Summer 8-11-2012

Plasma-Lyte vs. Normal Saline: Preventing Hyperchloremic Acidosis in Fluid Resuscitation for Diabetic Ketoacidosis.

Michele L. Stowe

Plasma-Lyte vs. Normal Saline: Preventing Hyperchloremic Acidosis in Fluid Resuscitation for Diabetic Ketoacidosis.

Abstract

BACKGROUND: Patients presenting with diabetic ketoacidosis (DKA) are hypovolemic, hyperglycemic, and acidotic. First line therapy is administration of resuscitation crystalloid fluids to increase systemic pressure for maintenance of tissue perfusion. Volume repletion can be measured by monitoring several physiological indicators including mean arterial pressure (MAP) and urine output (UO), where an increase of both indicate an improvement in volume status. The crystalloid fluid recommended by the American Diabetes Association (ADA) is normal saline (NS) because it has a track record of being a safe option. However, administration of NS can induce hyperchloremic metabolic acidosis (HMA) in many patients receiving it for rapid and large volume fluid replacement in a spectrum of circumstances and in most who receive it for DKA. An alternate crystalloid, Plasma-Lyte, is a balanced electrolyte solution (BES) with composition similarities to plasma, therefore it has less potential to cause biochemical changes in electrolytes, such as hyperchloremic acidosis. In this study evidence for use of a Plasma-Lyte (PL) versus NS was evaluated to determine if Plasma-Lyte is a better option for fluid resuscitation of DKA.

METHODS: A thorough search was conducted in three separate databases, Medscape, CINAHL, and Web of Science. Search terms included: *diabetic ketoacidosis, Plasma-Lyte, normal saline, hyperchloremic acidosis, and fluid resuscitation*. Eligibility criteria were limited to adult DKA patients receiving NS or PL fluid therapy. Data quality was assessed using the GRADE system.

RESULTS: Two studies were determined eligible. Results were significant for hyperchloremia in groups receiving NS in both studies. In one study, Chua et al showed significant increases ($p = < 0.01$) in bicarbonate in the PL group at two intervals between 4 and 12 hours after fluid therapy initiation. Mahler et al found only a relative difference ($p < .02$) in bicarbonate between groups. Chua et al also found the mean arterial blood pressure at 2-4 hours and urine output at 4-6 to be higher in Plasma-Lyte therapy compared with normal saline.

CONCLUSION: DKA patients treated with Plasma-Lyte had lower serum chloride concentrations and higher serum bicarbonate concentrations compared with NS. Inference can also be made for some benefit in time of recovery with more rapidly improved MAP and UO in DKA with a PL versus NS.

KEYWORDS: Diabetic Ketoacidosis; PlasmaLyte; Balanced Electrolyte Solution; Normal Saline; Hyperchloremic Metabolic Acidosis; Fluid Resuscitation

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Mark Pedemonte, MD

NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

Plasma-Lyte vs. Normal Saline: Preventing Hyperchloremic Acidosis in Fluid Resuscitation for Diabetic Ketoacidosis.

Michele L. Stowe

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, 11August 2012

Faculty Advisor: Mark Pedemonte, MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

[Information redacted for privacy]

Abstract

BACKGROUND: Patients presenting with diabetic ketoacidosis (DKA) are hypovolemic, hyperglycemic, and acidotic. First line therapy is administration of resuscitation crystalloid fluids to increase systemic pressure for maintenance of tissue perfusion. Volume repletion can be measured by monitoring several physiological indicators including mean arterial pressure (MAP) and urine output (UO), where an increase of both indicate an improvement in volume status. The crystalloid fluid recommended by the American Diabetes Association (ADA) is normal saline (NS) because it has a track record of being a safe option. However, administration of NS can induce hyperchloremic metabolic acidosis (HMA) in many patients receiving it for rapid and large volume fluid replacement in a spectrum of circumstances and in most who receive it for DKA. An alternate crystalloid, Plasma-Lyte, is a balanced electrolyte solution (BES) with composition similarities to plasma, therefore it has less potential to cause biochemical changes in electrolytes, such as hyperchloremic acidosis. In this study evidence for use of a Plasma-Lyte (PL) versus NS was evaluated to determine if Plasma-Lyte is a better option for fluid resuscitation of DKA.

