Suez Canal University Medical Journal Vol. 26 (1), 2023
Pages 21-30

Crystalloid Fluid Choice in Management of Pediatric Hyperglycemic Emergencies: Systematic Review and Meta-Analysis

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Abstract

Background: **Diabetic ketoacidosis in children and hyperglycemic hyperosmolar state are hyperglycemic emergencies that continue to account for the increased burden of hospitalizations.** ***Methods:*** **A systematic review included 426 patients to determine whether there are differences in biochemistries, clinical outcomes, and endocrine outcomes inpatients who are administered 0.9% saline as compared to buffered and non-buffered crystalloid fluids in the treatment of hyperglycemic emergencies.** ***Results:*** **Four studies evaluated serum bicarbonate levels after normal saline and other fluid types of use. We found no statistically significant difference between the 2 treatment groups (WMD, -0.04; 95% CI, -0.44-0.36). No statistically significant difference between the 2 treatment groups (WMD, 0.01; 95% CI, 0.00-0.02). Wefound no significant difference between the 2 groups for anion gap (WMD, 5.74; 95%CI, 4.67 to 6.81). Our results showed significant heterogeneity across the studies (I2 = 93%, P <.0001). Regarding serum chloride levels after other fluid typesand normal saline use. Our analysis found statistically significant difference betweenthe 2 treatment groups (WMD, 3.371; 95% CI, 3.26-3.4). We evaluated serum sodium levels after using normal saline compared to other fluid usage. No statisticallysignificant difference between two groups was noted (WMD, -0.1; 95% CI, -2.73- 2.53).** ***Conclusion:*** **For the treatment of hyperglycemic situations, normal saline performed statistically indistinguishable from other non-buffered and buffered crystalloid fluids in terms of bicarbonate level, pH, and anion gap. However, normal saline demonstrated significantly greater serum chloride levels in the therapy of hyperglycemic situations when compared to alternative fluids.**

Keywords: Crystalloid Fluid, Pediatric Hyperglycemic Emergencies**.**

Introduction

Hyperglycemic emergencies such hyperglycemic hyperosmolar state (HHS) and diabetic ketoacidosis (DKA) continue to be a major cause of hospitalizations. In the past, DKA and HHS were both first referred to as a single disorder before being identified as distinct illnesses. Although DKA and HHS mortality has decreased with the development of insulin, the risk still exists[(1)]. There is a lot of overlap in how DKA and HHS are treated. The treatment for both include giving insulin, giving crystalloid fluid to treat hypovolemia, closely monitoring electrolytes, and giving replacement fluid when re

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quired [2]. There are significant differences between the treatment of hyperglycemic situations in the pediatric population and the adult population. The risk for cerebral edema, a rare (1%) but potentially deadly consequence of DKA in children, should also be taken into account while treating DKA and HHS in children[3]. Selection of crystalloid fluid for acute resuscitation has recently attracted a lot of attention. 0.9% saline solution made of equal parts salt and chloride are included in a cheap intravenous fluid that is frequently utilized in acute settings. However, due to the high chloride content in saline and concomitant decrease in serum strong ion difference, infusion of 0.9% saline might result in a non-anion gap metabolic acidosis [4]. Saline 0.45% has an equal amount of sodium and chloride ions as 0.9% saline does. The bulk of a given volume of infused 0.45% saline is lost to the extravascular space due to the relative hypotonicity of 0.45% saline. While 0.45% saline is not frequently used as a resuscitation fluid in adults, multiple studies have looked at its usage in pediatric populations with DKA as a resuscitative and maintenance fluid[5]. Recent studies comparing 0.9% saline to balanced crystalloids (Ringer's Lactate and Plasma-Lyte) in the emergency room and intensive care unit found marginal differences in the "Major Adverse Kidney Events within 30 days" composite outcome, which included death, the need for dialysis, or persistent renal dysfunction in favor of balanced crystalloids; The clinical or biochemical outcomes for the DKA[6]. To find out whether patients who receive 0.9% saline for the treatment of hyperglycemic emergencies have different clinical outcomes, biochemistries, and endocrine-specific outcomes from those who receive other buffered and non-buffered crystalloid fluids, we performed a systematic review of the literature. This study aimed to improve the quality of the management and the out come of diabetic children.

