A COMPARATIVE STUDY OF ACETATED ISOTONIC ELECTROLYTE SOLUTION, NORMAL SALINE SOLUTION, AND LACTATED RINGER'S SOLUTION IN THE INITIAL FLUID RESUSCITATION OF CHILDREN 1 MONTH TO 18 YEARS OLD WITH SEVERE DENGUE AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER

ALLEN KILBY M. PALON, MD
MARY JOY S. TORRES, MD, ERVINA J. ASTIH, MD
MELLINOR A. ASPURIA-ANG, MD

ABSTRACT

BACKGROUND: At PCMC, acetated isotonic electrolyte solution is used in the initial resuscitation in severe dengue patients. However, no local study has comparedacetated isotonic electrolyte solution against normal saline and lactated Ringer's solutions.

OBJECTIVE: This study aims to determine the comparative recovery time to achieve initial and sustained cardiovascular stability in severe dengue patients using acetated isotonic electrolyte solution, normal saline solution, and lactated Ringer's solution.

METHODOLOGY: This is a retrospective cohort study involving 166 severe dengue patients 1 month to 18 years old admitted at the PICU from 2014 to 2016. They were divided into 3 groups based on the initial fluid used: 58 in the AIES group, 58 in the NSS group, and 50 in the LRS group.

RESULTS: AIES group had the shortest time to achieve initial and sustained stability among patients without re-shock. Also, AIES group needed less fluid to establish stability and had less re-shock, less use of colloid and inotropes, less blood transfusion,and less need for mechanical ventilation and dialysis. NSS had the most fluid shift to AIES and/or colloid while LRS had the most colloid used. Hyperchloremic metabolic acidosis was mostly seen in the NSS group. The length of ICU stay was almost the same in all groups. There was zero mortality in AIES group as compared to 3 on NSS group and 2 in LRS group.

CONCLUSION AND RECOMMENDATION: Acetated isotonic electrolyte solution is more effectivethan normal saline and lactated Ringer's solutions in initial fluid resuscitation among severe dengue patients. It should be the fluid of choice in the initial resuscitation among severe dengue patients. It is recommended that a randomized control study with more patients be conducted.

KEYWORDS: dengue, acetated isotonic electrolyte solution, normal saline, lactated Ringer's, resuscitation

INTRODUCTION

Dengue continues to be a health problem in the Philippines. The first dengue epidemic in Manila dates back in 1954.[1] From then on, the number of dengue cases increases every year. According to the 2010 World Health Organization's (WHO) annual dengue data report, the Philippines had the highest dengue cases (135,355 cases) and deaths (0.6%) in the Western Pacific Region.[2] But with the updates in the management of dengue in the region, the mortality rate has a decreasing trend.[2,3]

Local data from the Department of Health (DOH) showed a total of 101,401 suspected dengue cases nationwide from January to August 20, 2016. This number is 16% higher compared to 2015. Most of the cases were from the following regions: Region VI (11.1%), Region IV-A (10.7 %), Region VII (9.8%), Region X (8.8%) and Region XII (8.6%). The ages of these patients ranged from less than 1 month to 100 years old, with median of 13 years old, with more male patients at 52.4%. In addition to that, most of the cases belonged to the pediatric age group of 5 to 14 years old (38.8%).

Fluid management in dengue depends on its severity based on the WHO guideline, which was later adopted by the DOH. Based on the 2012 dengue guideline of the Philippine Pediatric Society (PPS) and the DOH, dengue is now classified as dengue with or without warning signs and severe dengue.[4] According to this guideline, crystalloids such as normal saline and lactated Ringer's solution, and colloids such as Dextran, Voluven, Tetraspan, and Gelatin, can be used as the first line in fluid resuscitation in severe dengue as these fluids have shown its effectiveness in reducing the recurrence of shock and mortality.[4] However, each has its own risks and benefits. Compared with crystalloids, colloids are more expensive and have higher risk for allergic reactions.[4] Because of these, several studies have been conducted comparing normal saline, lactated Ringer's solution and colloids. But there are still insufficient data on the advantage of one fluid over the other when it comes to fluid resuscitation in cases of severe dengue. In addition to that, there are also limited studies conducted using the balanced crystalloids these days. No extensive studies have been conducted comparing the use and effects of balanced crystalloid such as acetated Ringer's solution (isotonic electrolyte solution) to that of another balanced crystalloid such as lactated Ringer's solution, or isotonic electrolyte solution to that of normal saline and colloid.

Normal saline (0.9% NaCl solution) is the most used fluid not just in dengue cases for resuscitation or maintenance solution since it has shown that its use is equivalent or at times more superior than colloid solutions.[5] It is composed of 154 milliequivalent of sodium and 154 milliequivalent of chloride per 1000mL of the solution. On the other hand, colloid solutions, categorized as blood-derived and semi-synthetic, consist of large molecules combined in a base solution such as normal and hypertonic saline, and others. The main reason for its use is to expand the intravascular volume longer and effectively.[6]

Balanced crystalloid solutions are developed as it closely mimics the ionic composition of the blood. These solutions include the lactated Ringer's solution with lactate as the buffer and isotonic electrolyte solution with acetate and malate as the buffer. These solutions contain less sodium and chloride content as compared to that of normal saline and colloid solutions.

These ionic components, as well as the buffer of the balanced solutions, have varying effects on the acid-base balance, renal function, electrolyte level, and vascular permeability.[5] Hence, in severe dengue, which has severe plasma leakage, severe active bleeding and severe organ involvement, the choice of fluid, especially during the early resuscitation, plays a very important role in the management and eventual outcome in such cases. Hence, our aim was to determine the comparative recovery time to achieve sustained cardiovascular stability among severe dengue patients using acetated isotonic electrolyte solution, normal saline solution, and lactated Ringer's solution.

According to the PPS revised dengue guidelines released in 2012[4], the fluid of choice when it comes to severe dengue with compensated shock is crystalloid given for an hour, and if with hypotensive shock, crystalloid or colloid may be used as the first line of intravenous fluids, which is given for 15 minutes. Reassessment after fluid resuscitation is done and the next intravenous fluid to be used depends if there is improvement of the blood pressure, heart rate, respiratory rate, peripheral perfusion, capillary refill time, and sensorium. In addition to that, it has been stated in this guideline that normal saline can cause

hyperchloremic metabolic acidosis, which can be mistaken as lactic acidosis from prolonged shock. On the other hand, Ringer's lactate solution should be avoided in patients with liver failure and colloids may cause coagulopathy but none yet was seen in dengue patients.

In 2003, a local study done in our institution by Cifra and Nazareno compared the effectiveness of a colloid (6% Haes-Steril) and crystalloid (Ringer's lactate) as the first-line plasma substitute for the management of DSS.[9] Twenty-seven patients were included in this study. The colloid group had longer duration of control of shock as compared to the crystalloid group. Also, there was less recurrence of shock in the colloid group. Both groups have the same average hospital stay. However, when compared to the crystalloid group, the colloid group had a lower mortality rate when used initially.