METHODS: A thorough search was conducted in three separate databases, Medscape, CINAHL, and Web of Science. Search terms included: *diabetic ketoacidosis, Plasma-Lyte, normal saline, hyperchloremic acidosis, and fluid resuscitation*. Eligibility criteria were limited to adult DKA patients receiving NS or PL fluid therapy. Data quality was assessed using the GRADE system.

RESULTS: Two studies were determined eligible. Results were significant for hyperchloremia in groups receiving NS in both studies. In one study, Chua et al[15] showed significant increases (p = < 0.01) in bicarbonate in the PL group at two intervals between 4 and 12 hours after fluid therapy initiation. Mahler et al[14] found only a relative difference (p < .02) in bicarbonate between groups. Chua et al[15] also found the mean arterial blood pressure at 2-4 hours and urine output at 4-6 to be higher in Plasma-Lyte therapy compared with normal saline.

CONCLUSION: DKA patients treated with Plasma-Lyte had lower serum chloride concentrations and higher serum bicarbonate concentrations compared with NS. Inference can also be made for some benefit in time of recovery with more rapidly improved MAP and UO in DKA with a PL versus NS.

KEYWORDS: Diabetic Ketoacidosis; PlasmaLyte; Balanced Electrolyte Solution; Normal Saline; Hyperchloremic Metabolic Acidosis; Fluid Resuscitation

Acknowledgements

[Information redacted for privacy]

Table of Contents

List of Tables

List of Abbreviations

ADA = American Diabetes Association
BES = Balanced Electrolyte Solution
CDC = Center for Disease Control
CE = Cerebral Edema
DKA = Diabetic Ketoacidosis
DM = Diabetes Mellitus
HMA = Hyperchloremic Metabolic Acidosis
ICU = Intensive Care Unit
IV = Intravenous
MAP = Mean Arterial Pressure
NS = Normal Saline
PL = PlasmaLyte
SBE = Standard Base Excess
SIG = Strong Anion Gap
UO = Urine Output

Plasma-Lyte vs. Normal Saline: Preventing Hyperchloremic Acidosis in Fluid Resuscitation for Diabetic Ketoacidosis.

BACKGROUND

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM) and its mortality rate approaches 100% without treatment.[1] DKA comprises 8 -29% of all hospital admitted diabetes cases[2] and 30% of these are patients with first time diagnosis of diabetes.[3] The mortality rate with DKA is now < 5%, according to United States Center for Disease Control (CDC) statistics. The acuity and gravity of DKA make it a commonly treated condition in emergency medicine and intensive care units, with an increasing occurrence as we see a higher incidence of DM in the population.[2]

Diabetic ketoacidosis is defined as a triad of hyperglycemia, ketosis, and acidosis. Hyperglycemic complications in DKA are predominantly due to a significant increase in hepatic gluconeogenesis causing glycosuria, osmotic diuresis, and dehydration. Body fluid loss due to osmotic diuresis and hyperosmolar intracellular dehydration can be 5-10%, resulting in a reduction in systemic pressure and thus tissue perfusion.[4,5]

Fluid replacement therapy with a crystalloid solution is first line in the treatment of DKA with the goal of increasing volume and improving tissue perfusion. Also, it can reduce serum glucose up to 25% on its own.[6] Insulin is a secondary treatment which should be withheld in hypotensive and/or hypokalemic patients.[3] Current guidelines recommend NS as the replacement fluid of choice. However, evidence shows rapid, high volume fluid volume replacement with NS can lead to hyperchloremic metabolic acidosis (HMA), with increased serum levels of chloride and decreased bicarbonate. Significant increases in chloride levels and HMA have been shown in multiple uses of NS for fluid replacement, including intraabdominal

gynecological surgery,[7] intra-operative fluid therapy,[8] kidney replacement post-operative fluid therapy.[9]