Patients and Methods

A Systematic review and meta-analysis study was conducted using theprinciples of the Cochrane Collaboration guide for Systematic Reviews [7] and reported as preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [8] as detailed in figure (1).

Eligibility criteria

According to the PICOS (Population, Intervention, Comparison, Outcomes, Study Design) framework, all studies included in this review were chosen:

Population.

All pediatric diabetes mellitus children (0–18 years old) who are admitted to the hospital with a diagnosis of either DKA or HHS as described in the studies will be included in the study.

Intervention and Comparators

At any rate, buffered and various non-buffered crystalloid fluids injected will be contrasted with 0.9% saline. Solutions containing an anion buffer, such as Hartmann's solution, Plasma-Lyte, Ringer's lactate, and Ringer's acetate, are examples of buffered crystalloid fluids. 0.45% saline will be among the non-buffered crystalloid fluids available. Solutions containing dextrose will not be used because they are only used in the final phases of managing DKA and HHS, following normalization of serum glucose[9]. Three percent saline will not be used because it is only used to treat cerebral edema in hyperglycemic situations rather than as a resuscitative or maintenance fluid[10].

Outcome measures

In the included studies, we looked at several clinical, biochemical, and endocrine outcomes.

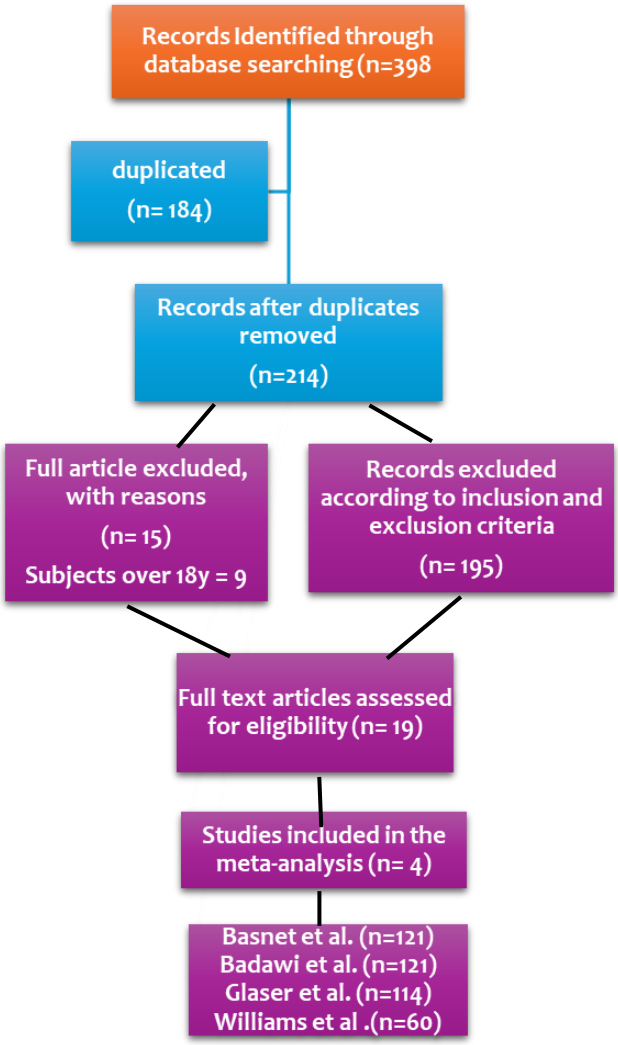

Figure 1: Flow chart

These particular results were picked because of their overall clinical importance and their unique relevance to the management of DKA/HHS. For instance, the time it takes for certain biochemical parameters, such as serum bicarbonate and anion gap, to return to normal may influence the course of treatment and the length of hospital stays for hyperglycemic situations. The comparison of buffered crystalloid fluids and various non-buffered crystalloid fluids with 0.9% saline was our main finding. Examining the differences between biochemical abnormalities (serum bicarbonate, pH, chloride, anion gap, sodium, glucose) and acute renal damage has been one of the secondary outcomes. Since crystalloid fluids may exacerbate the severe metabolic changes associated with DKA and cause an altered degree of consciousness to develop(e.g., due to changes in serum osmolality)[11], we included the Glasgow Coma Scale score as the operational definition for this outcome measure.

