

## **CHAPTER 6**

# **Fluid Management in diabetic-acidosis: Ringer's lactate versus normal saline: A randomised controlled trial**

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## **Abstract**

**Objective:** To determine if Ringers lactate is superior to 0.9% Sodium Chloride solution for resolution of acidosis in the management of diabetic ketoacidosis.

**Design:** Parallel double blind randomised controlled trial

**Methods:** Patients presenting with diabetic ketoacidosis at Kalafong and Steve Biko Academic hospitals were recruited for inclusion in this study if they were older than 18 years of age, had a venous pH  $>6.9$  and  $\leq 7.2$ , a blood glucose of  $>13$  mmol/L and had urine ketones of  $\geq 2+$ . All patients had to be alert enough to give informed consent and should have received less than one litre of resuscitation fluid prior to enrolment.

**Results:** Fifty-seven patients were randomly allocated, 29 were allocated to receive 0.9% Sodium Chloride solution and 28 to receive Ringer's lactate (of which 27 were included in the analysis in each group). An adjusted Cox proportional hazards analysis was done to compare the time to normalisation of pH between the 0.9% Sodium Chloride solution and Ringer's lactate groups. The hazard ratio (Ringer's compared with 0.9% Sodium Chloride solution) for time to venous pH normalisation (pH = 7.32) was 1.863 (CI: 0.937 to 3.705,  $p = 0.076$ ). The median time to reach a pH of 7.32 for the 0.9% Sodium Chloride solution group was 683 minutes (CI: 378 to 988) (IQR: 435 to 1095 minutes) and for Ringer's lactate solution 540 minutes (CI: 184 to 896) ( $p = 0.251$ ). The unadjusted time to lower blood glucose to 14 mmol/L was significantly longer in the Ringer's lactate solution group (410 minutes, IQR: 240 to 540) than the 0.9% Sodium chloride solution group (300 minutes, IQR: 235 to 420) ( $p = 0.044$ ). No difference could be demonstrated between the Ringer's lactate and 0.9% Sodium Chloride solution groups in the time to resolution of DKA (based on the ADA criteria) (unadjusted:  $p = 0.934$ , adjusted:  $p = 0.758$ )

**Conclusion:** This study failed to indicate benefit from using Ringer's lactate solution compared to 0.9% Sodium chloride solution regarding time to normalisation of pH in patients with diabetic ketoacidosis. The time to decrease blood glucose to 14 mmol/L took significantly longer with the Ringer's lactate solution..

## ***Introduction***

Diabetic ketoacidosis (DKA) is an acute complication of diabetes with potential life threatening metabolic and homeostatic derangement. DKA is common in diabetic patients and occurs most frequently in children and adolescents. Fifteen to 20% of adults with new onset diabetes mellitus type 1 will present with a DKA.<sup>1-3</sup> In the United States DKA is reported to be responsible for more than 100 000 hospital admission per year and it accounts for 4% to 9% of all hospital discharge diagnoses among patients with diabetes.<sup>4</sup> The EURODIAB<sup>5</sup> study reported that 8.6% of 3250 diabetic patients were admitted for DKA in the preceding year. In a Danish study the annual incidence of DKA in the general population was 12.9 per 100 000, with a mortality rate of 4%.<sup>6</sup> The mortality associated with DKA is less than 5%, with the prerequisite that standardised written guidelines are used.<sup>7 8</sup> In Africa the mortality is unacceptably high, with a death rate of 26 to 29%.<sup>9</sup> Most patients with DKA are type 1 diabetic patients, but it can occur in type 2 patients as well during episodes of acute stress such as infections or trauma.<sup>2 10</sup>