Alternative crystalloids, known as balanced electrolyte solutions (BES), are available. One such BES is the product Plasma-Lyte (PL). Plasma-Lyte products contain organic acid buffers like acetate and gluconate, and are engineered to be physiologically similar to plasma.[10] They are more similar to body fluid composition than NS, making them less likely to lead to hyperchloremic metabolic acidosis (HMA) as with NS.[10] In composition, NS has a higher chloride content than PL (154 mEq/L and 98 mEq/L respectively). The evidence for safety in use of PL is lacking and NS has had a long term safety record as fluid therapy. Also, the clinical significance of HMA is debatable with respect to changing patient outcomes, and may differ with the volume of fluid given over a period of time and across the spectrum of conditions requiring fluid resuscitation. A study of ED patients treated with NS vs. PL for dehydration had no difference in outcome of acid-base status, but they did show a significant occurrence of lower pH values compared with PL and lactated Ringers.[11] In the case of DKA, a secondary acidotic state, such as with NS induced HMA, may be impede an optimal recovery rate. Patients presenting with DKA have an inherent initial chloremic acidosis with a decrease in bicarbonate followed by proximal tubule reabsorption of chloride.[12] A solution which does not cause further derangements in physiological status may be the better option for treatment, and may be an even more important consideration with special populations of DKA patients, such as decreased renal function, pediatrics, and patients with various metabolic disorders. The purpose of this study is to evaluate the quality of the current evidence for the use of a PL versus NS to prevent hyperchloremic metabolic acidosis in the setting of DKA. Should fluid recommendations favor the use of Plasma-Lyte over normal saline?

METHODS

A thorough search was conducted in three separate databases including Medscape, CINAHL, and Web of Science. Search terms included, but were not limited to: *diabetic ketoacidosis, Plasma-Lyte, balanced electrolyte solution, normal saline, hyperchloremic acidosis, and fluid resuscitation*. Bibliographies were searched for additional literature. Studies evaluating normal saline versus Plasma-Lyte for fluid resuscitation therapy in DKA patients were selected.

Eligibility criteria were limited to human adults and English language. Each study was assessed for bias, and screened for strengths and weaknesses. Quality of the data from the two eligible studies included in this systematic review was assessed using the GRADE system (Table 1).

RESULTS

A search for the terms *Plasma-Lyte and diabetic ketoacidosis* produced 2 results in Medscape , 1 in CINAHL, and 2 in Web of Science. Use of alternate search word combinations provided results of 0-1, all of which were duplicates of the former. After duplicates between databases were eliminated and each was reviewed for content and two eligible results were obtained which included DKA as the diagnosis for which the fluid replacement therapies in question, Plasma-Lyte and normal saline, were compared.

The earlier of the two studies, Mahler et al,[13] was a double blinded, randomized controlled trial with intent to treat. The researchers compared the outcome of chloride and bicarbonate levels with separate use of the fluid replacement therapies Plasma-Lyte A and NS in a convenience sample of patients aged 18-65 with moderate to severe DKA admitted to the

Lousiana State University Health Sciences Center-Shreveport Emergency Department over 24 months (2006-2008). Eligibility criteria were described and excluded patients presenting with hyperosmolar hyperglycemic non-ketotic syndrome, hyperglycemia without signs of DKA, and those having received intervention of greater than 500 mL boluses of crystalloid solution or insulin boluses prior to study enrollment. Also excluded were patients presenting with possible myocardial infarction, sepsis, respiratory failure, cerebral edema, or patients receiving less than 4 hours of fluid therapy. All participants were recruited from a single location and the subject sampling included 23 in the NS group and 22 in the PL group. Patient demographics were balanced in all except for race, where 83% in the NS group and 68% in the PL group were African American. Blinding was described as a block randomization method of 8 consecutive participants, and all subjects and providers were blinded to the randomization schedule and treatment.[13]

A standardized resuscitation protocol was allotted in a 1:1 manner for 0.9% NS or Plasma-Lyte (Plasma-Lyte A 7.4; Baxter International, Deerfield, IL). Patient water deficits and maintenance fluid requirements were calculated before receiving fluid therapy. Blinded study fluids were provided by institution's pharmacy. A regular insulin drip was administered to all patients without boluses and use of sodium bicarbonate was avoided. Resuscitation therapy was completed in either the emergency department or the medical intensive care unit, and was considered complete at a target anion gap at 12 mEq/L or below.[13]

Data collection included baseline chemistry panels of serum sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and a calculated anion gap. Chemistry panels were repeated every 2 hours throughout the study. Statistical analysis used SPSS 11.0

(Chicago, IL) for Windows. Serum chloride and bicarbonate data comparisons for NS and PL groups were calculated using student *t* tests.[13]

Results showed a significant increase in serum chloride ($p = \leq 0.001$) and a relative decrease in bicarbonate concentrations ($p = 0.02$) in the NS group as shown in Table 2. The difference in serum chloride was the most significant and outside of normal limits, or hyperchloremic, at 111 mEq/L, (serum chloride reference range for adults = 96-106 mEq/L) in the NS group. The PL group serum chloride was within normal limits at 105 mEq/L. Also interesting was the comparison of the baseline concentrations, where the chloride baseline was lower for the NS group.[13]

