CHAPTER 1

1.0 INTRODUCTION

The purpose of this prospective observational study was to determine whether there were any differences in outcomes in patients who received normal saline versus Ringer’s lactate as initial fluid resuscitation for the treatment of diabetic ketoacidosis (DKA). This chapter gives an introduction and background to the topic as well as a recent review of the literature in this area.

1.1 Background

DKA continues to be a frequent cause of admission to the endocrine ward at Charlotte Maxeke Johannesburg Academic Hospital. As the incidence of type 1 diabetes mellitus appears to be increasing in almost all populations worldwide,\(^1\) it is likely that even more patients will present in DKA in the future. In the developed world, the overall mortality rate of adult patients in DKA has been reduced to less than 1%.\(^2\) However, in the South African setting, mortality rates remain between 6.8% and 9%,\(^3,4\) making DKA an important condition to recognize early and manage correctly.

The primary and most critical initial treatments of DKA are fluid replacement and insulin administration. In managing a patient who presents in DKA, the first priority should be to restore the circulating volume and improve tissue perfusion so that insulin may be adequately delivered to its sites of action.\(^5\) Hydration lowers serum osmolality thereby increasing the
effectiveness of insulin.\textsuperscript{6} Hydration alone lowers serum glucose even before insulin is administered and may lower the level of counter-regulatory hormones.\textsuperscript{7}

While it is accepted that fluid resuscitation is a crucial factor in the management of DKA, the exact type of fluid to be used remains controversial. The fluid lost in DKA is predominantly due to osmotic diuresis, caused by the glycosuria, with minor contributions from vomiting, pyrexia and hyperventilation.\textsuperscript{8} The osmolality of the fluid lost is similar to half-normal saline; therefore, a relatively hypotonic fluid. Half the fluid loss in DKA is derived from the intracellular compartment and the other half from the extracellular compartment.\textsuperscript{9} Although fluid is lost from all body fluid compartments, patients present clinically with hypovolaemia i.e. depletion of the intravascular compartment.

1.1.1 Choice of initial resuscitation solution

\textbf{Colloid versus crystalloid}

Colloid solutions are more effectively retained in the intravascular compartment than crystalloid solutions, and are most efficient for rapid resuscitation. However, a recent systematic review comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions, but not including DKA, showed no mortality benefit of colloid solutions.\textsuperscript{9} Crystalloids are preferred as they are readily available and inexpensive compared to colloid solutions. Unlike colloid solutions, crystalloid solutions do not carry the risk of anaphylaxis.
**Hypotonic solution versus isotonic solution**

With regard to crystalloid solutions, choices include hypotonic solutions such as half-normal saline, or isotonic solutions like normal saline or Ringer’s lactate. Hypotonic solutions do not remain intravascular, and for that reason are not ideal for the purposes of initial resuscitation. However, they do manage to restore total body fluid losses with distribution to all three fluid compartments. On the other hand, isotonic fluids are more efficient at restoring circulatory volume. For every litre of infused isotonic saline, a quarter normally remains in the circulatory volume. Because isotonic saline remains largely confined to the extracellular compartment, it does not provide free water to replace intracellular losses. Isotonic fluids are mainly distributed to the interstitial space, and if administered in excess, may lead to peripheral and pulmonary oedema when the interstitial compartment becomes overexpanded.

**Isotonic Infusion Solutions**

Two isotonic intravenous infusion solutions in common use today are normal saline and Ringer’s lactate. Table 1.1 compares these two solutions.

<table>
<thead>
<tr>
<th></th>
<th>Normal saline</th>
<th>Ringer’s lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ mmol/L</td>
<td>154</td>
<td>130</td>
</tr>
<tr>
<td>K⁺ mmol/L</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cl⁻ mmol/L</td>
<td>154</td>
<td>109</td>
</tr>
<tr>
<td>Ca²⁺ mmol/L</td>
<td>0</td>
<td>2.7</td>
</tr>
<tr>
<td>HCO₃⁻ mmol/L</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
1.1.2 Normal Saline

The cholera epidemic that swept through Europe in 1831 stimulated the first developments in intravenous fluid therapy and this is when normal saline is thought to have originated. However, closer examination of the composition of the fluids reveals that all the early solutions were hypotonic and in fact bear no similarity to currently used normal saline. Thomas Latta, in 1832, devised a solution containing 134 mmol/L of Na⁺, 118 mmol/L of Cl⁻ and 16 mmol/L of HCO₃⁻; a solution far more physiological than normal saline.