Current management of DKA includes: replacement of fluid losses, correction of hyperglycaemia with appropriate administration of insulin, correction of electrolyte losses, detection and correction of precipitating causes and maintenance insulin to prevent recurrence of DKA.<sup>11</sup> Normal saline (0.9% NaCl) has traditionally been used as replacement fluid in DKA and this is also reflected in recent guidelines.<sup>11-13</sup> However recent evidence suggests that the administration of large volumes of saline (0.9% NaCl) contributes to the development of metabolic acidosis.<sup>14</sup> The acidifying effect of saline is explained by the un-physiological excessive administration of Cl<sup>-</sup> ions contained in saline. This hyperchloraemic metabolic acidosis is described in endotoxemia,<sup>15</sup> and in patients undergoing surgery.<sup>16 17</sup> In diabetic ketoacidosis, the incidence of hyperchloraemia increases over time during treatment, with the most rapid rise coinciding with the period of most rapid fluid (saline) administration. Resolution

of ketoacidosis is masked by the acidifying effect of chloride, with ketones the major contributor to acidosis early and chloride late in the treatment of DKA.<sup>18</sup>

The aim of this study was to ascertain if the use of Ringer's lactate solution is superior to normal saline infusion if used as primary resuscitation fluid in patients with diabetic ketoacidosis regarding time to resolution of acidosis.

## **Methods**

### **Participants**

Patients were recruited from two sites in Pretoria namely Kalafong (secondary) hospital and Steve Biko Academic (tertiary) hospital. Recruitment for this study took place from February 2008 to November 2009. Patients were eligible for inclusion if they fulfilled the following criteria: newly diagnosed or previously known to have diabetes mellitus, type 1 or type 2 diabetes, age 18 years or older, a venous blood pH at presentation 6.9 to 7.2, presence of at least two plus ketones on urine dipstick test at presentation, a capillary blood glucose of more than 13 mmol/L at baseline and able to give verbal informed consent. Patients were excluded from participation if another cause for acidosis was present e.g. end-stage renal failure or lactic acidosis, if severely ill and in need of inotropic or ventilatory support, and if more than one litre of resuscitation fluid was administered before enrolment. Informed consent was obtained from all patients before enrolment to the study. The study protocol was approved by the ethics committee of the Faculty of Health Sciences of the University of Pretoria. The study was registered at the South African National Clinical trials register, registration number: DOH-27-0607-1612.

### **Patient management and procedures**

The study was a double blind randomised controlled trial with a parallel design and an allocation ratio of one to one. Stratified randomisation per centre was done by centre in blocks of ten using a sequential numbered opaque box system. Sequentially numbered boxes contained study material and resuscitation solution Blinding was achieved by using unlabeled coded one litre

resuscitation fluid bags (prepared by Dismed CritiCare (Lty) Ltd. Midrand, South Africa). All clinicians, patients and investigators were blinded for the coding of resuscitation fluid. Unblinding of the code was only done after analysis of the primary outcome was completed.

All patients were treated according to the same diabetic ketoacidosis protocol implemented at the two hospitals. Patients received study fluid as initial resuscitation fluid until blood glucose was less than 14 mmol/L. Subsequently the attending clinician could continue with any dextrose or glucose containing fluid according to preference. Blood samples were taken (as per DKA management protocol implemented at the hospitals) for electrolytes, urea and creatinine measurement at baseline, one hour later and once pH was normal. Calcium, magnesium, phosphate, albumin and total protein measurement was done at baseline and once pH was normal. All blood tests were analysed at the local NHLS laboratory of each of the hospitals. Venous blood gas and blood ketones and blood glucose were determined at baseline, one hour later and then according to a schedule becoming more frequent as the pH approached normal. All blood gas determinations were done utilising a Copenhagen Radiometer ABL 700 blood gas analyser (Kalafong hospital) and a Copenhagen Radiometer ABL 700 or Cobas B221 blood gas analyser (Steve Biko Academic hospital). Ketones were measured with a Medisense Optium Exceed ketone meter (Abbott Laboratories) and glucose was measured with an Accu-chek active glucometer (Roche diagnostics). Urine was assessed for ketone content using Combur 9 urine dipsticks (Roche diagnostics). Urine ketones were tested by urine dipstick at baseline and periodically until pH normalised. All patients were initially managed in the emergency department and transferred to the high care unit if beds were available otherwise they were managed in the medical wards until pH normalised. Insulin dose was adjusted for each patient hourly according to the DKA management protocol.