In 2010, a local study by Jalac et al reviewed the use of colloids and crystalloids in DSS among pediatric patients.[12] They did a systematic review and meta-analysis of both fluids comparing their effects in reducing the recurrence of shock, the need for rescue fluids, the need for diuretics, total volume of fluids infused, the hematocrit levels and pulse rates, and the mortality rates among these patients. They have found out that both colloids and crystalloids did not differ significantly in terms of decreasing the recurrence of shock, and the need for rescue fluids and diuretics. However, they have found out that there was an improvement of the hematocrit level and the pulse rates in the colloid group from the baseline after two hours of fluid resuscitation.

Also in 2010, Akech et al also did a review comparing the effects of using crystalloids and colloids in fluid resuscitation among children of aged 1 month to 12 years old with severe infection.[13] A total of nine trials were included in the review but only eight trials compared the use of crystalloid and colloid. They found that compared with crystalloids, a weak evidence that using colloids for volume expansion could have a better survival in children with certain severe infections.

In 2013, Perel did a review of randomized control trials comparing the effect of crystalloid and colloid in fluid resuscitation in patients with dengue fever.[16] Five trials were included in the review on the effects of colloids versus crystalloids. Three studies compared dextran (colloid) with crystalloids and two studies compared gelatins with crystalloids. He found out that there is no evidence that fluid resuscitation with colloids reduced the mortality as compared to crystalloids. However, because of the low quality of evidence included in his review, as outcomes other than mortality were included in the review, colloids should not be included for volume replacement in dengue patients.

In a review done by Córtes et al in 2014, they determined the advantages and disadvantages of using different isotonic crystalloid in surgical and non-surgical adult patients.[18] They have found out that the use of normal saline increased the incidence of hyperchloremic acidosis, which could have an adverse effect on inflammation and coagulation. Ringer's lactate increased the blood lactate levels when used in large amounts. It was also reported that hyperchloremic acidosis might cause renal vasoconstriction, however, its effect on renal function, needed more studies. Aside from that, the use of normal saline appeared to be associated with increased blood loss hence requiring more transfusions as compared to those patients in which Ringer's lactate were used. However, there was a clear association of lactate levels with mortality when large volume of Ringer's lactate was used. But in contrast, lactate may be used as a fuel for the myocardium, neurons, and red blood cells among others.

Another review of randomized trials done by McDermid et al in 2014 discussed the controversies of type, dose, and toxicity of different fluids used in acutely ill hospitalized patients.[19] When crystalloid was compared against colloid, differences in efficacy were modest but differences in safety were significant.

Moreover, differences in chloride load and strong ion difference across solutions appeared to be clinically important as a high chloride load could cause metabolic acidosis. Quantitative toxicity (fluid overload) was associated with adverse outcomes and could be diminished with fluid therapy based on functional hemodynamic parameters. Qualitative toxicity (fluid type), in particular for iatrogenic acute kidney injury and metabolic acidosis, remained to be a concern for synthetic colloids and isotonic saline, respectively. Because of these, physiologically balanced crystalloids may be utilized, as the fluid of choice for acutely ill patients.

In 2015, Varrier and Ostermann did a review of different fluids and their composition and its effect on acid-base status, renal function, and coagulation, hence affecting outcomes.[22] They reviewed three fluids – unbalanced crystalloids (normal saline, dextrose solutions, sodium bicarbonate solutions), balanced crystalloids (Ringer's lactate, Plasma-Lyte, Sterofundin), and colloids (albumin, gelatin, dextran, starch). In terms of volume expansion, the effects of fluid infused depend on the molecular weight and half-life of the molecular contents of the fluids, endothelial integrity, as well as hydrostatic and osmotic pressure gradient between the intravascular and extravascular compartment. In cases of acute volume loss or redistribution, the low hydrostatic pressure could cause prolonged filling effect of both crystalloids and colloids. Therefore, the benefit of both crystalloids and colloids were the same. Hyperchloremia and metabolic acidosis were more commonly seen in normal saline causing renal vasoconstriction, and in effect reduced glomerular filtration. When compared to Ringer's acetate, Ringer's lactate and normal saline, hydroxyethyl starches have shown an increased need for renal replacement therapy in patients with renal dysfunction. Negative effects on hemostasis were seen more in colloids. With this review, it preferred to use balanced crystalloid to normal saline to minimize fluid overload, and the avoidance of synthetic colloids.

METHODOLOGY

This is a retrospective cohort study that included the charts of all patients aged 1 month to 18 years of age with a diagnosis of severe dengue (DSS III and IV) at the emergency room and subsequently admitted to the intensive care unit of our institution from 2014 to 2016. The groups were divided based on the fluid of choice during the initial fluid resuscitation – (A) acetated isotonic electrolyte solution, (B) normal saline solution, and (C) lactated Ringer's solution. The age and sex in each group were recorded as well as the time of initial cardiovascular stability and sustained cardiovascular stability. Their physical examination findings (pulse pressure, heart rate) and urine output were also recorded. Laboratory findings – hematocrit level, platelet count, electrolytes level (sodium, potassium, chloride, calcium), lactate, venous blood gases (pH, pCO_2, HCO_3), alanine and aspartate transaminases, blood urea nitrogen, and creatinine – were recorded and assessed accordingly. The PELOD-2 Score was computed for each patient. The total volume of each intravenous fluid used per patient was also recorded accordingly. Rescue colloid was also recorded in groups A, B, and C, if given. The outcome after the first two hours of fluid resuscitation, the length of ICU stay and the need for renal replacement therapy, mechanical ventilation, and mortality rate were recorded in each group.

All the records of those patients who satisfied the inclusion criterion were reviewed and analyzed accordingly. All the fluids used, the volume of each fluid given, age, sex, blood pressure, heart rate, urine output, hematocrit level, white blood cell count, platelet count, serum sodium, potassium, chloride, calcium, and lactate levels, pH, pCO2, and HCO_3 levels, transaminases, blood urea nitrogen, creatinine, Glasgow Coma Scale, pupillary reaction, time of initial and sustained cardiovascular stability, presence of re-shock, need for colloids, inotropes, and blood transfusion, use of renal replacement therapy and mechanical ventilation, length of stay in the intensive care unit, and the

mortality rate were all recorded, reviewed, and analyzed accordingly.

The primary outcome was the time to achieve sustained cardiovascular stability from initial fluid resuscitation among severe dengue patients. Secondary outcomes were: time to achieve initial cardiovascular stability from the time of recognition of shock and re-shock; time to achieve sustained cardiovascular stability from re-shock; total volume of fluid to achieve cardiovascular stability; pattern of change in hematocrit level; presence of electrolyte imbalances and acid base disturbances before and after treatment, and their correlation with anion gap and strong ion difference; presence of deranged transaminases before and after treatment; PELOD-2 Score and the probability of mortality based on the initial white blood cell count and platelet count, Glasgow Coma Scale, pupillary reaction, serum lactate, mean airway pressure, serum creatinine, PaO_2, $PaCO_2$, and the use of mechanical ventilation; re-shock time and rate; use of other intravenous fluids, inotropes, and blood transfusions; need for dialysis; length of stay at the pediatric intensive care unit; and mortality rate in each group.

