal studies, observational studies and interventional studies

• Discuss adverse effects of normal saline including dilutional hyperchloremic acidosis

• Future directions for research
OBJECTIVES

• Describe the composition and clinical use of buffered versus non-buffered fluids.

• List the pros and cons of non-buffered crystalloid fluids leading to under- or over-resuscitation in clinical practice.

• Describe the adverse effects of dilutional hyperchloremic acidosis.
HISTORY OF CRYSTALLOID FLUIDS

1832
Latta’s Solution

1866
Murchison’s solution

1871
Marsden’s Solution

1883
Ringer’s Solution

1932
Hartmann’s Solution

1979
Plasma-lyte®
CRYSTALLOIDS

Buffered/Balanced/Chloride restrictive
Lactated Ringer's Plasma-lyte®

Non-buffered/Unbalanced/Chloride liberal
Sodium chloride 0.9%
ELECTROLYTE COMPOSITION OF CRYSTALLOIDS

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na⁺ (mmol/L)</th>
<th>Cl⁻ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Ca²⁺ (mmol/L)</th>
<th>Mg²⁺ (mmol/L)</th>
<th>Buffer¹ (mmol/L)</th>
<th>pH</th>
<th>[Na⁺]:[Cl⁻] ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>140</td>
<td>100</td>
<td>5</td>
<td>2.2</td>
<td>1</td>
<td>24</td>
<td>7.4</td>
<td>1.40:1</td>
</tr>
<tr>
<td>Sodium Chloride 0.9% (NS)</td>
<td>154</td>
<td>154</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1:1</td>
</tr>
<tr>
<td>Lactated Ringer’s (LR)</td>
<td>131</td>
<td>111</td>
<td>4</td>
<td>2.7</td>
<td>0</td>
<td>28</td>
<td>6.5</td>
<td>1.18:1</td>
</tr>
<tr>
<td>Plasma-lyte 148® (PL)</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>0</td>
<td>1.5</td>
<td>50</td>
<td>5.5</td>
<td>1.43:1</td>
</tr>
<tr>
<td>Plasma-lyte A® (PL)</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>50</td>
<td>7.4</td>
<td>1.43:1</td>
</tr>
<tr>
<td>Hartmann’s Solution²</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>29</td>
<td>6.5</td>
<td>1.18:1</td>
</tr>
</tbody>
</table>

¹Buffer = Plasma: bicarbonate, LR: lactate, PL: acetate & gluconate, Hartmann’s Solution: lactate
²Hartmann’s solution is not available in the United States
QUESTION #1

Which of the following statements is false?

1. Buffered fluids and balanced fluids are one in the same.
2. Buffered fluids refer to crystalloids and balanced fluids refer to colloids.
3. Buffered fluids contain additives, such as potassium.
4. Buffered solutions more closely resemble human plasma compared to sodium chloride 0.9%.
QUESTION #2

Which fluid most closely resembles human plasma?

1. Lactated Ringer’s
2. Sodium Chloride 0.9%
3. Sodium Chloride 3%
4. Plasma-lyte®
Crystalloid fluid therapy

Sumeet Reddy¹, Laurence Weinberg²³ and Paul Young¹⁴

Abstract
This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency medicine 2016. Other selected articles can be found online at http://www.biomedcentral.com/collections/annualupdate2016. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from http://www.springer.com/series/8901.

Here, we review the composition of different crystalloid fluids, potential pathophysiological responses following crystalloid fluid infusion, evidence from animal studies, observational studies, and interventional studies comparing crystalloid fluids, and suggest future directions for research on the comparative effectiveness of various crystalloid fluids.

Unbuffered/unbalanced crystalloids
The composition of 0.9 % saline was first mentioned by Jakob Hamburger in the 1890s. It is unknown how 0.9 %
## CRYSTALLOID FLUIDS: ANIMAL STUDIES

<table>
<thead>
<tr>
<th>Species</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zhou et al. 2014</strong></td>
<td><strong>60 Rats</strong></td>
<td>NS        PL</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>Traverso et al. 1986</strong></td>
<td><strong>116 Pigs</strong></td>
<td>NS        LR        PL</td>
<td>67% survival with LR</td>
</tr>
</tbody>
</table>

AKI = Acute Kidney Injury, LR = Lactated Ringer's, NS = Sodium chloride 0.9%, PL = Plasma-lyte®, RIFLE = Risk, Injury, Failure, Loss of function, End Stage Renal Disease

Buffered fluids preferred
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yunos et al. 2012</td>
<td>Prospective, sequential</td>
<td>Change in creatinine and incidence of AKI.</td>
<td>NS</td>
<td>p = 0.03, p &lt; 0.001</td>
<td>Buffered fluids had smaller increases in creatinine &amp; decreased risk of RIFLE defined AKI.</td>
</tr>
<tr>
<td>Raghunathan et al. 2014</td>
<td>Retrospective cohort study</td>
<td>In-hospital mortality (occurring after hospital day 2)</td>
<td>NS D5        LR</td>
<td>p = 0.001</td>
<td>Patient receiving buffered fluids had lower in-hospital mortality.</td>
</tr>
<tr>
<td>Shaw et al. 2012</td>
<td>Prospective, open-label sequential period pilot study</td>
<td>Major morbidity (≥ 1 major complication)</td>
<td>NS        PL-A        PL-148</td>
<td>p &lt; 0.001</td>
<td>Use of PL was associated with decreased postoperative morbidity.</td>
</tr>
</tbody>
</table>