Endpoints were: time to reach a venous pH of 7.32, to achieve serum glucose of 14 mmol/L and time to resolution of DKA. Time to achieve a serum glucose less

than 14 mmol/L was selected because according the DKA management protocol 14 mmol/L was the threshold for changing patients from glucose free resuscitation fluid to glucose or dextrose containing intravenous fluids. Time to resolution of DKA was defined as fulfillment of the following three criteria: venous pH >7.3, serum bicarbonate  $\geq 18$  mmol/L and blood glucose >11.1 mmol/L.<sup>11</sup>

### **Statistical analysis**

A pilot study consisting of ten patients was done with normal saline as resuscitation fluid only to obtain an estimate of the time to recovery of pH as well as a SD. The result of the pilot study was used to calculate the sample size. The sample size calculation assumed the following: alpha value of 0.05, power of 0.9, and difference between the two arms of the study 0.8 SD, equal SD in both arms and equal number of patients allocated to each arm. The calculated sample size was 37 patients per arm with a total sample size of 74 patients, and to compensate for potential losses, 40 patients per arm were targeted.

The primary endpoint was time to normalisation of pH; therefore comparison between the two arms of the study was done by Log-rank and Cox proportional hazards methods for time to event outcomes. Unadjusted as well as an adjusted analysis for baseline covariates was done. An adjusted analysis was planned a priori, irrespective of baseline imbalances, to compensate for minor differences between the Ringer's and 0.9% Sodium Chloride groups as well as to increase the power of the study. Repeated measures ANOVA analysis was done to assess within group and between group changes in blood parameters measured.