Analysis of variance and chi-square test were used to evaluate the association between the clinical and laboratory parameters, and the primary and secondary outcomes. A 95% confidence interval was set to measure the association among outcome measures and a p-value of less than 0.05 was considered significant. To eliminate heterogeneity and to test those statistically significant variables, multivariate regression analysis was used.

RESULTS

A total of 175 patients were admitted at the PICU with severe dengue from January 2014 to December 2016; 166 of these were included in the study and divided into 3 IVF groups:58 patients were included in the AIES group (acetated isotonic electrolyte solution); 58 patients were included in the NSS group (normal saline solution); and 50 patients in the LRS group (lactated Ringer's solution). Nine patients were excluded because of the presence of co-morbidities (rheumatic heart disease, pulmonary tuberculosis, and red cell aplasia), transfusion of packed red blood cell at the level of the emergency room, received fluid resuscitation from other institution and transferred to our institution, those patients who were initially admitted at the wards as dengue with warning signs, and in which colloid was initially used for fluid resuscitation.

The demographics of the patients and initial physical examination are summarized in Table 1. All three groups have the same gender distribution. NSS group had the youngest patients with mean age of 7.54 years while LRS group had the oldest patients at 9.3 years old, and AIES group at 8.0 years old. LRS group had the heaviest patients with mean weight of 30.7kgs as compared to 24.88kgs for the AIES group and 25.66kgs for the NSS group. Pulse pressure among the three groups was further divided according to age and was classified as (1) pulse pressure not detectable, or less than or equal to 20mmHg, and (2) pulse pressure between 21 – 40mmHg. Sixty-eight patients between 1 month old and 8 years of age have pulse pressure which were non-detectable or equal or less than 20mmHg. This finding was consistent among patients who were 9 – 18 years old, with a total of 52 patients. As a compensation for the shock, ninety-nine patients showed tachycardia, with a mean heart rate of 108 – 115 beats per minute among the three IVF groups. Further dividing the heart rate among age groups showed that 63 patients developed tachycardia among1 month to 8 years old as compared to 36 patients among patients who were 9 – 18 years old. Initial measurement of the urine output was adequate with a mean of 1.34mL/kg/hour for all the three IVF groups.

Table 1. Summary of the Demographics and Initial Physical Examination

	Acetated Isotonic Electrolyte Solution (n = 58)	Normal Saline Solution (n = 58)	Lactated Ringer's Solution (n = 50)	p value
Gender				
• **Male**	34	25	24	0.2337
• **Female**	24	33	26	
Age, years				
• **Mean ± SD**	8 ± 3.6	7.5 ± 3.9	9.2 ± 3.3	
• **1month to 8years old**	36	38	20	**0.0438**
• **9 – 18 years old**	22	20	30	
Body Weight, kg				
• **Mean ± SD**	24.88 ± 9.81	25.66 ± 10.99	30.68 ± 12.13	**0.01459**
Heart Rate, bpm				
• **Mean ± SD**	114.43 ± 20.62	114.63 ± 18.99	108.54 ± 23.06	
• **1 month to 8 years old**				
○ **Normal**	9	13	6	
○ **High**	26	23	14	0.23881
• **9 – 18 years old**				
○ **Normal**	12	9	18	
○ **High**	11	13	12	
Pulse Pressure, mmHg				
• **Mean ± SD**	24.13 ± 16.33	31.72 ± 22.49	25.8 ± 15.53	
• **1 month to 8 years old**				
○ **Non-detectable, palpatory, =<20mmHg**	27 (47%)	26 (45%)	15 (30%)	
○ **21 – 40mmHg**	9 (16%)	12 (21%)	5 (10%)	0.07250
• **9 – 18 years old**				
○ **Non-detectable, palpatory, =<20mmHg**	19 (32%)	13 (22%)	20 (40%)	
○ **21 – 40mmHg**	3 (5%)	7 (12%)	10 (20%)	
Urine Output, mL/kg/hour				
• **Mean ± SD**	1.22 ± 0.68	1.35 ± 0.75	1.46 ± 0.71	0.23121

Initial hematocrit level was determined prior to fluid resuscitation and repeat hematocrit level determination was done on the 4th, 8th, and 12th hour after fluid resuscitation as shown in Table 2. The levels of hematocrit on the 4th, 8th, and 12th hour after fluid resuscitation is shown on Figure 1. The mean initial hematocrit level in the AIES group was at 45.6, 44.5 in the NSS group, and 44.3 in the LRS group. There were 36 patients in the AIES group, 29 patients in the NSS group, and 24 patients in the LRS group who have hemoconcentration. Regardless of the IVF groups, more patients presented with hemoconcentration – 54 patients from the1 month to 8 years old age group as compared to 35 patients from the 9 – 18 years old age group. After the 4th, 8th, and 12th hour of fluid resuscitation, the hematocrit level showed a decreasing trend among the three IVF groups. The mean hematocrit level was that of 42.02among patients in the AIES group, 40.18 among patients in the NSS group, and 40.24

among patients in the LRS group after 12 hours of fluid resuscitation. This was translated to 7.85%, 9.71%, and 9.21% decrease from the initial hematocrit level among the AIES, NSS, and LRS groups, respectively, thus showing that the AIES group had the modest decrease of hematocrit levels that did not translate to bleeding, hemodilution, and/or the need for blood transfusion.

Figure 1. Pattern of Decrease of Hematocrit Level from Initial Determination

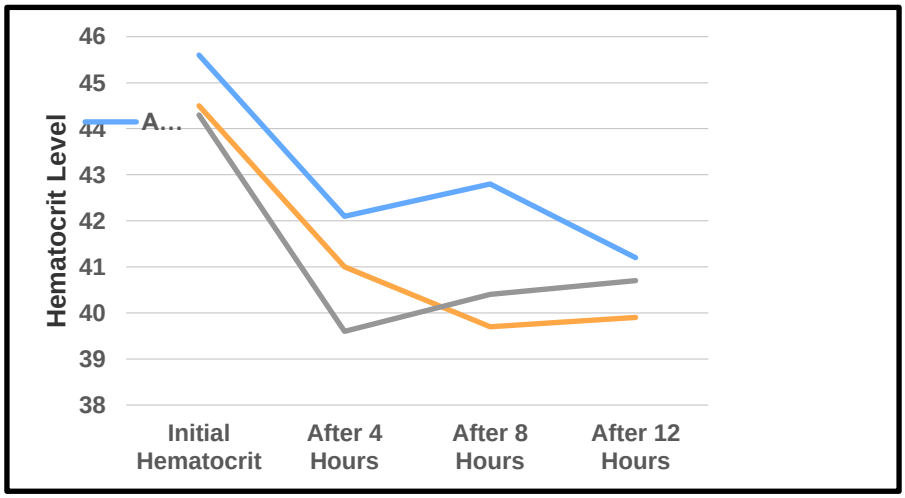

Table 2. Hematocrit Levels onInitial Presentation, and After 4, 8, and 12 Hours of Fluid Resuscitation