Early studies on DKA in the 1970s used normal saline, and its use continues to be advocated in modern textbooks today. Current guidelines written by diabetes specialists from the United States of America and the United Kingdom recommend intravenous isotonic fluid replacement in the management of DKA. A recent consensus statement from the American Diabetes Association advocates the use of isotonic saline as the initial fluid therapy in the absence of cardiac compromise. The Association of British Clinical Diabetologists’ guideline agrees.

It has been recognized that administration of large volumes of normal saline may be associated with the development of a hyperchloraemic metabolic acidosis. The hyperchloraemic acidosis results from the use of fluids with a [Na⁺]:[Cl⁻] ratio below the physiological normal
ratio. The Na\(^+\): Cl\(^-\) ratio in normal human serum is 1.38:1 while it is 1:1 in normal saline and 1.19:1 in Ringer’s lactate.\(^{21}\) As explained so eloquently by Veech,\(^{21}\) when large volumes of normal saline are infused, at some point the kidney is not able to excrete the excess Cl\(^-\). The law of electrical neutrality of solutions (equation 1)\(^{21}\) requires that in extracellular fluid where Na\(^+\) is the predominant cation, administering Cl\(^-\) in amounts equal to Na\(^+\) leaves no room for the second most common anion found in serum which is HCO\(_3\)\(^-\). The decrease in HCO\(_3\)\(^-\) leads to hyperchloraemic acidosis and cells expend precious metabolic energy to effect a proper distribution of electrolytes until the kidney can excrete the excessive Cl\(^-\) administered. The mechanism of development of hyperchloraemic acidosis is better explained using Stewart’s theory of interpretation of acid-base disorders.

**Equation 1**

Law of Electrical Neutrality of solutions\(^{21}\)

\[
\sum |Z'| [\text{cations}^{Z+}] = \sum |Z| [\text{anions}^{Z-}]
\]

\(\sum |Z|\) is the sum of charges on the ions

**Interpretation of Acid-base Disorders**

Over the past decade, a number of articles have compared two different approaches to interpreting acid-base disorders.\(^{22,23}\) The “traditional” approach uses the Henderson-Hasselbalch equation to describe and classify metabolic acidosis. A shortcoming of the
traditional approach is that it doesn’t allow a distinction between the various possible causes of metabolic acidosis. The “modern” approach is Stewart’s physical-chemical approach: a model more useful for quantifying acid-base disorders. In Stewart’s analysis, he determined that there are only three independent variables that determine pH:

- Partial CO₂ tension (PCO₂)
- Total concentration of weak acid (ATOT). In plasma, these consist of albumin and inorganic phosphate.
- Strong ion difference (SID). The SID describes the difference between the concentrations of the strong cations (Na⁺, K⁺, Mg²⁺, and Ca²⁺) and strong anions (Cl⁻, lactate, ketoacids, sulphate and others) in a fluid compartment, and may be calculated using the complex equation(equation 2) below.

**Equation 2**

**Calculation of strong ion gap (SIG)²⁴**

\[
\text{SIG} = [(\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}) - (\text{Cl}^- + \text{lactate}^-)] - (2.46 \times 10^{-8} \times \text{PCO}_2/10^{-\text{pH}} + [\text{albumin (g/dl)}]) \\
\times (0.123 \times \text{pH} - 0.631) + [\text{PO}_4^- (\text{mmol/L})] \\
\times (\text{pH} - 0.469)]
\]
Any change in pH must be because of a change in one or more of these three independent variables, or in the dependent variables, such as hydrogen ion concentration \([H^+]\) and bicarbonate concentration \([HCO_3^-]\).