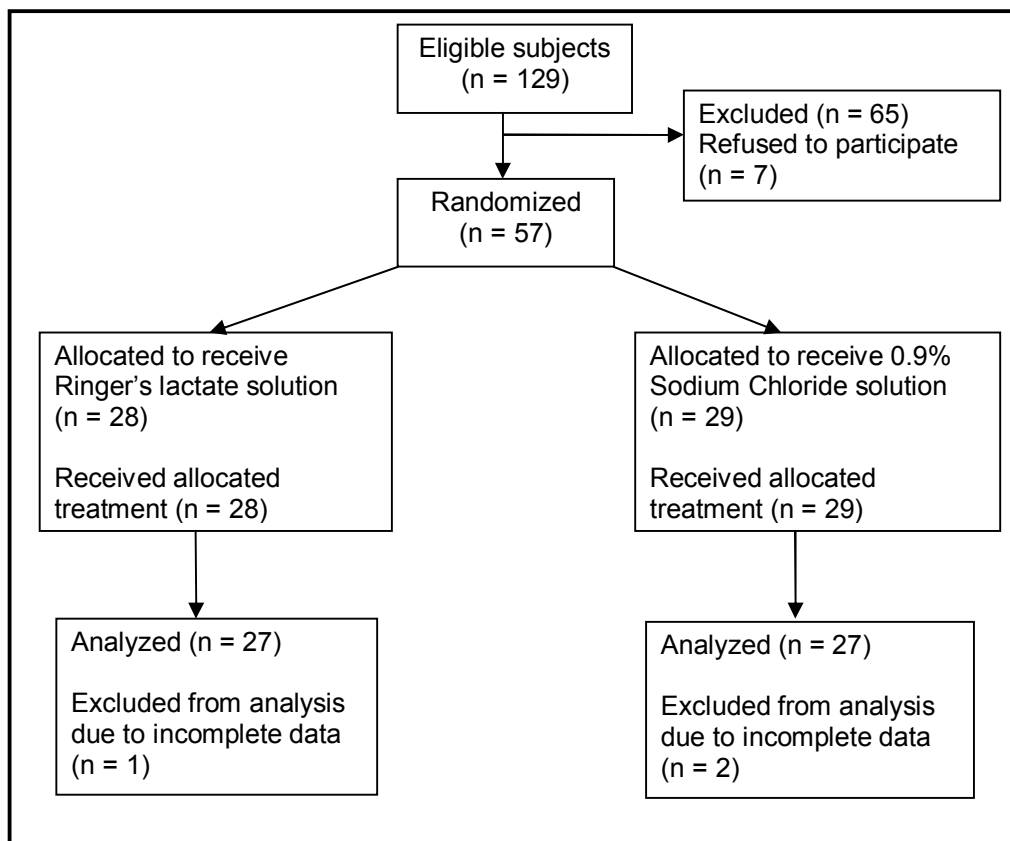
### **Results**

This study was stopped before the planned sample size was obtained due to slower than expected enrollment and expiry of consumables obtained for the study. At the time of termination 57 patients were enrolled with diabetic ketoacidosis (DKA), 52 patients had a pH  $\leq 7.2$  and 5 patient had a pH of 7.2 to 7.29. All patients fulfilled all the other inclusion criteria. All the enrolled patients

were followed up until clinical resolution of the DKA. Three patients were excluded from the analysis due to missing data: one patient had baseline information absent, one the insulin infusion rate was not recorded, and one patient fluid administration was not recorded (Fig 1). Of the 54 analyzable patients 32 were enrolled at Kalafong hospital and 22 at Steve Biko Academic Hospital. Of the analyzed patients 28 were managed only in casualties department, 21 in a high care unit and 5 in a general ward. In both groups 15 patients had an identifiable precipitating event, of which non-compliance was the most common (14/30) followed by infections (11/30).

### Baseline and descriptive

Table 1 presents baseline and pre-treatment characteristics of the patients included in the analysis. Differences between the groups were not statistically significant.



**Figure 1: Trial profile**



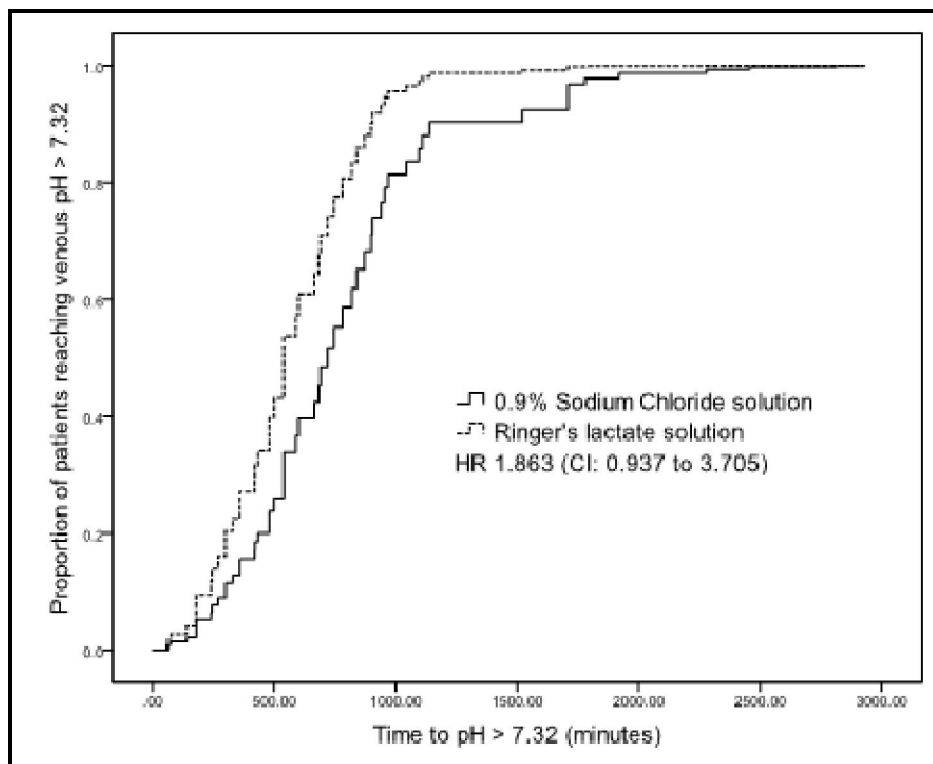
**Table I: Baseline characteristics (Numbers and mean (standard deviation))**