	Acetated Isotonic Electrolyte Solution (n = 58)	Normal Saline Solution (n = 58)	Lactated Ringer's Solution (n = 50)	p value
Hematocrit, Initial				
• **Mean ± SD**	45.6 ± 6.20	44.5 ± 5.81	44.32 ± 4.81	0.43482
• **1 month to 8 years old**				0.94904
○ **Low**	1	1	1	
○ **Normal**	13	16	8	
○ **High**	22	21	11	
• **9 – 18 years old**				
○ **Low**	1	0	0	
○ **Normal**	7	12	17	
○ **High**	14	8	13	
Hematocrit, after 4 hours				
• **Mean ± SD**	42.06 ± 4.81	40.97 ± 5.94	39.62 ± 5.44	0.10404
Hematocrit, after 8 hours				
• **Mean ± SD**	42.78 ± 4.78	39.69 ± 3.37	40.38 ± 4.57	**0.00678**
Hematocrit, after 12 hours				
• **Mean ± SD**	41.21 ± 5.01	39.87 ± 4.62	40.72 ± 5.92	0.38770
Hematocrit from 4 – 12 hours				
• **Mean ± SD**	42.02 ± 4.89	40.18 ± 4.84	40.24 ± 5.39	0.83982
• **% Decrease from Initial Hematocrit**	7.85	9.71	9.21	

Hyponatremia and hypocalcemia were noted in the initial serum electrolytes determination. Only 45 patients in the AIES group did a repeat serum electrolyte level determination as compared to 50 patients in the NSS group and 38 patients in the LRS group. Repeat serum sodium in the AIES and LRS group showed minimal effect on serum sodium level as it remained to be low which can be attributed to active plasma leakage due to increased permeability of the blood vessels in dengue infection. There was no incidence of hypernatremia in the AIES group while there was a decrease by 1.34-times (34% decrease) in the number of patients with hypernatremia in the LRS group. On the NSS group, 54% still have normal serum sodium level but there was a2.9-times increase (190% increase)in the number of patients who developed hypernatremia. Repeat serum potassium levels were maintained normal but there was persistence of hypocalcemia on the three IVF groups.

Most patients in the AIES group have a repeat serum chloride levels which were normal, but it is important to note that there was an increase by 1.3-times (29% increase) in the number of patients who developed hyperchloremia. On the other hand, the LRS group also had a normal repeat serum chloride levels in most of the patients but there was an increase by 3.9-times (294% increase) in the number of patients who developed hyperchloremia. This is comparable to the NSS group as there was an increase by 3.8-times (277% increase) in the number of patients who developed hyperchloremia.

Same initial serum pH levels were noted among the three IVF groups. The AIES group showed marked reversal of metabolic acidosis as compared to the NSS and LRS groups as evident on the serum pH at the 4^{th} to 12^{th} hours after fluid resuscitation. This normalization of the serum pH was more consistent with the increase in serum HCO_3 in the AIES group as compared to the NSS and LRS groups, of which the HCO_3 levels remained to be low. The changes in serum pH and HCO3 are shown in Figures 2 and 3, respectively.

Different references have different normal values of anion gap and strong ion difference. In this study, a normal anion gap has a range of 5 – 20mmol/L and a normal strong ion difference is between 38 to 46mmol/L. Anion gap in all groups were normal even on repeat determination after the 12^{th} hour of fluid resuscitation as shown in Table 3. However, there was a trend of closure of the anion gap in the AIES and LRS groups as compared to the NSS group, which remained to be on the high-normal side. The initial strong ion difference in the AIES and LRS group were normal as compared to the low strong ion difference in the NSS group. However, all the three IVF groups have lower strong ion difference after the 12^{th} hour of fluid resuscitation.

The presence of a buffer system in AIES and LRS produces more bicarbonate to correct the acidosis as compared to NSS which do not have a buffer system. But due to the presence of hepatic insult, lactate from LRS is converted to lactic acid instead of bicarbonate, thus, producing more acidosis. This can explain why the LRS group remained to have metabolic acidosis despite the presence of buffer systems. Moreover, NSS contains higher chloride content as compared to AIES and LRS. This high chloride content of the NSS can also contribute in the development of metabolic acidosis. In hyperchloremic metabolic acidosis, there is a normal anion gap and low strong ion difference. Hence, hyperchloremic metabolic acidosis can be seen mostly in the NSS group as most patients presented with hyperchloremia with associated normal anion gap metabolic acidosis and low strong ion difference.

Table 3. Change in Serum pH, HCO3, Anion Gap, and Strong Ion Difference Among the AIES, NSS, and LRS Groups

	Acetated Isotonic Electrolyte Solution (Mean ± SD)	Normal Saline Solution (Mean ± SD)	Lactated Ringer's Solution (Mean ± SD)	p value
pH				
• Initial	7.34 ± 0.07	7.33 ± 0.07	7.36 ± 0.07	0.32669
• After 4 Hours	7.36 ± 0.05	7.32 ± 0.09	7.38 ± 0.70	0.07336
• After 8 Hours	7.28 ± 0.084	7.36 ± 0.10	7.35 ± 0.88	0.24513
• After 12 Hours	7.41 ± 0.057	7.36 ± 0.073	7.32 ± 0.10	0.10164
HCO_3				
• Initial	15.38 ± 4.78	14.69 ± 3.48	17.68 ± 6.17	**0.00522**
• After 4 Hours	16.04 ± 3.35	15.20 ± 4.06	19.08 ± 7.06	0.08408
• After 8 Hours	13.35 ± 5.02	16.80 ± 3.33	20.31 ± 9.06	0.07722
• After 12 Hours	18.30 ± 3.83	16.36 ± 3.55	16.37 ± 7.34	0.66395
Anion Gap				
• Initial	18.69 ± 5.05	17.89 ± 14.23	18.97 ± 6.22	0.82540
• Repeat	14.95 ± 3.91	18.27 ± 4.80	13.51 ± 7.24	0.05012
Strong Ion Difference				
• Initial	38.39 ± 4.34	36.71 ± 13.75	40.72 ± 4.44	0.06715
• Repeat	36.48 ± 3.76	35.31 ± 4.94	37.36 ± 3.73	0.07843