Hyperchloraemic acidosis may be more accurately described as a strong ion acidosis.\(^{25}\) The problem arises when clinicians use the base deficit in preference to the anion gap to document an improvement in the DKA. The base deficit, although an accurate measure of the total metabolic component of an acidosis, cannot differentiate between coexistent causes of the acidosis like ketosis and hyperchloraemia. Hyperchloraemia, if not explicitly recognized as giving rise to acidosis, may mask resolution of the ketoacidosis. The unwary clinician may erroneously interpret the low bicarbonate as being due to ongoing ketoacidosis or hypovolaemia, and this may prompt an unnecessary alteration in therapy: either a change in insulin dose and/or increased fluid administration.

This is where Stewart’s theory is helpful. The “traditional” Henderson-Hasselbalch model assumes that bicarbonate is an independent variable and is not influenced by chloride, hence it cannot satisfactorily explain the mechanism of the hyperchloraemic acidosis. However, Stewart’s strong ion approach provides a mechanistic explanation for hyperchloraemic acidosis by using a set of equilibria that describes the chemistry of plasma.\(^{26}\)

Besides the development of hyperchloraemic acidosis, the administration of large volumes of normal saline may theoretically cause hyperkalaemia through an extracellular shift of \(K^+\) ions caused by acute changes in blood hydrogen ion concentration, which occurs secondary to the hyperchloraemic acidosis.\(^{27}\) A randomized double-blind comparison of Ringer’s solution and
normal saline during renal transplantation by O’Malley et al\textsuperscript{17} found that 19% of patients who received normal saline during renal transplantation developed hyperkalaemia (> 6mmol/L) and required treatment versus no hyperkalaemia in the patients who received Ringer’s lactate. The study was terminated early due to the increased incidence of life-threatening hyperkalaemia with the use of normal saline. O’Malley et al did not find that normal saline adversely affected renal function when used during renal transplantation.\textsuperscript{17} Wilcox, in the canine kidney model, showed that sustained renal vasoconstriction was related specifically to hyperchloraemia and was accompanied by a reduction in glomerular filtration rate (GFR).\textsuperscript{28}

Despite the problems, normal saline continues to be widely used as resuscitation fluid. A study comparing the effects of normal saline and Hartmann’s solution (a solution similar to Ringer’s lactate) in normal healthy adult volunteers\textsuperscript{18} showed that normal saline has greater and more prolonged blood and plasma volume-expanding effects than Hartmann’s solution. The study showed, by changes in body weight, that 56% of infused normal saline was retained compared to 30% of Hartmann’s solution after 6 hours.

\textbf{1.1.3 Ringer’s Lactate}

Sydney Ringer was born in 1834 and trained as a physician at University College Hospital in London. His major area of research was the effect of inorganic salts on body tissues and he developed Ringer’s solution which could be used as a ‘blood substitute’. In the 1930s Alexis Frank Hartmann from St Louis Missouri, who was a clinician with an interest in paediatrics, sought an isotonic solution that had a more moderately alkalinizing effect than sodium bicarbonate but which would retain an electrolyte composition similar to plasma. Hartmann
recognized that “chloride increase claimed base”; in other words, an increase in chloride lowered bicarbonate levels and showed that Ringer’s solution was a better alternative to normal saline in the treatment of acidosis as a result of diarrhoea in infants. Lactate was used to replace some of the chloride in normal saline, the reasoning being that lactate is metabolized to CO₂ and H₂O and could be safely added to fluid as a bicarbonate equivalent. The lactate in Ringer’s lactate is metabolized in the liver by one of two routes – either by gluconeogenesis (70%) or oxidation (30%) which are both H⁺-consuming processes. The consumption of H⁺ leaves an excess of OH⁻ which then combines with CO₂ to form HCO₃⁻.

Table 1.2 below lists the constituents of Ringer’s lactate and Hartmann’s solution as we know them today.

<table>
<thead>
<tr>
<th></th>
<th>Ringer’s lactate</th>
<th>Hartmann’s solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ mmol/L</td>
<td>130</td>
<td>131</td>
</tr>
<tr>
<td>K⁺ mmol/L</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cl⁻ mmol/L</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>Ca²⁺ mmol/L</td>
<td>2.7</td>
<td>2</td>
</tr>
<tr>
<td>Lactate mmol/L</td>
<td>28</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 1.2 Constituents of Ringer’s lactate and Hartmann’s solution