| Variables                           | Ringers Lactate Solution | 0.9% Sodium chloride Solution |
|-------------------------------------|--------------------------|-------------------------------|
| Total number of patients            | 27                       | 27                            |
| Gender (M/F)                        | 18/9                     | 13/14                         |
| Age (years) median (IQR)            | 36.1 (24.1 to 46.6)      | 36.6 (25.5 to 42.2)           |
| Newly diagnosed                     | 12                       | 10                            |
| Type of diabetes                    |                          |                               |
| Uncertain                           | 13                       | 9                             |
| Type 1                              | 12                       | 15                            |
| Type 2                              | 1                        | 3                             |
| Secondary                           | 1                        | 0                             |
| Identifiable precipitant            | 15                       | 15                            |
| Hospital enrolled                   |                          |                               |
| Kalafong /SBAH                      | 17/10                    | 15/12                         |
| Baseline pH                         | 7.10 (0.105)             | 7.12 (0.099)                  |
| Baseline HCO <sub>3</sub> (mmol/L)  | 6.74 (3.36)              | 7.66 (3.71)                   |
| Baseline Potassium (mmol/L)         | 4.87 (1.01)              | 4.93 (1.09)                   |
| Baseline capillary glucose (mmol/L) | 25.01 (5.9)              | 27.66 (10.02)                 |
| Baseline capillary ketones (mmol/L) | 4.47 (1.41)              | 4.27 (1.40)                   |

### Normalization of pH

An unadjusted Kaplan Meyer plot and Log Rank analysis was done for duration to recovery of pH (venous pH 7.32). The median time to reach a venous pH of 7.32 for the 0.9% Sodium chloride solution was 683 minutes (CI: 378 to 988) (IQR: 435 to 1095 minutes) and for Ringer's lactate solution 540 minutes (CI: 184 to 896) (IQR: 300 to 940). The log rank analysis did not indicate a significant difference between the two treatment groups ( $p = 0.251$ ).

A Cox proportional hazards analysis was done to adjust for differences between the two treatment groups (Figure 2). The difference between the two groups was adjusted for the following: baseline bicarbonate concentration, baseline capillary glucose concentration, baseline capillary Beta-hydroxy-buterate concentration, amount of study fluid administered (liters), mean hourly insulin administered and the hospital to which patients were enrolled. After adjustment the difference between time to pH normalization was non-significant ( $p = 0.076$ ). Resolution of pH in patients resuscitated with Ringers lactate solution occurred non-significantly earlier than those treated with 0.9% Sodium chloride solution (HR: 1.863, CI: 0.937 to 3.705).