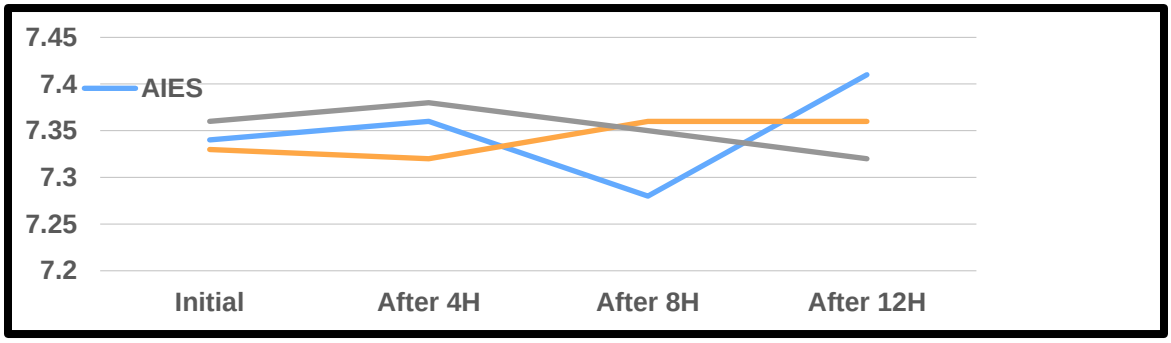

Figure 2. Change in Serum pH in the AIES, NSS, and LRS Groups

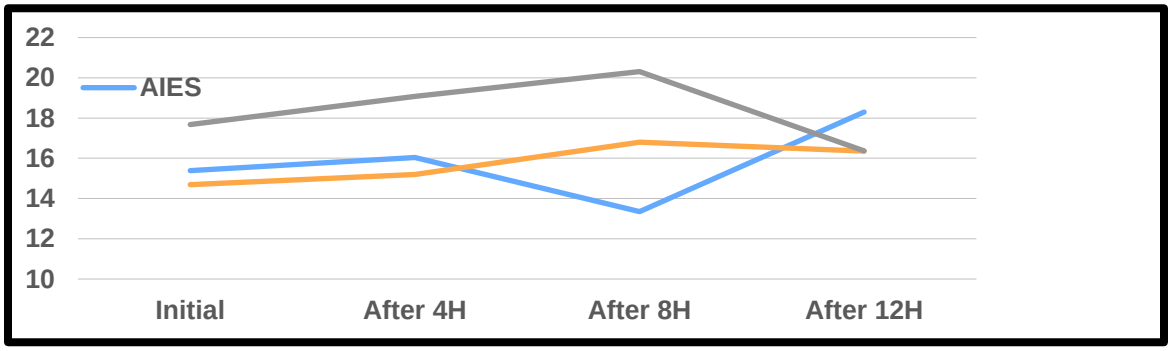

Figure 3. Change in Serum HCO_3 in the AIES, NSS, and LRS Groups

All patients in the three IVF groups have elevated liver transaminases. However, by following the WHO criteria for elevated liver enzymes, only 4patients in the AIES group have elevated liver enzymes of more than 1000mmol/L – 1patient had elevated alanine transaminase and 3patients have elevated aspartate transaminase. Out of these 4 patients, only 1 patient did a repeat transaminase level and although the level was still elevated based on normal range, it showed a 68% decrease from the initial aspartate transaminase level.

Moreover, 42 patients in the NSS group have elevated serum aspartate transaminase levels but only 2 out of these 42 patients have more than 1000mmol/L. These 2 patients were also included in the 8 patients who have repeat serum transaminase determination. Like the AIES group, these patients still have elevated serum aspartate levels but there was a decreasing trend.

The LRS group have a total of 34 patients with elevated transaminase levels but only 2 patients have levels more than 1000mmol/L, one of which eventually died. Only 3 patients did a repeat determination of the transaminase levels and like the AIES and NSS groups, the levels showed a decreasing trend.

Normally, the buffer systems of the AIES and LRS produce more bicarbonate with the conversion of the acetate and malate from the AIES and lactate from the LRS. Acetate and malate are metabolized primarily in the muscle as compared to lactate which is metabolized mainly in the liver. In the presence of hepatic injury, the lactate in the LRS produces more lactic acid instead of bicarbonate, rendering the serum pH more acidotic as seen in the repeat pH determination among the three groups.

N-acetylcysteine is commonly used for paracetamol toxicity. Its role in dengue-associated hepatitis is not yet well-studied. In this study, all patients with serum transaminase levels of more than 1000mmol/L were given N-acetylcysteine. However, it is important to note that only half of the patients in the AIES group with elevated transaminase levels was given N-acetycysteine as compared to 62% in the NSS group and 42% in the LRS group. Although still elevated, there was a decreasing trend on repeat determination of serum transaminase levels in those patients that were given N-acetylcysteine as shown in Figure 4.

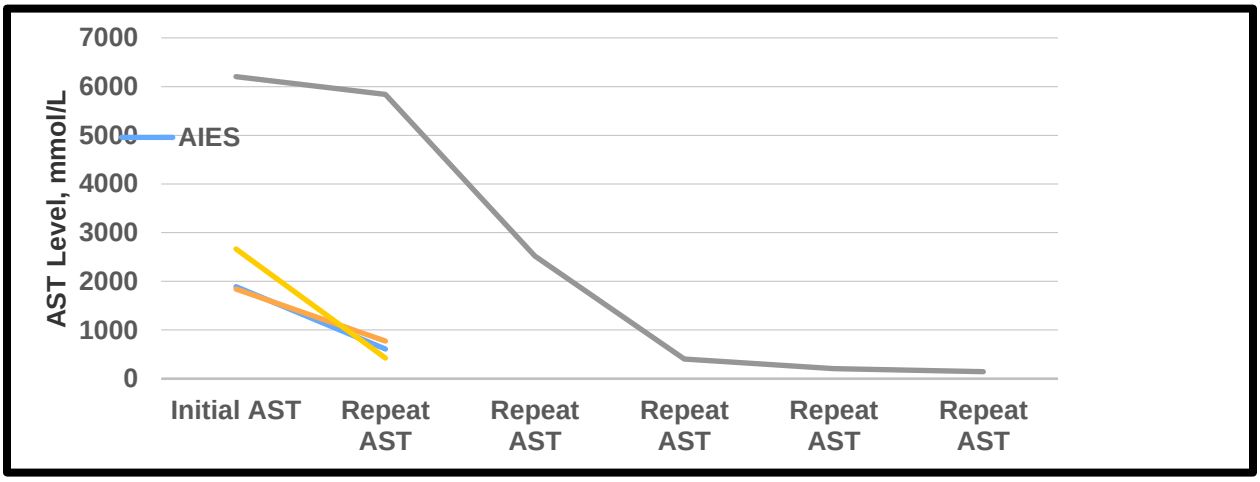

Figure 4. Pattern of Decrease of Serum Aspartate Transaminase Levels

Half of the patients in the three IVF groups have a low initial BUN levels and most have normal initial creatinine levels. The trend of the BUN and creatinine levels is shown on Figures 5 and 6, respectively. In the AIES group, only 1 patient had repeat determination of BUN and creatinine, however, both remained to be normal. In the NSS group, 3 patients have repeat BUN and creatinine levels – 2 patients remained to have normal repeat BUN determination and

with normalization of the creatinine levels; the other 1 patient who initially presented with an elevation of both BUN and creatinine still have further increase of both BUN and creatinine levels which warranted renal replacement therapy. In the LRS group, only 3 patients have repeat determination of BUN and creatinine levels – 2 patients have an increasing trend, of which 1 underwent renal replacement therapy, however, both eventually died; the other 1 patient have BUN level which was both normal on initial and repeat determination, and although there was a 28% increase in the creatinine level, this patient did not require renal replacement therapy.