While few studies have examined the use of Ringer’s lactate in DKA, there are several theoretical arguments against its use in DKA. The ratio of lactate: pyruvate is tightly controlled in the blood of healthy individuals and increases with injury and disease. Lactate induces
reduction of the cytosolic [NAD\(^+\)]: [NADH] ratio, reflecting an abnormally reduced redox state which leads to a decrease in the extent of most of the cell’s energy-linked reactions.\(^{21}\) Patients in DKA already have a high lactate to pyruvate ratio, and the 28 mmol/L of lactate in Ringer’s lactate could exacerbate this.\(^{33}\) However, in a study to test the hypothesis that intravenous Ringer’s lactate would increase the circulating lactate concentration, Didwania et al found no significant differences in circulating lactate levels in healthy adults who received an infusion of 1 litre of Ringer’s lactate over an hour compared to those who received the same amount of normal saline or 5% dextrose water.\(^{34}\)

The osmolality of Ringer’s lactate is lower than, and that of normal saline is equal to or higher than, the osmolality of normal human serum (285 – 295 mOsm/kg) as shown in Table 1.1. Animal studies\(^ {35, 36}\) confirmed that haemodilution with large volumes of Ringer’s lactate led to a decrease in serum osmolality accompanied by an increase in cerebral water content, hence the need for caution when using Ringer’s lactate in patients with neurosurgical problems.\(^ {36}\) A study by Williams et al\(^ {37}\) showed that the serum osmolality of healthy humans was reduced transiently after receiving 50ml/kg of Ringer’s lactate over an hour and normalized within an hour of ending the infusion. Cerebral oedema is a rare but recognized complication of DKA and although it is more common in children, has been reported in adults.\(^ {38, 39}\) If a Ringer’s lactate infusion can lower serum osmolality, perhaps it can predispose to the development of cerebral oedema. A study by Duck and Wyatt\(^ {40}\) looked at 42 cases of DKA associated with cerebral oedema in children and found that the overall rate of fluid administration correlated inversely with the time to onset of herniation. Glaser et al\(^ {41}\) retrospectively examined 6977 cases of childhood DKA and identified 61 cases of cerebral oedema. When analyzing therapeutic factors
causing cerebral oedema, only treatment with bicarbonate was significantly associated. A literature review by Brown asked the question ‘Is the treatment of DKA in children responsible for the development of cerebral oedema?’ and concluded that the idea that treatment for DKA causes cerebral oedema was an ‘unsubstantiated myth’.

A litre of Ringer’s lactate contains 4 mmol of potassium, which may be life-threatening for a patient who is initially hyperkalaemic. Another consideration is the cost. One litre of Ringer’s lactate currently costs approximately three times that of a litre of normal saline.

### 1.1.4 Normal saline versus Ringer’s lactate

The Joint British Diabetes Societies (JBDS) guideline from 2010 recognizes the debate between the recommendation of normal saline versus Ringer’s lactate in patients with DKA and discusses the type of fluid to be used under the heading ‘Controversial Areas’. The guideline recommends the use of normal saline over Hartmann’s solution for resuscitation in DKA. Table 1.3 (adapted from the JBDS guideline) lists the advantages and disadvantages of normal saline and Ringer’s lactate.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>- decades of clinical experience</td>
<td>- hyperchloraeamic metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>- readily available</td>
<td>may slow resolution of acidosis</td>
</tr>
<tr>
<td></td>
<td>- cheaper</td>
<td>- sustained renal vasoconstriction →</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓GFR</td>
</tr>
</tbody>
</table>

11
Ringer’s lactate

- isotonic
- less chloride – minimal tendency to hyperchloremic acidosis
- lactate may precipitate high lactate: pyruvate ratio
- contains potassium
- more expensive

Table 1.3 Advantages and Disadvantages of normal saline and Ringer’s lactate

1.2 Justification of this study

The question of which infusion solution is optimal in DKA still remains unanswered. Although current guidelines advocate the use of normal saline as initial resuscitation fluid in the management of DKA, a literature search revealed no randomized controlled studies that have compared normal saline against any other fluid infusions in this clinical scenario. Studies have compared the effect of normal saline and Ringer’s lactate infusions in normal human volunteers,\textsuperscript{18, 37} in patients undergoing elective gynaecological surgery,\textsuperscript{19} in patients undergoing abdominal aortic aneurysm repair\textsuperscript{20} and in renal transplantation.\textsuperscript{45} Some of these studies have found that normal saline causes a hyperchloremic metabolic acidosis, while most of the studies found that normal saline infusion was associated with significant hyperchloremia. Yet, there is no evidence in the literature that the hyperchloremic acidosis induced by normal saline infusion is clinically significant or dangerous to patients. The purpose of my study was to contribute to this area of research.
1.3 Purpose of this study

1.3.1 Aim

To compare the differences in patient outcomes in patients who received normal saline as initial resuscitation fluid for the treatment of DKA compared to patients who received Ringer’s lactate.