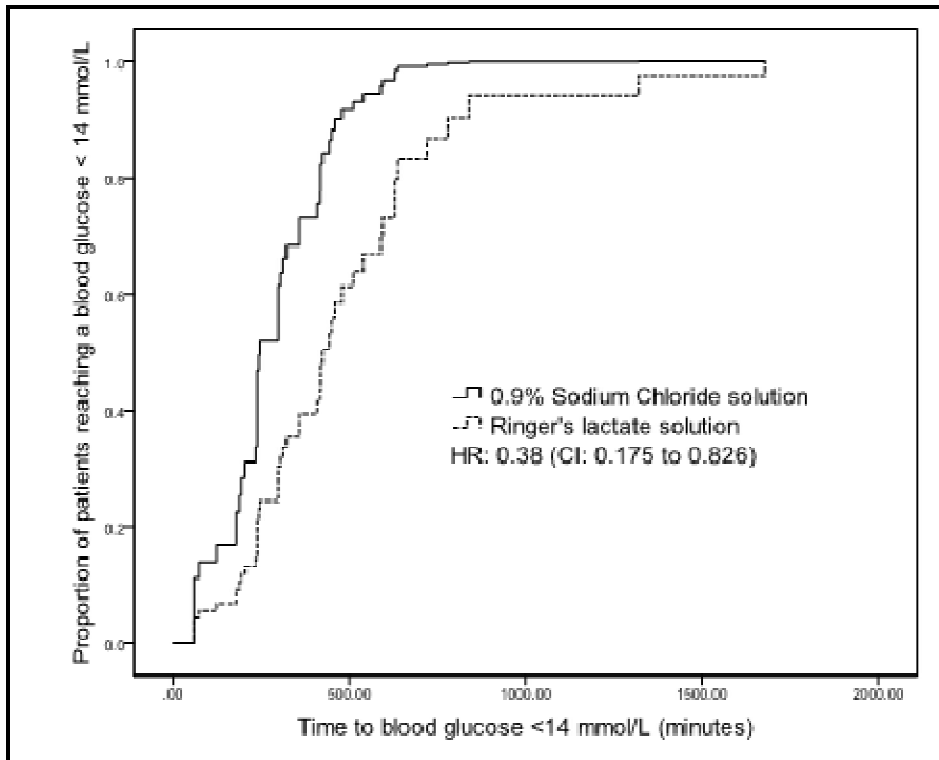


**Figure 2: Cox proportional hazards model for time to venous pH more than 7.32**

Normalisation of bicarbonate to 18 mmol/L was non-significantly longer in the 0.9% Sodium chloride group (743 minutes, IQR: 552 to 934) than the Ringer's lactate group (540 minutes, IQR: 261 to 819) (unadjusted Log Rank:  $p = 0.902$ ). After adjustment for the same factors as for pH above, the hazard for bicarbonate to reach 18 mmol/L was non-significantly increased in the Ringer's lactate group (HR: 2.042, CI: 0.621 to 6.715,  $p = 0.24$ ).

### Glycaemic endpoints

The time to lower blood glucose to 14 mmol/L in the Ringer's lactate group was 410 minutes (median) (IQR: 240 to 540), which was significantly longer in comparison to that of 0.9% Sodium chloride 300 minutes (median) (IQR: 235 to 420) (unadjusted Log Rank:  $p = 0.044$ ). When adjusted for blood glucose at baseline, liters study fluid administered, mean insulin administered per hour, hospital enrolled to and unit where managed, the time taken to obtain a blood glucose concentration of 14 mmol/L or less was significantly longer in the Ringer's lactate group than in the 0.9% Sodium chloride group (HR: 0.38, CI: 0.175 to 0.826,  $p = 0.014$ ) (figure 3).



**Figure3: Cox proportional hazards model for time to glucose less than 14 mmol/L**

The number of hypoglycaemic events (blood glucose less than 3.5 mmol/L) during the study was non-significantly more in the 0.9% Sodium chloride group (6 events, 2 events in 2 patients and 1 in two patients) versus no events in the Ringer's lactate group ( $p = 0.111$ ). The group receiving Ringer's lactate required non-significantly more insulin per hour (Median: 5.6 units, IQR: 4.63 to 7.54) in comparison to the 0.9% Sodium chloride group (Median: 5.05 units, IQR: 4.1 to 6.13) ( $p = 0.414$ ). The total units insulin used per patient was significantly more during the first six hours for the Ringer's lactate group (Median: 44 units, IQR: 36 to 48) in comparison to the 0.9% Sodium chloride group (Median: 36 units, IQR: 30 to 44) ( $p = 0.02$ ). This difference in total insulin utilization between the two groups was not significant after 8 hours of treatment.

### Other endpoints

No deaths occurred in any of the two groups. The median duration of hospital stay for both groups was 7 days ( $p = 0.547$ ).

Significant changes in the blood parameters from baseline to the end occurred for all the parameters over time ( $p < 0.001$ ). However no significant different changes could be demonstrated between the 0.9% Sodium Chloride and Ringer's lactate solution groups (Table 2). After one hour of fluid resuscitation one patient in the 0.9% Sodium Chloride group had a serum potassium of more than 5.2 mmol/L as did five patients in the Ringer's group. After the first hour of administration of resuscitation fluid and insulin the mean serum potassium decreased more in the 0.9% Sodium Chloride group than the Ringers Lactate group ( $p > 0.05$ ), thereafter the potassium levels were equal. The serum Chloride increased non-significantly in the 0.9% Sodium Chloride group after 1 hour of fluid administration, but the difference was not evident at the time the ketoacidosis resolved.