Study design of selected articles

There will also be interventional studies. We specifically included controlled trials that contrast 0.9% saline with other buffered or non-buffered crystalloid fluids.

Data sources

The Cochrane Library of Systematic Reviews, MEDLINE, and Embase databases were used to conduct the literature search. For pertinent papers, we searched the pri

mary study references as well as published narrative and systematic reviews. Additionally, we looked via ClinicalTrials.gov for any current or unpublished clinical trials through August 2022.

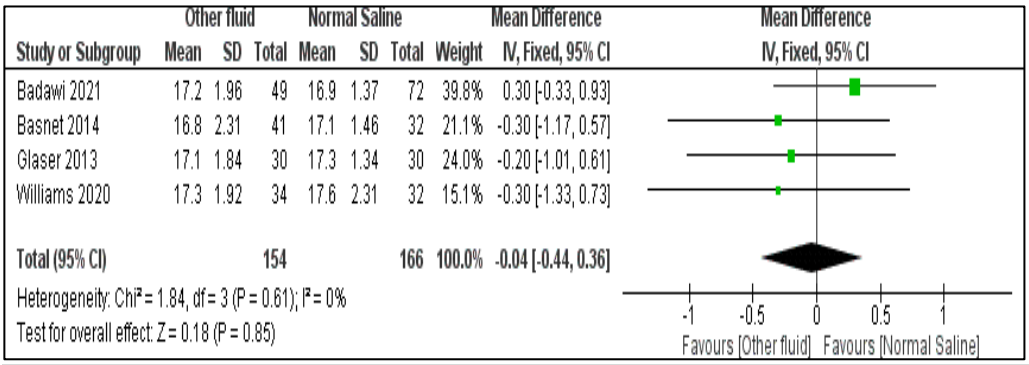

Figure (2): Forest plot comparing two treatment groups according to bicarbonate levels (*Heterogeneity is variability in the intervention effects being evaluated in the different studies*

Search strategy.

To address the pertinent facets of the study question, medical subject headings were utilized in the search approach. Hyperglycemic hyperosmolar non-ketotic coma (HONK), another name for HHS, is frequently used; for this reason, the search method will also contain this term. Additionally, a variety of liquids are considered buffered crystalloids. These include Plasma-Lyte, Hartmann's solution, Ringer's lactate, and Ringer's acetate. The plan will also incorporate all these keywords.

Study selection process

The list of studies produced by the search strategy was cleaned up of duplicate citations. All titles and abstracts were evaluated after de-duplication. The full-text reports were reviewed along with any possibly pertinent abstracts, and eligibility standards were used to choose the final number of studies to be included in the review.

Data extraction and management

Data extraction was done using a pre-tested computerized data collection form. The research's title, authors, year of publication, English language, country, journal, study design, sample size, and inclusion/exclusion criteria were all collected from the data along with other study-related information. demographics (including DKA and HHS definitions, pediatric, age, sex, admission diagnosis, comorbidities, and biochemical and physiological baseline measurements of serum bicarbonate, glucose, pH, serum anion gap, serum creatinine, and Glasgow Coma Scale); interventions and comparators (including types of crystalloid resuscitation fluid, fluid protocol details, including bolused and infused volumes, length of study period, co-interventions); and eligibility criteria. and various studies may report various "normal" levels for elements like serum glucose and bicarbonate; these definitions will be listed in our data abstraction form.