1.3.2 Objectives

1. To determine whether there was a difference in the time to resolution of DKA in patients who received normal saline compared to those who received Ringer’s lactate.

2. To determine whether there were differences in the occurrence of the following biochemical complications during the treatment of DKA in patients who received normal saline compared to those who received Ringer’s lactate:
   - hypernatraemia
   - hyperchloreaemia
   - acid-base abnormalities
   - hypoglycaemia
3. To determine whether there was a difference in length of hospitalization in patients who received normal saline compared to those who received Ringer’s lactate.

4. To contribute towards the next guideline for the treatment of DKA at Charlotte Maxeke Johannesburg Academic Hospital based on the findings of this study.
2.0 METHODS

This chapter describes the methods and materials used to conduct this study.

2.1 Patient Selection

Adult patients admitted to Charlotte Maxeke Johannesburg Academic Hospital with a diagnosis of DKA were screened for eligibility to the prospective observational study designed to compare the use of normal saline and Ringer’s lactate as initial fluid replacement for DKA. Patients were admitted through the casualty department at Charlotte Maxeke Johannesburg Academic Hospital which is also a referral centre for Southrand Hospital, Edenvale Hospital and Far East Rand Hospital.

2.2 Inclusion Criteria

Adults aged 18 years or older who fulfilled the diagnostic criteria for DKA as shown in Table 2.1 were included in the study.

<table>
<thead>
<tr>
<th>Diagnostic Criteria for DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/L)</td>
</tr>
<tr>
<td>Arterial pH</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
</tr>
<tr>
<td>Urine ketones</td>
</tr>
</tbody>
</table>
Serum ketones | Positive
---|---
Anion gap * (mmol/L) | > 10

Table 2.1 Diagnostic Criteria for DKA

* Anion Gap = Na⁺ – (Cl⁻ + HCO₃⁻)

2.3 Exclusion Criteria

Patients with the biochemical abnormalities on admission as shown in Table 2.2 were excluded from the study.

<table>
<thead>
<tr>
<th>Electrolyte Abnormality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>&gt; 113</td>
</tr>
</tbody>
</table>

Table 2.2 Electrolyte abnormalities that were exclusion criteria

Patients admitted from the casualty department directly to the High Care or Intensive Care Units (ICU) were not included in this study. Patients who were enrolled and later required admission to ICU from the endocrine ward were withdrawn from the study.

Patients who were referred from Southrand, Edenvale or Far East Rand hospitals were excluded if there was any doubt regarding the intravenous fluid they had received prior to arrival at Charlotte Maxeke Johannesburg Academic Hospital.
2.4 Ethics

The University of the Witwatersrand Human Research Ethics Committee granted ethical approval for the study in November 2008 (Clearance certificate number M080804 – Appendix A) before data collection began.

2.5 Consent

Written informed consent was obtained from each participant in the study with the aid of a patient information sheet (Appendix B). For patients who had an impaired mental status on admission, an accompanying relative was informed about the study using a relative information sheet (Appendix C) and written consent was obtained retrospectively from the patient. Patient and relative information sheets and consent forms were in English only. Nurses were requested to translate to local languages if required.

2.6 Study Procedure

2.6.1 Admission

Patients were admitted by the casualty officer on duty. The casualty officer took an initial history, examined the patient, ordered the baseline blood investigations and started intravenous fluid resuscitation and other emergency treatment at his/her discretion. All patients were transferred to the endocrine ward on diagnosis of DKA for further treatment and monitoring.
2.6.1.1 History

The following points in the history were noted:

- prior diagnosis of diabetes mellitus
- duration of diabetes mellitus
- previous admissions for DKA and number of DKA episodes
- prior diagnosis of hypertension
- habits – alcohol or cigarette use
- previous treatment of diabetes

2.6.1.2 Examination

The following parts of the examination were recorded:

- Admission Vital Signs
  
The admission blood pressure, pulse rate, temperature and Glasgow Coma Scale were taken from the admission clerking notes.