Table 4 shows that the AIES group had the shortest time to achieve initial stability at 2.29 hours among those patients without re-shock after the initial fluid resuscitation as compared to 2.5 hours in the NSS group and 2.68 hours in the LRS group. This was consistent with the shortest time of 4.37 hours to achieve sustained cardiovascular stability in the AIES group as compared to4.63 hours in the NSS group and 4.94 hours in the LRS group.

Table 4. Summary of Time to Achieve Initial and Sustained Cardiovascular Stability

	Acetated Isotonic Electrolyte Solution (n = 58)	**Normal Saline Solution (n = 58)**	**Lactated Ringer's Solution (n = 50)**	**p value**
Time to Achieve Initial Stability from Initial Shock, hours				
• Mean ± SD	2.29 ± 0.59	2.5 ± 0.68	2.68 ± 0.97	**0.03148**
Time to Achieve Sustained Stability from Initial Shock, hours				
• Mean ± SD	4.37 ± 0.53	4.63 ± 0.94	4.94 ± 1.06	**0.01192**
Time to Achieve Initial Stability from Re-Shock, hours				
• Mean ± SD	2.3 ± 0.48	2.18 ± 0.40	2.35 ± 0.74	0.70603
Time to Achieve Sustained Stability from Re-shock, hours				
• Mean ± SD	4.2 ± 0.42	4.06 ± 0.59	5.33 ± 3.52	0.25341

Moreover, the AIES group had less tendencies to have re-shock at 17% versus 28% for the LRS group and 29% for the NSS group. However, in patients who have re-shock, the NSS group had the shortest time to achieve initial and sustained cardiovascular stability at 2.2 hours and 4.1 hours, respectively, as compared to 2.3 hours and 4.2 hours for the AIES group, and 2.4 hours and 5.3 hours for the LRS group.

The AIES group needed less fluid to establish initial cardiovascular stability at 0.84L as compared to 1.1L for the LRS group and 1.0L for the NSS group as shown in Table 5. Likewise, the AIES group needed less fluid to achieve sustained cardiovascular stability at 1.3L as compared to 2.0L for the LRS group and 1.9L for the NSS group. Since the LRS group had the heaviest mean body weight among the three IVF groups and had a longer time to achieve initial and sustained cardiovascular stability, it had the least amount of fluid at 13.22mL/kg and 10.09mL/kg to achieve initial and sustained cardiovascular stability, respectively, as compared to 15.12mL/kg and 10.51mL/kg for the AIES group and 15.72mL/kg and 10.98mL/kg for the NSS group.

Table 5. Total Volume to Achieve Initial and Sustained Cardiovascular Stability

	Acetated Isotonic Electrolyte Solution (n = 58)	Normal Saline Solution (n = 58)	Lactated Ringer's Solution (n = 50)	p value
Total Volume of IVFto Achieve Initial Stability, mL				
• Mean ± SD	839.66 ± 478.28	993.79 ± 614.86	1090.66 ± 580.03	0.06663
Total Volume per Body Weightto Achieve Initial Stability, mL/kg				
• Mean ± SD	15.12 ± 4.67	15.72 ± 5.63	13.22 ± 2.98	**0.01705**
Total Volume of IVFto Achieve Sustained Stability, mL				
• Mean ± SD	1326.43 ± 618	1922.29 ± 2285	2045.74 ± 1726	0.05856
Total Volume per Body Weightto Achieve Sustained Stability, mL/kg				
• Mean ± SD	10.51 ± 2.53	10.98 ± 3.48	10.09 ± 1.87	0.25032

Table 6 summarizes the differences between the three IVF groups on the use of another crystalloid and/or colloid, transfusion of blood, use of inotropes, and mechanical ventilation. All three IVF groups required the use of colloids especially in episodes of re-shocks. Among the three IVF groups, the LRS group had more tendencies of using colloid at 34%, hence, the LRS group did not necessitate the use of another crystalloid. This result is comparable to the NSS group at 31%, which has higher re-shock rates. In contrast, the NSS group had the tendency to use another crystalloid (AIES) in 12% of its patients because of NSS's higher chloride content, thus causing further increase in the serum chloride levels leading to the development of hyperchloremic metabolic acidosis. Because of higher re-shock rates in the NSS group, it needed more transfusion of packed red blood cells and use of inotropes. The need for mechanical ventilation was comparable in the NSS and LRS groups at 13.8% and 14%, respectively, as both groups have 50% of its patients having episodes of re-shocks.

Table 6. Summary on the Use of Colloid, Another Crystalloid, Packed Red Blood Cells Transfusion, Inotropes, and Mechanical Ventilation

	Acetated Isotonic Electrolyte Solution (n = 58)	Normal Saline Solution (n = 58)	Lactated Ringer's Solution (n = 50)	p value
Use of Colloid	11 (18.97%)	18 (31.03%)	17 (34%)	0.1719
Use of Another Crystalloid	0	7 (12.07%) – AIES	0	0.5078
pRBC Transfusion	4 (6.89%)	9 (15.52%)	6 (12%)	0.3416
Use of Inotropes	6 (10.34%)	13 (22.41%)	6 (12%)	0.1476
Use of Mechanical Ventilator	1 (1.72%)	8 (13.79%)	7 (14%)	0.0875
Need for Dialysis	0	1 (1.72%)	1 (2%)	0.9928

The length of stay in all the three IVF groups was almost the same and was not statistically significant.

The PELOD-2 score is based on the initial white blood cell count and platelet count, Glasgow Coma Scale, pupillary reaction, serum lactate, mean airway pressure, serum creatinine, PaO_2, $PaCO_2$, and the use of mechanical ventilation. But when a parameter is not measured, that parameter is considered normal. PELOD-2 score predicts the probability of death

– the higher the score, the higher the probability that the patient may expire. Among the three IVF groups, the NSS group had the highest PELOD-2 score, thus having the highest probability of mortality as shown in Table 7. This was consistent with the actual number and percent mortality in the NSS group with 3 mortalities (5.2%) as compared to the LRS group with 2 mortalities (4%) and the AIES group with none.

Table 8. PELOD-2 Scores and Number of Mortalities

	Acetated Isotonic Electrolyte Solution (n = 58)	**Normal Saline Solution (n = 58)**	**Lactated Ringer's Solution (n = 50)**	**p value**
PELOD-2 Scores Upon Admission				
1 month – 8 years old				
• Mean	3.88	4.57	4.05	0.06331
• Probability of Death	0.83	1.14	0.89	
9 – 18 years old				
• Mean	3.63	5.35	3.13	**0.031225**
• Probability of Death	0.73	1.63	0.58	
Mean PELOD-2 Scores	3.79	4.84	3.5	0.053307
Mortality				
• 1 month – 8 years old	0	2	1	0.2352
• 9 – 18 years old	0	1	1	
Total Mortality	0	3	2	
% Mortality	0	5.17%	4%	

Patients who were 1 month – 8 years old also showed the highest PELOD-2 scores, thus having the highest probability of mortality. Moreover, those patients who eventually expired have PELOD-2 scores of more than 10, except for 1 patient with a score of 5.