Data synthesis and analysis

We provided a concise description of each study that was incorporated into the review using tables and text. For all research

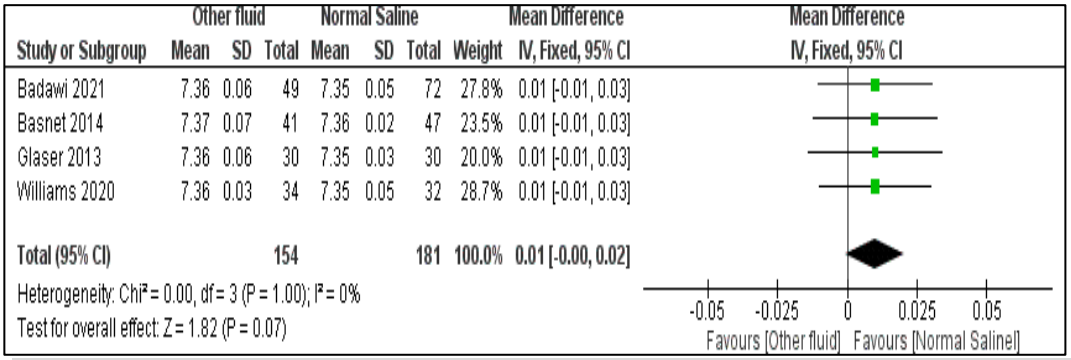

Figure (3): Forest plot comparing two treatment groups according to pH

outcomes, buffered and non-buffered crystalloids will be contrasted with 0.9% saline as the control fluid. Primary and secondary outcomes were combined and assessed independently for pediatric studies, randomized controlled trials, and observational studies. Given the level of expected heterogeneity across included papers, we will conduct meta-analyses using a random effects model [12]. To assess the suitability of data pooling and the execution of meta-analyses, we estimated statistical heterogeneity among the included studies and used this measure in addition to clinical heterogeneity. If there are enough trials included, statistical heterogeneity will be expressed using the I2 statistic and through visual inspection of a funnel plot [12]. For observational studies and randomized controlled trials, respectively, dichotomous variables will be aggregated according to odds ratios (OR) and relative risks (RR) with 95% confidence intervals. We anticipate that most of our secondary outcomes will be reported as continuous measures. In accordance with mean differences and 95% confidence intervals, continuous variables will be pooled.

Subgroup analyses

Because of the anticipated clinical heterogeneity among the included studies, we performed subgroup analyses to examine differences in the primary and secondary outcomes for DKA patients, for patients with prior chronic kidney disease according to the definitions used in the included studies, for patients who received an initial bolus of crystalloid for resuscitation, and for patients with severe DKA. Severe DKA was recognized in accordance with specified guidelines [13]. The differences between different buffered and non-buffer crystalloid fluids will also be compared, including 0.9% saline versus Ringer's lactate, 0.9% saline versus Ringer's acetate, 0.9% saline versus Hartmann's, and 0.9% saline vs. 0.45% saline.

Sensitivity analysis

Sensitivity analyses examined the robustness of the treatment effect on the primary outcome according to randomized controlled trials and observational studies that are considered low risk of bias across all domains.

Assessment of methodological quality

Risk of bias among the included studies will be assessed by using the Cochrane Collaboration tool for assessment of the risk of bias for RCTs[7]

