UAMS Journal Club Summary
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Outcomes of patients resuscitated with isotonic saline vs balanced crystalloids

Clinical Bottom Line

Balanced fluids (specifically lactated ringers) should be used instead of isotonic saline as the primary resuscitative fluid in the ED. Patients with closed head injuries and suspected hyperkalemia should be excluded pending further study.

PICO Question

P- Patients receiving intravenous fluids in the ED who were admitted to the hospital
I- Balanced crystalloids (lactated ringers or plasma-lyte)
C- Isotonic crystalloids (normal saline)
O- Incidence of MAKE30 (major adverse kidney events in 30 days, defined as mortality, new renal replacement therapy, or doubling of creatinine during stay)

Background

The debate in medicine regarding the utility and benefits of various resuscitative fluids has been present for decades. Many potential mechanisms for harm or benefits of various fluids—balanced crystalloids, isotonic crystalloids, and colloids such as albumin, starches, and gelatin—have been suggested. It is unclear whether there is truly a benefit from choosing one type of fluid crystalloid over another.

The discussion of balanced vs isotonic crystalloids is particularly relevant since crystalloids are, by far, the most commonly used fluids in the ED and inpatient settings, and as fluid resuscitation is increasingly emphasized in sepsis guidelines, they are a treatment consistently used in our sickest populations.

The decades long discussion of balanced crystalloids vs isotonic saline hinges primarily around the premise that since lactated ringers (and similarly composed fluids) has lower sodium and chloride contents (130 meq Na, 109 meq Cl for LR; 140 Na, 98 Cl for Plasma-Lyte) compared to isotonic saline (150 meq of both Na and Cl) they are less prone to causing hyperchloremic metabolic acidosis and renal injury.

Previous studies have either been retrospective or prospective (RCTs such as the 2015 SPLIT trial) with limited generalizability to the ED and sepsis populations.

Trial 1

Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED)

Validity Rating: low risk of bias

The Basics:

Single-center, pragmatic, unblinded, multiple-crossover trial comparing balanced crystalloids (LR or Plasma-Lyte A) vs Normal saline. 13,347 adults treated with IVF in the ED and admitted to the hospital outside of the ICU. IVF use was alternated monthly between NS and balanced crystalloids. During balanced crystalloids months, clinicians had the option of choosing between LR or Plasma-Lyte A. The primary outcome tracked in this study was hospital free days (days alive after discharge before day 28). The secondary outcome was Major Adverse Kidney Events at 30d (MAKE30), a composite of death from any cause, new renal replacement therapy or persistent renal dysfunction.

Inclusion Criteria:

Adults ≥18 years of age
Received at least 500cc isotonic crystalloids in ED
Patients with ESRD on HD were not eligible to meet renal outcomes but could meet MAKE30

Exclusion Criteria:

Patients receiving less than 500cc IVF in ED
Patients less than 18 years of age

Primary Outcomes:

hospital free days (days alive after discharge before day 28).

Secondary Outcomes:

Major Adverse Kidney Events at 30d (MAKE30), a composite of death from any cause, new renal replacement therapy or persistent renal dysfunction.

- Death
- New renal replacement therapy (RRT, PD, or HD)
- Final inpatient Cr value of 200% of baseline Cr

Follow Up:

Data was extracted from the electronic medical record. Study endpoint was at time of discharge or 30 days, whichever came first.

Results:

In non-critically ill adults admitted to the hospital (non-ICU) from the ED, there was no statistically significant difference in hospital free days OR (95% CI) of 0.98 (0.92-1.04). Among secondary outcomes, there was a statistically significant decrease in MAKE30 with balanced crystalloids compared to NS with OR (95% CI) of 0.82 (0.70-0.95); NNT of 111. This difference was primarily driven by doubling of Cr, not mortality or need for RRT.

Limitations/Bias:
A large limitation of study was it being a single center trial. Also, physicians and patients were not blinded to the type of IVF used. Also, physicians had the option of ordering off-protocol crystalloids and these were included in primary analyses which could affect results of study, though patients who received fluids following the study protocol were analyzed in a per-protocol analysis. Another limitation of the study is that most patients received Lactated Ringers (95.3%) when given balanced crystalloids, reducing the ability to draw conclusions about Plasma-Lyte-A. Finally, any IVF given after admission to the hospital and IVF used as medication carriers were not controlled for in the study.

Trial 2
SMART

Validity Rating: low risk of bias

The Basics:
This pragmatic, unblinded, cluster-randomized, multiple crossover trial was composed of 15,802 critically ill adults who were admitted to one of five ICUs and received crystalloids. Group assignments occurred at the level of the ED. On admission, each ICU used either BC or NS for a month and then alternated to the other at the start of each new month. The primary outcome tracked in this study is the same MAKE30 composite that measured in the SALT-ED trial. The population in this trial was notable for having 50% of its patients admitted from the ED and 15% having sepsis or septic shock.

Exclusion Criteria:
Age<18
Physicians were given the option to use NS in TBI patients regardless of randomized arm
Hyperkalemia was treated as a relative contraindication to balanced crystalloids

Inclusion Criteria:
Age>18
Admitted to ICU

Primary Outcomes:
MAKE30 (Major Adverse Kidney Event within 30 days)

- Death
- New renal replacement therapy (RRT, PD, or HD)
- Final inpatient Cr value of 200% of baseline Cr

Secondary Outcomes:
Death before ICU discharge
Death at 30 days
Death at 60 days
ICU-free days
Ventilator free days
Days alive
Days free of renal replacement therapy for 28 days after enrollment
New receipt of renal replacement therapy
Persistent renal dysfunction
Acute renal injury of stage 2 or higher
Highest Cr during stay
Change from baseline to the highest Cr level
Final Cr level before hospital discharge

Follow Up:
Study endpoint was at time of discharge or 30 days, whichever came first

Results:
Primary outcome:
Reduced MAKE30 (death before 30d, new RRT, or final Cr >200% baseline); BC better than NS.
OR 0.9 (95% CI 0.82-0.99, p=0.04)

Components:

In-hospital death before 30 days:	0.9 (0.80-1.01, p=0.06)
New RRT:	0.84 (0.68-1.02, p=0.08)
Final Cr > 200% of baseline:	0.96 (0.84-1.11, p=0.60)

Secondary outcomes:
No difference in ICU-free days, ventilator-free days, vasopressor-free days, or RRT-free days
No difference in rates of Stage 2 or higher AKI, no difference in highest Cr or change from baseline

Subgroup analyses:
Septic patients showed reduction of MAKE30 in BC vs NS
OR 0.8 (0.67-0.94, p=0.01)

Previous recipients of renal replacement therapy showed reduction of MAKE30 in BC vs NS
OR 0.61 (0.41-0.91, p=0.01)

Limitations/Bias:
Single center study
Unblinded- patients and physicians were aware of the arm of the study and fluids being given
Fluids used in IV piggybacks not controlled for

LR was used in 95% of the balanced crystalloids group, so inferences about Plasma-Lyte are difficult to make

Physicians allowed to go off-protocol for TBI and hyperkalemia

Relatively small amount of fluids received (1L median for both groups) compared to many institutions with 30cc/kg bolus policies for sepsis

Due to month-to-month crossing over of each ICU, patients who were admitted toward the end of each month would be switched to the other fluid at the change of the month

- This is somewhat mitigated by the fact this effected only 4-5% of patients in both groups and that both groups on average received roughly similar amounts of the "incorrect" fluid