### **Combined endpoint**

Resolution of diabetic ketoacidosis according to the 2006 ADA is based on three criteria: venous pH  $>7.3$ , serum bicarbonate  $\geq 18$  mmol/L and blood glucose  $<11.1$  mmol/L. According to these criteria only 21 of the 54 (39%) DKA episodes have achieved resolution by the time follow up was stopped. Follow up was continued in an attempt to ensure fulfillment of the serum bicarbonate criteria for resolution of the 2006 ADA criteria. By the time the venous pH has reached 7.36, which was achieved in 46 DKA episodes only 22 episodes (47.8%) had a bicarbonate of  $\geq 18$  mmol/L. Of this 46 episodes 11 of 22 were receiving 0.9% Sodium chloride solution and 11 of 24 received Ringer's lactates solution ( $p = 0.777$ ). The time to resolution between the 0.9% Sodium chloride solution (1621 minutes) and the Ringers lactate solution (1710 minutes) groups were not significantly different (Log Rank:  $p = 0.934$ ). After adjustment there was no difference in the time to resolution (HR 1.78, CI: 0.415 to 30342,  $p = 0.758$ ).

The ADA (2009) reduced the bicarbonate criterion to 15 mmol/L and added an anion gap criterion to the criteria for resolution of DKA. In this study the electrolytes was not routinely measured to allow calculation of the anion gap. If

the 2009 criteria are implemented for resolution of DKA, excluding the anion gap: 39 of the 54 (72%) of the DKA episodes would have reached resolution. Of the patients achieving resolution according to this criteria 19 (48.7%) were receiving 0.9% Sodium chloride solution and 20 (51.3%) Ringer's lactate solution. By the time the venous pH has reached 7.36, 5 of 46 (10.9%) of the DKA episodes had not yet reached a serum bicarbonate of 15 mmol/L. A Kaplan-Meier analysis to assess the time to resolution of DKA between Ringers lactate (median: 870 minutes, IQR: 421 to 1650) and 0.9% Sodium Chloride solution (median: 845 minutes, IQR: 563 to 1380) indicated a non-significant difference (Log rank:  $p = 0.923$ ). After adjustment for baseline bicarbonate concentration, baseline capillary glucose concentration, baseline capillary Beta-hydroxy-buterate concentration, amount of study fluid administered (liters), mean hourly insulin administered and the hospital to which patients were enrolled in a Cox-proportional hazards model, no difference could be demonstrated between the Ringer's and 0.9% Sodium Chloride groups in the time to resolution of DKA (HR: 0.886, CI: 0.417 to 1.88,  $p = 0.752$ )

**Table II: Biochemical parameters at baseline and over time in the 0.9% Sodium chloride and Ringer's lactate groups**

| Parameter               | Group              | Baseline         | 1 hour           | End              | Between groups P-value |
|-------------------------|--------------------|------------------|------------------|------------------|------------------------|
| sAlbumin mg/dL          | Saline<br>Ringer's | 36.15<br>34.70   |                  | 26.65<br>26.05   | 0.566                  |
| sProtein mg/dL          | Saline<br>Ringer's | 76.37<br>74.70   |                  | 58.67<br>60.57   | 0.618                  |
| sCalcium mmol/L         | Saline<br>Ringer's | 2.213<br>2.213   | 2.11<br>2.14     | 1.98<br>2.113    | 0.372                  |
| sMagnesium mmol/L       | Saline<br>Ringer's | 1.004<br>0.96    | 0.89<br>0.85     | 0.716<br>0.731   | 0.981                  |
| sPhosphate mmol/L       | Saline<br>Ringer's | 1.48<br>1.453    | 0.86<br>1.02     | 0.505<br>0.537   | 0.576                  |
| sSodium mmol/L          | Saline<br>Ringer's | 133.83<br>134.13 | 134.93<br>136.94 | 137.24<br>137.35 | 0.504                  |
| sPotassium mmol/L       | Saline<br>Ringer's | 5.056<br>5.081   | 4.41<br>4.52     | 3.8<br>3.88      | 0.722                  |
| sChloride mmol/L        | Saline<br>Ringer's | 101.65<br>101.37 | 111.36<br>104.95 | 108.83<br>109.02 | 0.421                  |
| sCO <sub>2</sub> mmol/L | Saline<br>Ringer's | 8.86<br>7.71     | 8.21<br>8.83     | 16.38<br>17.00   | 0.605                  |
| sUrea mmol/L            | Saline<br>Ringer's | 8.9<br>9.34      | 6.69<br>8.58     | 4.25<br>4.85     | 0.314                  |
| sCreatinine mmol/L      | Saline<br>Ringer's | 136.96<br>139.65 | 111.79<br>127.11 | 80.14<br>89.09   | 0.716                  |