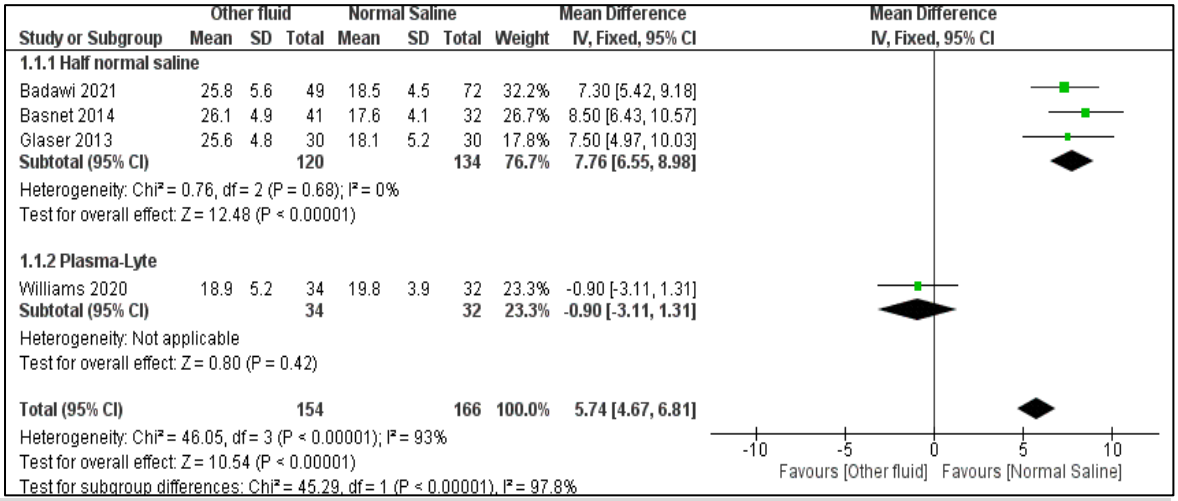

Figure 4: Forest plot comparing two treatment groups according to anion gap

Results

Four RCTs level after normal saline and other fluid types of use. We found no statistically significant difference between the 2 treatment groups (weighted mean difference, -0.04; 95% CI,-0.44-0.36). No significant heterogeneity was found among these studies (I^2= 0%; P = 0.61). as detailed in figure (2). Four studies had evaluated pH after other fluid types and normal saline use. Our analysis found no statistically significant difference between the 2 treatment groups (weighted mean difference, 0.01; 95% CI, 0.00-0.02). Nosignificant heterogeneity was found among these studies (I^2 = 0%; P = 1). asdetailed in figure (3). Moreover, four studies included in our analysis had evaluated anion gapafter using normal saline in comparison to other fluids. We found no significant difference between the 2 groups for anion gap (weighted mean difference, 5.74; 95% CI, 4.67 to 6.81). Our results showed significant heterogeneity across the studies (I2 = 93%, P < .0001). To investigate one possible reason for this heterogeneity, we performed subgroup analysis on populations based on type of other fluidused. Our analysis revealed that this outcome was similar across the studies, with 3 studies half normal saline, 1 study for plasma-Lyte as detailed in figure (4). Regarding serum chloride level after other fluid types and normal salineuse. Our analysis found statistically significant difference between the 2 treatment groups (weighted mean difference, 3.371; 95% CI, 3.26-3.4). as detailed in figure (5). According to our results, other buffered and non- buffered crystalloid group showed better results regarding serum chloride levels (P <0.001). We also evaluated serum sodium levels after using normal saline compared to other non-buffered and buffered crystalloid group. No statistically significant difference between two groups was noted (weighted mean difference, -0.1; 95% CI, -2.73-2.53). Thus, no significant difference was found between the 2 groups as detailed in figure (6) in terms of serum sodium levels. We also evaluated incidence of acute kidney injury after using normal saline compared to other buffered and non-buffered crystalloid group. No statistically significant difference between two groups was noted (weighted mean difference, -1.06; 95% CI, 0.55-2.5). Thus, no significant difference was found between the 2 groups as detailed in figure (7) in terms of acute kidney injury.

