Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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0.9% saline versus Plasma-Lyte as initial fluid in children with diabetic ketoacidosis (SPinK trial): a double-blind randomized controlled trial

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BASED ON ARTICLE

Vijai Williams, Muralidharan Jayashree, Karthi Nallasamy, Devi Dayal and Amit Rawat
Critical Care (2020) 24:1 https://doi.org/10.1186/s13054-019-2683-3

ABSTRACT

Background: Acute kidney injury (AKI) is an important complication encountered during the course of diabetic ketoacidosis (DKA). Plasma-Lyte with lower chloride concentration than saline has been shown to be associated with reduced incidence of AKI in adults with septic shock. No study has compared this in DKA.

Methods: This double-blind, parallel-arm, investigator-initiated, randomized controlled trial compared 0.9% saline with Plasma-Lyte-A as initial fluid in pediatric DKA. The study was done in a tertiary care, teaching, and referral hospital in India in children (> 1 month–12 years) with DKA as defined by ISPAD. Children with cerebral edema or known chronic kidney/liver disease or who had received pre-referral fluids and/or insulin were excluded. Sixty-six children were randomized to receive either Plasma-Lyte (n = 34) or 0.9% saline (n = 32).

Main outcomes: Primary outcome was incidence of new or progressive AKI, defined as a composite outcome of change in creatinine (defined by KDIGO), estimated creatinine clearance (defined by p-RIFLE), and NGAL levels. The secondary outcomes were resolution of AKI, time to resolution of DKA (pH > 7.3, bicarbonate> 15 mEq/L & normal sensorium), change in chloride, pH and bicarbonate levels, proportion of in-hospital all-cause mortality, need for renal replacement therapy (RRT), and length of ICU and hospital stay.

Results: Baseline characteristics were similar in both groups. The incidence of new or progressive AKI was similar in both [Plasma-Lyte 13 (38.2%) versus 0.9% saline 15 (46.9%); adjusted OR 1.22; 95% CI 0.43–3.43, p = 0.70]. The median (IQR) time to resolution of DKA in Plasma-Lyte-A and 0.9% saline were 14.5 (12 to 20) and 16 (8 to 20)hr respectively. Time to resolution of AKI was similar in both [Plasma-Lyte 22.1 versus 0.9% saline 18.8 h (adjusted HR 1.72; 95% CI 0.83–3.57; p = 0.14)]. Length of hospital stay was also similar in both [Plasma-Lyte 9 (8 to 12) versus 0.9% saline 10 (8.25 to 11) days; p = 0.39].

Conclusions: The incidence of new or progressive AKI and resolution of AKI were similar in both groups. Plasma-Lyte-A was similar to 0.9% Saline in time to resolution of DKA, need for RRT, mortality, and lengths of PICU and hospital stay.

SUMMARY

Background: Diabetic ketoacidosis (DKA) is becoming more prevalent in children and requires treatment with fluids and insulin. A higher complication rate is associated with paediatric DKA, and untreated dehydration increases the risk of acute kidney injury (AKI). Available crystalloids for resuscitation include 0.9% saline, Ringer's Lactate (RL), and Plasma-Lyte. Concerns have been raised regarding the use of 0.9% saline due to its non-physiological sodium and chloride concentrations. Studies suggest that hyperchloremia and AKI are related. Plasma-Lyte, which has lower chloride concentrations, has been linked to a lower incidence of AKI in septic shock, but it has not been compared in DKA. Identifying potential risk factors is essential for reducing the risk of AKI in children with DKA.

About the study: A prospective, double-blind, parallel assignment, investigator-initiated randomised controlled trial was conducted in the Paediatric Emergency and Intensive Care Units of a large tertiary, teaching, and referral hospital in India from August 2017 to December 2018. All children ages 1 month to 12 years old who presented to the paediatric emergency department with DKA as defined by the International Society for Paediatric and Adolescent Diabetes (ISPAD-2014) were included in the study. Exclusion criteria included children with symptomatic cerebral edoema (GCS 8 at presentation), known chronic kidney or liver disease, or who had received pre-referral fluids and/or insulin. The sample size was estimated using multivariate Cox Proportional Hazard Analysis and AKI as the composite outcome. It was estimated that a total of 60 individuals (approximately 30 in each group) met at least one composite AKI criterion, with 30 individuals meeting this threshold. We hypothesised, with an alpha error of 5% and a power of 80%, that the risks of AKI in Plasma-Lyte are 0.3 times lower than in saline, and that this ratio remains constant throughout the research. Using a web-based programme for 1:1 allocation, a person unaffiliated with the study generated the randomization scheme number.