In the second and more recent study, Chua et al,[14] used biochemical and hemodynamic parameters to assess the efficacy and safety of NS compared to Plasma-Lyte 148 (PL) in fluid resuscitation of DKA. The study design was a multicenter retrospective study of adult patients admitted to intensive care units (ICUs) in three separate tertiary hospital locations in Australia. Included were patients 16 years and older who received only or predominantly NS or PL for the first 12 hours of fluid replacement. A set baseline of 0-2 hours from ED admission was meant to offset pre-admission fluid administration confounders. Excluded were: 1) patients who had received more than 500 mL of a non-study crystalloid within 12 hours from baseline, 2) patients who had received more than 50 mEq of sodium bicarbonate and/or potassium acetate within 12 hours from baseline, and 3) patients with end stage or advanced chronic kidney disease with an estimated glomerular filtration rate less than 30 mL/min/1.73 at baseline.[14]

DKA resolution, the primary outcome, was measured by the following indicators: serum pH, bicarbonate levels, standard base excess (SBE), and strong ion gap (SIG). The secondary outcomes included: 1) cumulative insulin requirement and glycemic control measured by

cumulative dose all given insulin, intravenous (IV) and subcutaneous, and duration of IV insulin administered over 24 hours, and 12 hours post-therapy glucose level reduction, 2) potassium balance over 24 hours, 3) mean arterial blood pressure (MAP) and heart rate over 24 hours, 4) cumulative urine output and serum creatinine decline over 24 hours, and 5) time spent in the intensive care unit for treatment. There were 9 subjects in the PL group and 14 in the NS group.[14]

Serum biochemistry and clinical indicator values were taken from timed intervals of therapy from baseline 2-4 hours, 4-6 hours, 6-12 hours, and 20-28 hours. Serum bicarbonate levels were calculated using empiric formulas. Statistical analysis comparing NS to PL groups compared serum biochemistries and clinical indicators with respect to baseline values. A *P* value < .05 was used as a measure of significance. Baseline characteristics were compared with obtained median values (interquartile ranges, IQRs) using Kruskal-Wallis for continuous variables and Fisher exact test for categorical variables. Baseline differences in serum biochemistries were significant only for apparent strong ion difference (appSID) and SIG (p = < .05), which was higher in the NS group (SIG is calculated using appSID and effective SID). The variables of age, sex, DKA precipitant, illness severity, and remaining serum biochemistries were not significantly different between groups at baseline. Resolution of DKA was determined by SIG reduction over time.[14]

Results showed that the change in serum bicarbonate levels was significant at the 4-6 hour interval (p = < .01) and at the 6-12 hour interval (p = < .05) with a more rapid increase in levels for the PL group. The change in chloride levels was significant between groups at all time intervals (p = < .01), with a steady lower chloride level in the PL group and an increasing rise in level in the NS group over time. Also of significance were the secondary outcomes of mean

arterial blood pressure (MAP) at the 2-4 hour interval ($p = < .05$), and urine output (UO) at the 4-6 hour interval. Both were higher for the PL group.[14]

DISCUSSION

Evaluations comparing the use NS vs. PL in both Mahler et al[13] and Chua et al[14] illustrate evidence favoring the use of PL for preventing HMA in DKA patients. Plasma-Lyte use has been shown to prevent hyperchloremic acidosis in fluid replacement therapy in DKA, as compared to normal saline, which induces it. The clinical significance of hyperchloremia has yet to be determined, but the evidence from Chua et al[14] shows PL may improve recovery of DKA with findings of a significantly more rapid increase in MAP and UO with PL fluid therapy, indicators of volume repletion. It is also important to note there were no adverse effects from the use of PL in this study.

Increasing systemic volume is priority and the induced hyperchloremic acidosis in use of NS is transient and has not been considered clinically significant except with cases of acute renal failure and extreme oliguria.[3] In that regard, diabetes is often associated with end organ damage, especially with respect to kidney function. As many as 30% of DKA cases, are associated with first time diagnosis[15], and extent of end organ damage may be unknown in these patients, and will vary by population. Considerations for beneficial application may be more important in special populations, for example, populations that are diagnosed in later stages of disease, including older populations, and African American men. Data from the CDC shows African American men account for more hospital admissions for DKA and have a higher rate of DM associated end stage renal disease.