- Anthropometric Measurements
  
  Weight
  
  Weight was measured using a standard calibrated scale placed on the floor. Patients were weighed while wearing a hospital gown and barefoot and were instructed not to hold onto any form of support.
**Height**

Height was measured with a tape measure and recorded to the nearest centimeter. The patient was requested to stand barefoot with his/her heels together and touching the wall, with his/her back against a wall.

**Waist Circumference**

Waist circumference was measured with a tape measure with the patient’s abdomen exposed. Measurements were done with the patient standing upright in a horizontal plane midway between the anterior superior iliac crest and the ribcage.

- Microvascular Complications

  **Neuropathy**

  A 10g microfilament was used to assess sensation. A patellar hammer was used to assess knee and ankle reflexes.

  **Retinopathy**

  Tropicamide (Mydriacyl) drops were inserted into both eyes to dilate the pupils and fundoscopy was performed in the ward.

**2.6.1.3 Baseline Blood Investigations**

Baseline blood investigations included the following:

- Venous blood gas
- Finger-prick glucose measurement
- Full blood count (FBC)
- Urea and electrolytes (U&E)
- C-reactive protein (CRP)
- Calcium, magnesium, phosphate (CMP)
- Glycated haemoglobin (HbA1c)

All specimens of blood and urine were processed and analyzed by the National Health Laboratory Services (NHLS) within Charlotte Maxeke Johannesburg Academic Hospital.

2.6.2 Treatment

All patients received standard care in the endocrine ward as per the current protocol for the management of DKA at Charlotte Maxeke Johannesburg Academic Hospital (Appendix D).

2.6.2.1 Bicarbonate Administration

All patients with an admission pH of < 7.00 received sodium bicarbonate as per the protocol for management of DKA. Information about whether bicarbonate was administered and the quantity that was administered was taken from the admission clerking notes.

2.6.2.2 Fluid Administration

Intravenous fluid administration was started at the discretion of the casualty officer. The type and quantity of fluid administered was read from the Balfec chart (24 hour
inpatient fluid balance chart to record fluid intake and output) in the patient’s nursing notes.

Patients who received normal saline in casualty were allowed to receive only normal saline or 0.45% normal saline as initial fluid resuscitation at the discretion of the attending doctor. Patients who received Ringer’s lactate in casualty received only Ringer’s lactate. All patients received 5% dextrose water as subsequent fluid resuscitation when their glucose levels dropped below 15mmol/L.

2.6.2.3 Insulin Administration

All patients received hourly boluses of 10 units of regular human insulin intravenously until DKA resolution.

2.6.2.4 Potassium Replacement

Potassium was replaced as shown in Table 2.3 below as per the current protocol for the management of DKA at Charlotte Maxeke Johannesburg Academic Hospital.

<table>
<thead>
<tr>
<th>Serum Potassium</th>
<th>Required Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 mmol/L</td>
<td>40 mmol KCl per litre</td>
</tr>
<tr>
<td>3.1 – 4.0 mmol/L</td>
<td>30 mmol KCl per litre</td>
</tr>
<tr>
<td>4.1 – 5.0 mmol/L</td>
<td>20 mmol KCl per litre</td>
</tr>
<tr>
<td>&gt; 5 mmol/L</td>
<td>Omit KCl</td>
</tr>
</tbody>
</table>

Table 2.3 Guide to Potassium Chloride (KCl) replacement
2.6.3 Monitoring

Patients were monitored during recovery from DKA with the following investigations:

- Hourly finger-prick glucose measurements (Accu-Chek active glucometer, model GC, Roche)
- One to four-hourly venous blood gas measurements (Cobas b 221 blood gas analyzer, Roche)
- Four-hourly laboratory urea and electrolyte measurements.

Serial glucose measurements and corresponding blood gas measurements were recorded from the patient’s file and entered onto the data collection sheet.