Multivariate linear regression was done to eliminate heterogeneity among variables, specifically that of the demographics of the patient. All the demographics were not statistically significant after regression analysis, hence considered homogenous.

Table 9. Summary of the clinical and laboratory parameters, and management of the mortalities among the NSS and LRS Groups

		Age, years	Gender	Actual Body Weight, kg	Ideal Body Weight, kg	Interpretation	Initial BP, mmHg	Initial HR, bpm	Initial pH level	Initial HCO_3 level	Initial ALT, mmol /L	Initial AST, mmol/L	Initial Na level, mmol/L	# of Re-shocks
NSS	**1**	4	F	28	16	Obese	90/60	160	7.34	10.9	548	629	128	3
	2	5	M	21	18	Normal	0	180	7.34	12.9	113	444	117	2
	3	11	F	43	36	Overweight	Palp 60	130	7.3	16.2	230	292	134	3
LRS	**1**	8	M	30.5	25.5	Overweight	Palp 90	140	7.12	16.6	220	237	145	2
	2	14	F	50	46.5	Normal	0	140	7.28	7.8	498	1364	143	5

		Initial Hct	Repeat Hct (% Change)	PRBC Transfusion	Initial WBC Count	Initial Platelet Count	Dengue Serology Test	Mechanical Ventilation	Initial Creatinine Level	Initial BUN Level	Dialysis	% Fluid Over load	GCS
NSS	**1**	50	40 (20%)	Yes	7.2	12	IgM +	Yes	Elevated	Normal	No	20	13
	2	49	31 (37%)	Yes	6	19	NS1Ag +	Yes	Normal	Normal	No	12.5	7
	3	53	36 (32%)	Yes	5.7	40	NS1Ag +	Yes	Normal	Low	No	43	12
LRS	**1**	45	37 (18%)	Yes	10.6	75	NS1Ag +	Yes	Elevated	Normal	Yes	12.6	12
	2	44	36 (18%)	Yes	8.2	10	IgM +	Yes	Normal	Normal	No	19	13

DISCUSSION

Crystalloid solutions remain to be the first line in the fluid resuscitation among dengue patients. But the choice of which intravenous fluid to be used in the initial resuscitation plays a very important role as it influences the course of dengue infection. With the introduction of another balanced crystalloid solution, there are limited local studies comparing its efficacy versus what is recommended based on the dengue fluid resuscitation protocol of the WHO and PPS. In this study, the use of acetated isotonic electrolyte solution produced better outcomes than normal saline and lactated Ringer's solutions.

In our country, there is no study conducted on the use of acetated isotonic electrolyte solution in dengue. To date, this is the first study conducted comparing its use versus the conventional use of normal saline and lactated Ringer's solution in dengue.

Theoretically, both acetated isotonic electrolyte solution and lactated Ringer's solution are both balanced crystalloid solutions and normal saline is not considered normal because of its high sodium content. The plasma-expanding capacity of these crystalloids is related to the sodium concentration.[8] However, all crystalloid fluids have no additional effect on the plasma volume since most are likely lost from the circulation because of sodium's molecular weight and vascular leakage in dengue. But of the three crystalloid intravenous fluids being studied, acetated isotonic electrolyte solution performed better as compared to both normal saline and lactated Ringer's solutions.

For the primary outcome, despite having more patients with hemoconcentration, narrower pulse pressure, and acidosis upon initial presentation, acetated isotonic electrolyte solution had the shortest time to achieve initial and sustained cardiovascular stability among severe dengue patients who did not have re-shock. It also needed less fluid volume to establish initial and sustained cardiovascular stability. In this study, these were attributed to the buffer system and electrolyte concentration, specifically that of sodium and chloride concentrations.

The buffer system of any crystalloid solution is important in the cellular level as it maintain the normal cellular physiology in varied conditions. It resists rapid changes in the blood pH. Acetated isotonic electrolyte solution has acetate and malate as the buffer system while lactated Ringer's solution has lactate. However, normal saline solution does not have any buffer systems, thus called unbuffered solution. Due to severe liver insufficiency in dengue patients, the metabolism of lactate in the liver produces more lactic acid, making the pH more acidotic, hence, worsening the pH level in patients with circulatory insufficiency. The advantage of acetate and malate of isotonic electrolyte solution is that they are not primarily metabolized in the damaged liver in dengue patients and they are converted to bicarbonate ions. This study showed that a crystalloid solution containing acetate, in addition with malate, was more effective in restoring blood pH and plasma bicarbonate within the normal range among patients with severe dengue and metabolic acidosis. This is beneficial among dengue patients because acidosis produces various deleterious effects in the different organ systems like the renal and respiratory systems, thus increasing risk of developing complications which may be prevented by using the most appropriate intravenous fluid on the initial recognition of shock.

Another advantage of the acetated isotonic electrolyte solution is its electrolyte concentration. Based on previous studies for fluid resuscitation, sodium concentration of the intravenous fluid must be at 130 – 155mmol/L. However, plasma sodium concentration is just at 135 – 145mmol/L. An ideal fluid for resuscitation must have electrolyte contents that are close enough to that of plasma. Hence, what is considered as normal saline is not actually normal and is sometimes termed as unbalanced crystalloid.The term balanced crystalloid solution was introduced as it closely resembles the physiologic level of serum sodium concentration. Both acetated isotonic electrolyte solution and lactated Ringer's solution are

balanced crystalloid. However, lactated Ringer's solution has sodium concentration of 130mmol/L as compared to acetated isotonic electrolyte solution which has 145mmol/L sodium concentration. With this, acetated isotonic electrolyte solution is the betterfluid of choice.

Aside from sodium, chloride concentration is also important. The chloride concentration of lactated Ringer's solution is within the physiologic level. However, the buffer system seemed to be the problem in dengue patients with hepatic damage. Between the three crystalloids, normal saline has the highest chloride concentration. The chloride load of an intravenous fluid contributes to the development of hyperchloremic metabolic acidosis. In this study, this was evident on the normal saline group with increased levels of chloride and metabolic acidosis. The presence of hyperchloremic acidosis can lead to acute kidney injury and at times, needing renal replacement therapy. In this study, this was comparable between the normal saline solution and lactated Ringer's solution groups in which as much as 2% of the patients required dialysis.