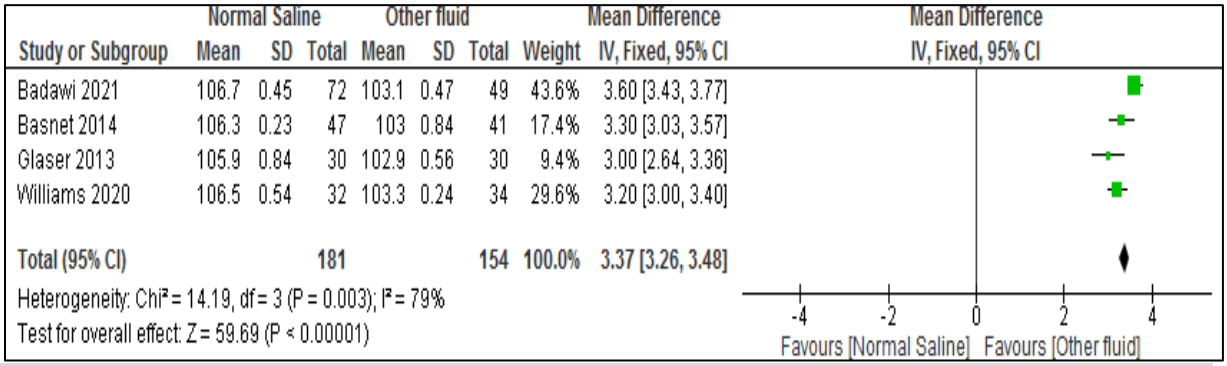

Figure (5): Forest plot comparing two treatment groups according to serum chloride levels

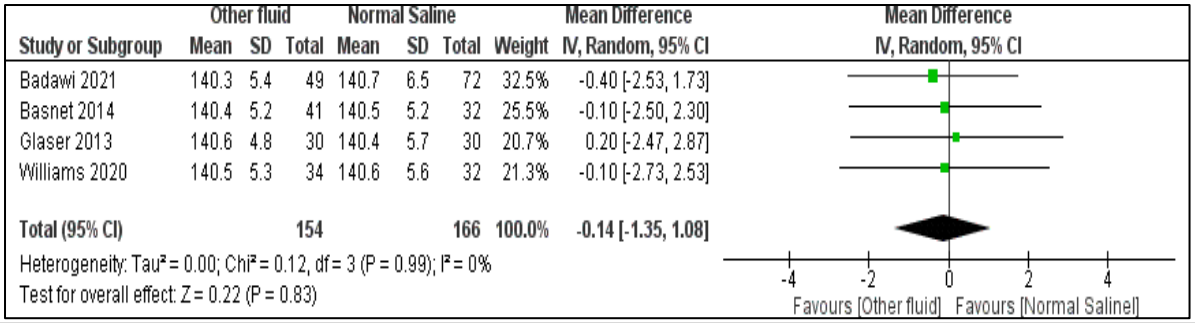

Figure (6): Forest plot comparing two treatment groups according to serum sodium levels (%)

Discussion

To prevent potential consequences, the care of hyperglycemic situations should attempt to return normal homeostasis and tissue perfusion while gradually lowering acidosis and blood glucose. According to pediatric and adult standards, isotonic normal saline is the most frequently utilized fluid for resuscitation and the start of rehydration during the management of hyperglycemia. However, there is growing understanding that the non-physiological character might result in renal vasoconstriction, which can cause acute renal damage and hyperchloremic metabolic acidosis. Normal saline does not adversely affect renal or overall mortality, according to other researchers. The question of whether other solutions with various Na contents should take the place of ordinary saline is still up for dispute[14]. When comparing 0.9% saline to various buffered and non-buffered crystalloid fluids for the treatment of hyperglycemic situations, we looked at clinical outcomes and biochemistry to see whether there were any differences. After using normal saline and various forms of fluids, the blood bicarbonate level in the two treatment groups did not differ statistically significantly in the current analysis (WMD, -0.04; 95% CI, -0.44-0.36). These studies did not exhibit any discernible heterogeneity (I2 = 0%; P = 0.61). Similar to this, giving normal saline as resuscitation to infants and kids who have diarrhea and septic shock might result in hyperchloremic acidosis[15]. According to a study done on adults in the emergency room, resuscitating a hyperglycemic emergency for 4 hours with normal saline instead of a balanced electrolyte solution can lead to hyperchloremia[16]. Because of the loss of bicarbonate and renal retention of sodium chloride, hyperglycemia during..