Although not included in these studies, the special population of diabetic pediatric patients may benefit greatly from use of PL over NS. Currently guidelines recommend strict protocols[16] in fluid resuscitation in pediatric DKA because of the risk of cerebral edema (CE) which has high a morbidity and mortality rate. Sodium bicarbonate has been used as therapy for treating metabolic acidosis, however it has been shown to be ineffective therapy in pediatric DKA[17] and has been associated with increased risk of CE in this population, and should be avoided.[18]

The Mahler et al[13] study had a small population, used a single location for recruitment, and had a potential for bias by use of a convenience population, thus limiting the precision and application of its findings. The small population also may have contributed to the slight differences in baseline chloride between groups with a lower baseline chloride in the NS group. However, the fact that the NS group was lower at baseline than the PL group further supports the study's outcomes of hyperchloremia prevention with PL.[13]

Also, as addressed and described by Mahler et al,[13] this study may not be generally applicable because of DKA diagnostic and monitoring protocol differences from that of the ADA. The ADA protocol uses blood gases and pH values to determine mild, moderate, and severe DKA. Blood gases and pH were not utilized in this study for defining DKA in subjects per institutional practice feasibility, thus limiting generalization to institutions using strict ADA protocol.[13]

The Chua et al[14] study had similar limitations with population size. The small sample size may have been responsible for creating baseline characteristic imbalances, specifically with appSID and SIG for this study, which was the major contribution to downgrading the study quality. As explained by the authors, the acid-base effects were rapidly apparent and strongly

significant despite this. Conclusions of clinical data for the secondary outcomes of time in ICU, discharge from hospital, and survival are also not feasible with a small sample size. Some of the data for recovery time at the later time intervals may also be imprecise because of the administration of mixed fluids in some patients beyond the 12th hour of resuscitation.[14]

Limitations of this systematic review include those of the studies themselves being of moderate and low quality for reasons described above (Table 1), and also some of the differences between each study. Though both studies used Plasma-Lyte as a comparison to NS, the formulations of the PL fluids had a variation in the solution pH, but were otherwise equal in formulation. Plasma-Lyte 148 has a pH of 5.5 (4.0-8.0) and the pH of Plama-Lyte A is 7.4 (6.5 to 8.0). The significance of this cannot be determined, but may alter the precision of the results.

For the purpose of this review there were no flaws in study design, no significant limitations, and no inconsistencies found in either study. Though the baseline characteristics were different between groups in Chua et al,[14] the specific differences were not the parameters of interest for this review. Imprecision was the greatest limitation for each, and this can mostly be attributed to population size.

Improvement and maintenance of tissue perfusion by increasing systemic volume is the goal of fluid replacement. A more rapid improvement without side effects would appear to be the better option. Overall, the effects were strong in both studies, suggesting use of Plasma-Lyte is a safe and better option for biochemical stability in DKA when compared to the currently recommended use of NS.

CONCLUSION

DKA patients treated with Plasma-Lyte had lower serum chloride concentrations and higher serum bicarbonate concentrations compared with NS. Inference can also be made for some benefit in time of recovery with more rapidly improved MAP and UO in DKA with PL versus NS. Overall, Plasma-Lyte had better biochemical profiles for chloride and bicarbonate. The clinical significance of this will require further investigation, but these studies support the value of such inquiries.

References

1. Charfen MA, and Fernandez-Frackelton M. Diabetic ketoacidosis. *Emergency Medicine Clinics of North America* 2005; 23(3): 609-628.

2. Kitabchi AE, and Nyenwe EA(2006). Hyperglycemic crises in diabetes mellitus: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinology & Metabolism Clinics of North America* 2006; 35*(*4): 725-751.

3. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. (2004). Hyperglycemic crises in diabetes. *Diabetes Care* 2004; 27(Suppl 1): S94-102.

4. Atchley DW, Loeb RF, Richards DW, Benedict EM, and Driscoll ME. (1933). On Diabetic Acidosis: A detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy. *Journal of Clinical Investigation* 1933; 12(2): 297-326.

5. Nabarro JD, Spencer AG, and Stowers JM. Metabolic studies in severe diabetic ketosis. *Quarterly Journal of Medicine* 1952*; 21*(82): 225-248.