For the secondary outcomes, acetated isotonic electrolyte solution had less tendencies to have re-shock with minimal use of colloids and inotropes, and blood transfusion during re-shock, and less probability of requiring mechanical ventilator. In this study, common risk factors for re-shock were patients who presented with hypotension or profound shock with pulse pressure of less than 20mmHg and hemoconcentration on initial presentation. This was the same finding in the previous study by Ngo et al in 2001 in which patients with profound shock with pulse pressure of less than 10mmHg developed subsequent and prolonged shocks.[8]More re-shocks were noted in the normal saline group hence, more use of inotropes, blood transfusion, use of a balanced crystalloid, which is acetated isotonic electrolyte solution, and more probability that the patient get intubated and required mechanical ventilation, which was comparable to that of the lactated Ringer's solution group. In this study, this was attributed to the presence of hyperchloremic acidosis hence more adverse outcomes of acidosis and hyperchloremia. However, in this study, the normal saline group has the shortest time to achieve initial and sustained cardiovascular stability in patients who have re-shock. This was closely followed by the acetated isotonic electrolyte solution and then the lactated Ringer's solution. The use of colloid was highest in the lactated Ringer's solution group and this finding was again consistent with the study done by Ngo et al.[8]

Mortality in dengue cases is multifactorial. However, in this study, patients who expired from the normal saline solution and lactated Ringer's solution groups have the following common risk factors as summarized in Table 18 – overweight to obese, profound shock with associated tachycardia, presence of metabolic acidosis, elevated transaminase levels, multiple re-shocks requiring inotropic support and the use of mechanical ventilation, active plasma leakage with associated hemoconcentration, more than 10% decrease from the initial hematocrit level and needed packed red blood cell transfusion, Glasgow coma scale score of 13 and less, and fluid overload of more than 10%. This finding was consistent with the study done by Almas et al in 2010 in which the predictors of mortality among dengue patients included bleeding, altered consciousness and profound shock on initial presentation.[26]

Furthermore, cost-effectiveness of these crystalloids should be put into consideration since most of the patients were charity patients. In this institution, a liter of acetated isotonic electrolyte solution costs PhP250 as compared to Php60 per liter of normal saline and lactated Ringer's solutions. However, because more adverse effects were determined in using normal saline and lactated Ringer's solutions in severe dengue despite having a lower price, using acetated isotonic electrolyte solution iscost-effective as it has more favorable outcome.

CONCLUSION AND RECOMMENDATION

In conclusion, acetated isotonic electrolyte solution is more effective as compared to normal saline solution and lactated Ringer's solution in the initial fluid resuscitation among patients with severe dengue. It must be used as the fluid of choice in severe dengue patients who need fluid resuscitation. Its use produces less re-shock, less use of cardiovascular support, less rescue colloid use, more stable acid-base balance, less bleeding and blood transfusion, and less need for mechanical ventilation and dialysis. We recommend that a randomized control trialcomparing these crystalloids with larger number of patients with severe denguemust be conducted.

BIBLIOGRAPHY/REFERENCES

1. Bravo L, Roque VG, Brett J, Dizon R, L'Azou M. Epidemiology of dengue disease in the Philippines (2000–2011): a systematic literature review. PLoSNegl Trop Dis. 2014;8(11):e3027.

2. Annual dengue data in the western pacific region, WHO Western Pacific Regional Office 2010.

3. Arima Y, Matsui T. Epidemiologic update on the dengue situation in the Western Pacific Region 2010. WPSAR. 2011;2(2):4-8.

4. Philippine Pediatric Society. Revised dengue guidelines. October 2012.

5. Santi M, Lava SA, Camozzi P, Giannini O, Milani GP, Simonetti GD, et al. The great fluid debate: saline or so-called "balanced" salt solutions. Ital J Pediatr. 2015;41:47.

6. Bartels K, Thiele RH, Gan TJ. Rational fluid management in today's ICU practice. Crit Care. 2013;17 Suppl1:S6.

7. Varrier M, Ostermann M. Fluid composition and clinical effects. Crit Care Clin. 2015;31:823–37.

8. Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: a randomized double blind comparison of 4 intravenous fluid regimes in the first hour. Clin Infect Dis. 2001;32(2):204–13.

9. Cifra HL, Velasco JNJ. A comparative study of the efficacy of 6% Haes-Steril and Ringer's lactate in the management of dengue shock syndrome. Crit Care Shock. 2003;6:95-100.

10. Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Eng J Med. 2005;353:877–89.

11. Karyanti MR, Satari HI, Sjarif DR. The effect of Ringer's acetate versus Ringer's lactate on aminotransferase changes in dengue hemorrhagic fever. PaediatrIndones. 2005;45:81-6.

12. Jalac SLR, de Vera M, Alejandria MM. The use of colloids and crystalloids in pediatric dengue shock syndrome: a systematic review and meta-analysis. PJMID. 2010;39:14-27.

13. Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. BMJ. 2010;341:c4416.

14. Hofmann-Kiefer KF, Chappell D, Kammerer T, Jacob M, Paptistella M, Conzen P, et al. Influence of an acetate- and a lactate-based balanced infusion solution on acid base physiology and hemodynamics: an observational pilot study. Eur J Med Res. 2012;17:21.

15. Soegijanto S, Sari D, Yamanaka A, Kotaki T, Kameoka M, Konishi E. Awareness of using Ringer lactate solution in dengue virus infection could induce severity. IJTID. 2013;4(4):35-41.

16. Perel P. Colloids versus crystalloids for fluid resuscitation in Dengue fever patients – a review. For WHO Secretariat. 2013.

17. Somasetia DH, Setiati TE, Sjahrodji AM, Idjradinata PS, Setiabudi D, Roth H, et al. Early resuscitation of dengue shock syndrome in children with hyperosmolar sodium-lactate: a randomized single-blind clinical trial of efficacy and safety. Crit Care. 2014;18:466.

18. Córtes DO, Rayo Bonor A, Vincent JL. Isotonic crystalloid solutions; a structured review of the literature. Br J Anesth. 2014;112(6):968–81.

19. McDermid RC, Raghunathan K, Romanovsky A, Shaw AD, Bagshaw SM. Controversies in fluid therapy: type, dose and toxicity. World J Crit Care Med 2014;3(1):24-33.

20. Lam PK, Hoai Tam DT, Dung NM, Hanh Tien NT, Thanh Kieu NT, Simmons C, et al. A prognostic model for development of profound shock among children presenting with dengue shock syndrome. PLoS ONE. 2015;10(5):e0126134.

21. Raghunathan K, Bonavia A, Nathanson BH, Beadles CA, Shaw AD, Brookhart MA, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. Anesthesiology. 2015;123:1385-93.

22. Varrier M, Ostermann M. Fluid composition and clinical effects. Crit Care Clin. 2015;31:823-37.

23. Chameides L, Samson R, Schexnayder S, Hazinski MF. Pediatric Advanced Life Support Provider Manual. American Heart Association; 2011.

24. Handbook for clinical management of dengue. WHO 2012.

25. Hung N. Fluid management for dengue in children. PediatrInt Child Health. 2012;32(S1).

26. Almas A, Parkash O, Akhter J. Clinical factors associated with mortality in dengue infection at a tertiary care center. Southeast Asian J Trop Med Public Health. 2010;4(2):333-340.