Patients’ data were collected until they resolved from DKA as defined by all the following criteria shown in Table 2.4 below. The criteria for DKA resolution are similar to the American Diabetes Association guideline\textsuperscript{15} criteria.

<table>
<thead>
<tr>
<th>Resolution of DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Base Excess (mmol/L)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
</tr>
</tbody>
</table>

Table 2.4 Criteria for DKA resolution
2.7 Data Management

In order to maintain patient confidentiality, the patients’ names, dates of birth, gender and hospital numbers were collected on a separate list from the data collection sheet (Appendix E). Each patient was allocated a unique patient identification number in the sequence that they were admitted. Only the principal investigator had access to the list linking patients’ names and unique identification numbers.

Data was collected initially on data collection sheets and later transferred to a Microsoft Office Access 2007 database and a Microsoft Excel 2007 spreadsheet. Graphs were generated using Microsoft Office Excel 2007.

2.8 Statistical Analysis

Statistical analysis was performed using Graphpad Instat 3, Graphpad software, San Diego California USA, www.graphpad.com. Interquartile ranges were calculated at http://www.statisticshowto.com/calculators/interquartile-range-calculator/. Continuous data are presented as median values with interquartile ranges and categorical data are described using proportions. Student t-tests for unpaired data were performed to compare medians between groups when the data were normally distributed; Mann-Whitney tests were used when the data were not normally distributed. Fisher’s exact test was used to compare categorical variables between groups. P ≤ 0.05 was considered significant.
CHAPTER 3

3.0 RESULTS

3.1 Study Sample

Between November 2008 and November 2010, 40 patients and 43 episodes of DKA were assessed for eligibility into the study as shown in Figure 3.1. Three patients met the exclusion criteria due to either hyperkalaemia or hyperchloraemia. The final study sample consisted of 22 episodes of DKA where patients received normal saline and 18 episodes of DKA where patients received Ringer’s lactate.

Figure 3.1 Consort diagram
3.2 Patient Demographic Profile

The demographic profile of patients enrolled in the study is summarized in Table 3.1. Males comprised 13 (59.1%) patients in the normal saline group and 9 (50%) patients in the Ringer’s lactate group. The median age of patients in the normal saline group was 24.7 years and that of patients in the Ringer’s lactate group was 31.1 years.

Regarding ethnicity, Blacks comprised 29 (72.5%) patients while 8 (20%) White patients, 2 (5%) Coloured patients and 1 (2.5%) Indian patient made up the remainder of the study sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Saline</th>
<th>Ringer’s Lactate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.7 (19.4 – 36.7)</td>
<td>31.1 (23.9 – 32.8)</td>
<td>0.55</td>
</tr>
<tr>
<td>Male Gender</td>
<td>13 (59.1)</td>
<td>9 (50)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 3.1 Demographic profile of study sample

Data are expressed as number (interquartile range).

3.3 Diabetes Status

As shown in Table 3.2, 7 (31.8%) patients in the normal saline group were newly diagnosed with diabetes when they presented in DKA compared to 3 (16.7%) patients in the Ringer’s lactate group. Nine (60.0%) of the 15 patients known with Type 1 diabetes mellitus in the normal saline group reported that they had been admitted previously with DKA compared to 5 (33.3%) of the 15 patients known with T1DM in the Ringer’s lactate group. The median duration of diabetes of
patients in the normal saline group was 33 months, not statistically different from that of patients in the Ringer’s lactate group which was 33.5 months (p=1.00). Patients in the normal saline arm had a median HbA1c of 13.3% compared to a median HbA1c of 13.5% in the Ringer’s lactate group (p=0.76).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Saline</th>
<th>Ringer’s Lactate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 22</td>
<td>N = 18</td>
<td></td>
</tr>
<tr>
<td>Newly-diagnosed DM</td>
<td>7 (31.8)</td>
<td>3 (16.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Duration of DM (months)</td>
<td>33 (0 – 96)</td>
<td>33.5 (10 – 52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous DKA episodes</td>
<td>9 (40.9)</td>
<td>5 (27.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Number of previous DKA episodes</td>
<td>0 (0 – 3)</td>
<td>0 (0 – 1)</td>
<td>0.53</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>13.3 (10.9 – 17.2)</td>
<td>13.5 (12.1 – 15.2)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 3.2 Diabetes status of study patients

Data are expressed as medians (interquartile ranges) for continuous variables and number (%) for categorical variables.