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## CRYSTALLOID FLUIDS: INTERVENTIONAL STUDIES - SURGICAL

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<tr>
<th>Study Design</th>
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<th>Primary Outcome</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takil et al. 2002</td>
<td>Randomized, open</td>
<td>Effects on electrolytes &amp; acid-base balance</td>
<td>NS, LR</td>
<td>p &lt; 0.05</td>
<td>Increased chloride, sodium concentrations &amp; decreased pH when NS administered. No clinically significant effects.</td>
</tr>
<tr>
<td>Hadimioglu et al. 2008</td>
<td>double-blind, single center</td>
<td>Coagulation and acid-base balance</td>
<td>NS, LR</td>
<td>p &lt; 0.05</td>
<td>Decreased pH &amp; increased sodium concentration when NS administered.</td>
</tr>
<tr>
<td>Song et al. 2015</td>
<td>Randomized, open</td>
<td></td>
<td>NS, PL-148</td>
<td>&lt; 0.05</td>
<td>No difference in coagulation profiles.</td>
</tr>
</tbody>
</table>

AKI = Acute Kidney Injury, LR = Lactated Ringer’s, NS = Sodium chloride 0.9%, PL = Plasma-lyte®
## CRYSTALLOID FLUIDS: INTERVENTIONAL STUDIES - ACUTELY ILL

<table>
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<tr>
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<th>Population</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, double-crossover</td>
<td>Acutely ill - ICU</td>
<td>Proportion of patient with AKI</td>
<td>NS, PL</td>
<td>$p = 0.77$</td>
<td>Use of buffered crystalloids did not reduce the risk of AKI compared with NS.</td>
</tr>
<tr>
<td>Randomized, double-blind, double-crossover</td>
<td>2278</td>
<td></td>
<td>PL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, multi-center</td>
<td>Dehydrated</td>
<td>Change in base excess from 0 to 24 hours</td>
<td>NS, LR, PL</td>
<td>Relative Risk = 3.1, 95% CI = 0.5–5.6</td>
<td>Use of PL resulted in improved acid-base status at 24 hours compared to NS.</td>
</tr>
<tr>
<td>Randomized, double-blind</td>
<td>Trauma</td>
<td>Average change in base excess from 0 to 24 hours</td>
<td>PL</td>
<td>$p = 0.076$</td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, prospective</td>
<td>Diabetic ketoacidosis</td>
<td>Time to pH (7.32) normalization</td>
<td>NS, LR</td>
<td>Hazard Ratio = 1.863, $p = 0.076$</td>
<td>No difference in time to pH normalization between NS or LR.</td>
</tr>
<tr>
<td>Randomized, double-blind, prospective</td>
<td>Dehydrated</td>
<td>Change in pH (venous blood gas) at 1 and 2 hours post fluid administration</td>
<td>NS, LR, PL</td>
<td>$p = &lt; 0.001$ at 1 and 2 hours</td>
<td>Use of NS led to lower pH values compared to PL and LR.</td>
</tr>
</tbody>
</table>

AKI = Acute Kidney Injury, LR = Lactated Ringer’s, NS = Sodium chloride 0.9%, PL = Plasma-lyte®
REDDY ET AL. CONCLUSIONS

• NS and PL result in similar rates of renal complications

• Further large randomized control trials of buffered fluids are necessary to evaluate the efficacy and mortality effect before they can routinely be recommended over non-buffered fluids.
ADVERSE EFFECTS ASSOCIATED WITH SODIUM CHLORIDE 0.9%

OVER RESUSCITATION
- Tissue edema & hypoxigenation
- Compartment syndrome
- Renal dysfunction
- Dilutional hyperchloremic acidosis
- Risk for hypernatremia
- GI disturbances
- Pulmonary edema
- Hepatic congestion/injury
- Prolonged mechanical ventilation

UNDER RESUSCITATION
- Tissue hypoxigenation
- Risk for acute kidney injury
- Lactate & unmeasured anion acidosis
- GI disturbances

Patient Case

KT is a 45 year old male who had an emergency appendectomy. He has received 6 liters of 0.9% saline and his chloride has increased from 134 to 145. He has a history of heart failure that is well controlled.
QUESTION #3

Which of the following adverse events is KT most likely experiencing?

1. Increased serum pH
2. Dilutional hyperchloremic acidosis
3. Acute kidney injury
4. None of the above
DILUTIONAL HYPERCHLOREMIC ACIDOSIS IS IT CLINICALLY RELEVANT?

- No significant difference.
- No significant effect.
- No convincing evidence.
- Not clinically relevant.

Renal
Coagulation & Bleeding
GI Function
Mortality

## FINANCIAL IMPACT

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Volume</th>
<th>Manufacturer</th>
<th>Cost Per Bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Sodium Chloride</td>
<td>1000 mL</td>
<td>Baxter</td>
<td>$1.00</td>
</tr>
<tr>
<td>Lactated Ringer's</td>
<td>1000 mL</td>
<td>Baxter</td>
<td>$1.10</td>
</tr>
<tr>
<td>Plasma-lyte A®</td>
<td>1000 mL</td>
<td>Baxter</td>
<td>$2.02</td>
</tr>
</tbody>
</table>
FUTURE DIRECTIONS

• Further research comparing crystalloid, buffered and non-buffered, fluids are needed to evaluate the clinical significance of the physiological changes.

• Additional studies are needed to evaluate the effect dilutional hyperchloremic acidosis has on clinical outcomes.
SUMMARY

• For both acutely ill and surgical patients there is a trend toward better outcomes when buffered solutions are used.

• Dilutional hyperchloremic acidosis appears to be transient but may have adverse effects.

• The risk and benefits of using NS should be considered prior to perioperative or hypovolemic fluid resuscitation.
Controversy Regarding Use of Buffered Versus Non-Buffered Fluids

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