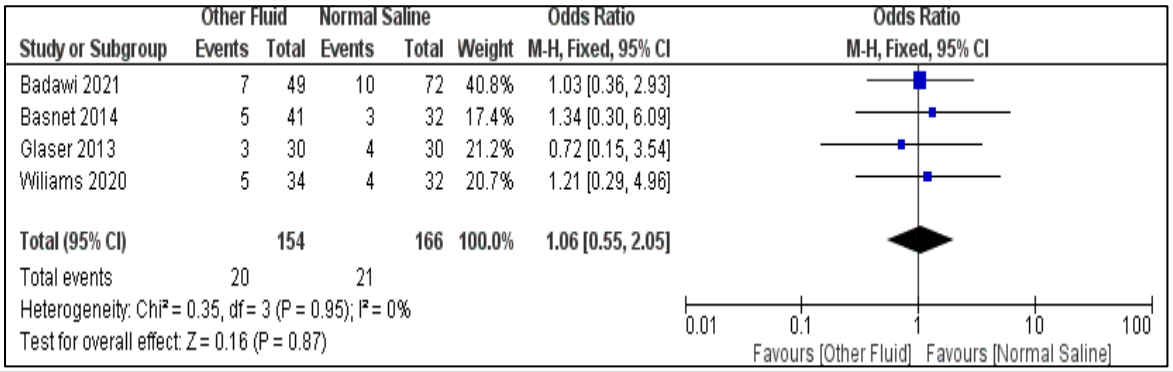

Figure 7: Forest plot comparing two treatment groups according to acute kidney injury (%)

the recovery phase can also result in hyperchloremia and normal gap acidosis Additionally, hyperchloremia and normal gap acidosis might lengthen the time that insulin is infused and make it necessary for a longer stay in the PICU to treat hyperglycemia. This may be explained by the notion that the hyperchloremic impact can mistakenly be regarded as continuing ketoacidosis, causing the management of DKA to be prolonged[17]. Our analysis demonstrates that the use of regular saline amplifies the acidifying impact. In the group receiving regular saline, there was a noticeable hyperchloremia. According to the Basnet et al study, both groups of patients had similar chloride levels upon admission (102.7 vs. 102.9mmol/L), but differences emerged later in the study when both groups had been receiving normal saline and before the second group's rehydration fluids were changed (106.3 vs. 103mmol/L)[18]. However, they noted that more patients in the normal saline group had already experienced a change in their serum chloride levels as a result of receiving anti-shock treatment with normal saline boluses (79.2% vs. 49%) [18]. Additionally, there was no discernible difference in chloride levels between patients in the two groups who did not receive any shock therapy (0.9% versus 0.45%) [18]. The highest chloride levels were discovered in previous research in various circumstances to occur during intervals of fast rehydration with significant volumes of normal saline. However, anti-shock therapy can sometimes save lives by increasing glomerular filtration and restoring perfusion[19]. The anion gap between the two groups (normal saline and other fluids) did not differ significantly (WMD, 5.74; 95% CI, 4.67 to 6.81). Our findings revealed high study-to-study heterogeneity (I2 = 93%, P .0001). We conducted subgroup analysis on populations

based on the type of other fluid utilized in order to look at one potential cause for this heterogeneity. Our research showed that this result was consistent across all the investigations, with three studies using half normal saline and one using plasma-Lyte. Since there were no discernible discrepancies between our results and those of that study, blood sodium levels over the course of managing hyperglycemia between the analysis groups. Serum sodium levels were examined between the use of regular saline and different fluids. There was no discernible difference between the two

groups statistically (WMD, -0.1; 95% CI, -2.73-2.53). Consequently, there was no discernible difference between the two groups. This is also consistent with the findings of Rother et al., who discovered that rehydrating with 75 mmol/L of sodium did

not cause a drop in the serum Na level[20]. According to our findings, there was no discernible difference between kidney injury and treatment with various crystalloids had no discernible impact on acute renal injury. Williams et al.'s work, in which this is also presented, showed no discernible difference between plasmalyte and saline fluids. Regarding the progression of glycemia, neither the initial glucose level nor the rate at which it fell significantly differed between the two study groups.

Conclusion

For the treatment of hyperglycemic situations, normal saline performed statistically indistinguishable from other non-buffered and buffered crystalloid fluids in terms of bicarbonate level, pH, and anion gap. However, normal saline demonstrated significantly greater serum chloride levels in the therapy of hyperglycemic situations when compared to alternative fluids.

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