Using unstratified block randomization with varying block sizes, patients were randomly assigned to one of two groups: 0.9% saline or Plasma-Lyte-A. The primary outcome was incidence of new onset or progressive AKI as defined by ONE of the following composite outcomes: change in serum creatinine or urine output according to KDIGO classification OR, change in GFR as calculated using the Schwartz formula OR, and change in urinary NGAL. The worst quartile of individual outcomes was used to define acute kidney injury (AKI). Rate of resolution of AKI, time to resolution of DKA (pH> 7.3, bicarbonate > 15mEq/L and normal sensorium), change in chloride, pH and bicarbonate levels (baseline, 24 h), proportion of in-hospital all-cause mortality, proportion of children requiring renal replacement therapy (RRT), length of ICU and hospital stay were the secondary outcomes.

During the study period, 75 eligible children with a total of 77 DKA episodes were admitted to the Paediatric Emergency Department. Of these, eleven were excluded; eight had received insulin and fluids, two presented with cerebral edoema, and one with mild DKA refused consent. The remaining 66 DKA episodes in 64 children were randomly assigned to receive either 0.9% saline or Plasma-Lyte-A.

The 0.9% saline group had a higher incidence of new-onset DKA (75%) than the PlasmaLyte-A group (50%) (p = 0.03), and the PlasmaLyte-A group had a higher median admission blood glucose (488 mg/dl vs 430 mg/dl; p = 0.003). In both groups, fluid infusion rate, urine output, and fluid balance were comparable. The incidence of new or progressive AKI was comparable in both groups [Plasma-Lyte 13 (38.2%) versus 0.9% saline 15 (46.9%); adjusted OR 1.22; 95% CI 0.43–3.43; p = 0.5].

The median (interquartile range) time to resolution of DKA was 14.5 (12 to 20) hours with Plasma-Lyte-A and 16 (8 to 20) hours with 0.9% saline. The AKI resolution time was comparable in both groups [Plasma-Lyte 22.1 versus 0.9% saline 18.8 h (adjusted HR 1.72; 95% CI 0.83–3.57; p = 0.14)]. In both groups, the median (IQR) chloride concentration at baseline was high: 112.5 (103.7 to 117.7) mEq/L for Plasma-Lyte-A and 111 (105.2 to 117.7) mEq/L for 0.9% saline. The difference was not statistically significant despite an increase in chloride levels during the initial hours of therapy. Length of hospitalisation was comparable in both groups [Plasma-Lyte 9 (8 to 12) days versus 0.9% saline 10 (8.25 to 11) days; p = 0.39]. The overall mortality rate of the study population was 3% (n = 2); there was no difference in mortality between groups (p = 0.94). At 72 hours of PICU stay, one child succumbed to fungal sepsis, shock, and MODS. The second child was admitted with AKI stage 2 and developed cerebral oedema at 6 hours, when the trial fluid was discontinued, and a restricted fluid regimen was initiated. Subgroup analysis assuming a normal GFR mean of 90 ml/min at baseline also failed to reveal a statistically significant difference in AKI between study groups. Two of the 64 discharged children were lost to follow-up 28 days after discharge.

Strengths: This is the first trial comparing Plasma-Lyte A to 0.9% saline as the initial fluid of choice in a group of patients with severe metabolic decompensation and a high risk of AKI. It was an investigator-initiated randomised controlled trial with double blinding. Patient enrollment and screening were conducted with rigour. No group contamination occurred. There was near-perfect compliance with the fluid protocol, stringent monitoring, and no missing values that required assumptions. This study is one of the first to include NGAL as part of the composite definition for AKI, as it is the first to include NGAL.

Limitations: Even though the primary outcome was a composite variable, it occurred infrequently in both groups, leaving the study underpowered. It is difficult to obtain a larger sample size in a single-center study, necessitating a multicentric investigation.

What is the way forward? The authors concluded that 0.9% saline and Plasma-Lyte-A were comparable in terms of incidence of new or progressive AKI, time to resolution of DKA, change in chloride levels, need for RRT, and ICU or hospital length of stay. Rather than fluid type or volume, the cause of hyperchloremia appears to be a typical physiological response to bicarbonate loss over chloride with increased renal perfusion. The dose-related effect on hyperchloremia, however, requires further study. A small increase in chloride levels in both arms did not result in an increase in AKI, according to this study. Given the limitations of statistical power, our finding that Plasma-Lyte-A reduces AKI is hypothesis-generating and warrants further investigation.