## ***Discussion***

The results of this study indicate that normalization of pH occurs non-significantly faster if the primary resuscitation solution in patients with diabetic ketoacidosis is Ringer's lactate solution instead of 0.9% Sodium Chloride solution. Glycaemic recovery to the 14 mmol/L and 11.1 mmol/L levels is significantly delayed with Ringer's lactate solution.

This result makes sense pathophysiologically, because the Lactate in Ringer's lactate solution is metabolized via two routes. Firstly, lactate undergoes gluconeogenesis predominantly in the liver but also in the kidneys. This mechanism accounts for about 70% of the clearance of lactate. Gluconeogenesis of lactate occurs via the production of pyrovate and results in a transient increase in blood glucose in normal individuals who has an

appropriate insulin response, which is not the case in patients with diabetic ketoacidosis.<sup>19 20</sup>

The second mechanism of lactate clearance is via oxidation, which accounts for about 30% of the metabolism of lactate. The oxidation of lactate occurs predominantly in the liver but also to a lesser extent in the kidneys, heart and skeletal muscle cells. During the oxidation of lactate  $\text{CO}_2$  and  $\text{H}_2\text{O}$  is formed and Hydrogen ions is consumed. Hydrogen is also consumed during the gluconeogenesis process; therefore both reactions play a role in limiting acidosis. The consumption of  $\text{H}^+$  leaves  $\text{OH}^-$  to bind to  $\text{CO}_2$  to form  $\text{HCO}_3^-$ . The production of bicarbonate from lactate has a half-life of 10 to 15 minutes. Thus in patients with acidosis the use of Ringer's lactate is of benefit in acidotic patients as in patients with DKA, however the current study failed to show significance of this effect.<sup>21</sup>

The decrease in potassium was not (as expected) significantly less in the Ringer's group (Ringer's contains 4 mmol Potassium per liter compared to zero in 0.9% Sodium Chloride solution) The opposite is also true for chloride which did increase in the 0.9% Sodium Chloride solution (containing 150 mmol/L Chloride) group but not statistically significantly more than in the Ringer's (containing 110 mmol/L chloride) group.

This study had a time to event design with progressively shortening of the intervals of sequential blood sampling in an attempt to obtain the time of resolution of DKA as accurately as possible. This design however limits the comparability and assessment of sequential measurements much more than if blood would have been drawn at fixed intervals. No clear harm in the use of any one of the two resuscitation fluids could be demonstrated.

The major limitation of this study was the inability to obtain the sample size as calculated. This could have led to less precise comparisons between the two arms of the study.

The time to resolution of DKA according to ADA criteria of 2006 was not significantly influenced by whether 0.9% Sodium chloride or Ringer's lactate solution was used. The same accounts for the 2009 ADA resolution criteria, although it could not be fully assessed due to unavailability of the anion gap.

## **Conclusion**

This study failed to demonstrate that the normalisation (venous pH > 7.32) of acidosis when using Ringer's lactate as initial resuscitation fluid occur more rapidly than when 0.9% Sodium Chloride solution is used. Blood glucose threshold values, for changing to glucose containing intravenous fluids, occurs faster with administration of 0.9% Sodium Chloride solution than with Ringer's lactate solution. For resolution of DKA according to the ADA criteria no difference could be demonstrated between the use of Sodium chloride and Ringers lactate solutions.

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*Conflict of interest:* None declared.

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