6. West ML, Marsden PA, Singer GG, et al. Quantitative analysis of glucose loss during acute therapy for hyperglycemic hyperosmolar syndrome. *Diabetes Care* 1986; 9(5):465-471.

7. Scheingraber, S., Rehm, M., Sehmisch, C., & Finsterer, U. (1999). Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology, 90*(5), 1265-1270.

8. McFarlane, C., & Lee, A. (1994). A comparison of plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia, 49*(9), 779-781.

9. Hadimioglu, N., Saadawy, I., Saglam, T., Ertug, Z., & Dinckan, A. (2008). The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. *Anesthesia & Analgesia, 107*(1), 264-269.

10. Rizoli, S. (2011). PlasmaLyte. *Journal of Trauma-Injury Infection & Critical Care, 70*(5 Suppl), S17-8.

11. Hasman, H., Cinar, O., Uzun, A., Cevik, E., Jay, L., & Comert, B. (2012). A randomized clinical trial comparing the effect of rapidly infused crystalloids on acid-base status in dehydrated patients in the emergency department. *International Journal of Medical Sciences, 9*(1), 59-64.

12. Adrogue, H. J., Eknoyan, G., & Suki, W. K. (1984). Diabetic ketoacidosis: Role of the kidney in the acid-base homeostasis re-evaluated. *Kidney International, 25*(4), 591-598.

13. Mahler SA, Conrad SA, Wang H, and Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *American Journal of Emergency* 2011; 29(6): 670-674.

14. Chua HR, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, et al. Plasma-lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *Journal of Critical Care* 2012; 27(2): 138-145.

15. Fishbein H, Palumbo PJ. Acute metabolic complications in diabetes. Bethesda (MD):National Institutes of Health; 1995 #NIH 95-1468.

16. Green SM, Rothrock SG, Ho JD, Gallant RD, Borger R, Thomas TL, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Annals of Emergency Medicine* 1998; 31(1): 41-48.

17. Fogel N, Zimmerman D. Management of diabetic ketoacidosis in the emergency department. *Diabetic Ketoacidosis in the Emergency Department* 2009; 10(4):246-251.

18. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The pediatric emergency medicine collaborative research committee of the American Academy of Pediatrics. *New England Journal of Medicine* 2001; 344(4): 264-269.

19. Handy JM, and Soni N. Physiological effects of hyperchloraemia and acidosis. *British Journal of Anaesthesia* 2008; 101(2): 141-150.

Table 1. Characteristics of Reviewed Studies

Table 1. Characteristics of Reviewed Studies

Use of PlasmaLyte versus Normal Saline for Preventing Hyperchloremic Acidosos in Fluid Resuscitation of DKA.

Quality Assessment

Study	# Patients		Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality (GRADE)	Importance of Outcomes	Notes
	NS	PL								
Mahler et al	23	26	RCT	no limitations	none	None	no serious (-1)	moderate	moderate	End measurements taken post-resuscitation
Chua et al	14	9	Retrospective, non-randomized, unblinded	no limitations	none	None	no serious (-1)	very low	moderate	Measurements taken at timed intervals over 28 hours (2-4 h, 4-6 h, 6-12 h, 20-28 h)

Table 2. Summary of Change in Chloride and Bicarbonate Levels

Table 2.	Summary of Change in Chloride and Bicarbonate Levels						
Δ Chloride	(mEq/L)	NS	IQR	BES	IQR	95% CI	*P* value
Mahler et al	Post-Resuscitation	16.5	--	8	--	14-19	≤ .001
Chua et al	2-4 h	10	7 to 12	3	2 to 5		<.01
	4-6 h	13	7 to 23	3	-1 to 7		<.01
	6-12 h	18	10 to 29	5	1 to 11		<.01
	20-28 h	21	11 to 28	5	-2 to 11		<.01
Δ Bicarbonate	(mEq/L)						
Mahler et al	Post-Resuscitation	7	--	9	--	5-8	0.023
Chua et al	2-4 h	-0.03	-1.2 to 0.4	1.7	-0.2 to 4.2		0.078
	4-6 h	1.7	-0.1 to 5.9	8.4	5.4 to 9.4		<.01
	6-12 h	6.2	3.7 to 10.1	12.8	11.2 to 15.2		<.05
	20-28 h	10	8.2 to 12.9	16.6	11.9 to 18.1		0.16

IQR = interquartile range
NS = normal saline
BES = Balanced Electrolyte Solution
95% CI = 95% Confidence Interval