3.4 Prior Treatment of Diabetes Mellitus

Of the 30 patients enrolled in the study who were known with T1DM, 14 (46.7%) patients were on a basal-bolus insulin regimen, 12 (40%) patients were on a biphasic insulin regimen and 4 (13.3%) patients were on another treatment regimen prior to admission in DKA.
3.5 Anthropometric Measurements

Patients in the normal saline group had a median BMI of 20.6 kg/m$^2$ while patients in the Ringer’s lactate group had a median BMI of 21.2 kg/m$^2$ (p=0.25). There was no significant difference between the median waist circumference of 75 cm in patients in the normal saline group and 80 cm in patients in the Ringer’s lactate group (p=0.17).

3.6 Severity of DKA

Figure 3.2 depicts the severity of DKA in the fluid groups based on the pH on admission. Six (27.3%) patients in the normal saline group and 6 (33.3%) in the Ringer’s lactate group had a mild DKA as defined by an admission pH between 7.25 and 7.30. Twelve (54.5%) patients in the normal saline group and 8 (44%) patients in the Ringer’s lactate group had a moderately severe DKA (pH between 7.00 and 7.24 at admission) while 4 (18.2%) patients the normal saline group and 4 (22.2%) patients in the Ringer’s lactate group had a severe DKA with an admission pH < 7.00. The difference in DKA severity was not significant in the patients who received normal saline versus Ringer’s lactate (p=0.82).
3.7 Precipitants of DKA

Precipitants of DKA in the study group are shown in Figure 3.3. In the normal saline group, the DKA was precipitated by infection in 3 (13.6%) patients compared to 5 (27.8%) patients in the Ringer’s lactate group. In 6 (27.3%) patients and 8 (44.4%) patients in the normal saline and Ringer’s lactate groups respectively, the DKA was precipitated by non-adherence to insulin therapy. In 2 (9.1%) patients in the normal saline group and 1 (5.6%) patient in the Ringer’s lactate group, the DKA episode was precipitated by other causes including an alcoholic binge and cocaine abuse. No obvious precipitant of the DKA was identified in 7 (31.8%) patients in the normal saline group and 1 (5.6%) patient in the Ringer’s lactate group. In 4 (18.2%) patients in
the normal saline group and 3 (16.7%) patients in the Ringer’s lactate group, there were missing data regarding the precipitant of the DKA episode. There was no significant difference (p=0.26) on comparison of the precipitants of DKA in the two fluid groups.

![Bar chart showing DKA precipitants in study patients](image)

**Figure 3.3 DKA precipitants in study patients**

### 3.8 Biochemistry at Admission

The biochemistry at admission in the normal saline and Ringer’s lactate groups is shown in Table 3.3. Acidaemia, hyperglycaemia and a markedly increased anion gap were present in all patients. There were no significant differences in any of the baseline biochemical characteristics except for chloride (p=0.02) which was lower in the normal saline group.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Saline</th>
<th>Ringer’s Lactate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 22</td>
<td>N = 18</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.14 (7.08 – 7.28)</td>
<td>7.18 (7.04 – 7.25)</td>
<td>0.75</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>134 (128.5 – 137)</td>
<td>137.5 (132 – 141.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 (4.2 – 5.1)</td>
<td>4.9 (4.1 – 5.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>96 (87.5 – 98)</td>
<td>98.5 (96.5 – 104)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>4.7 (3.1 – 8)</td>
<td>6.4 (3.7 – 8.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Base Excess (mmol/L)</td>
<td>-21.8 (-24.2 – (-16.3))</td>
<td>-19.1 (-25.4 – (-16.9))</td>
<td>0.80</td>
</tr>
<tr>
<td>Anion Gap* (mmol/L)</td>
<td>30 (23 – 35.5)</td>
<td>29 (25 – 34)</td>
<td>0.69</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>26.7 (21.6 - 35.4)</td>
<td>31.6 (24.1-33.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>127 (99.5 – 220)</td>
<td>120.5 (92.5 – 143.5)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

**Table 3.3 Biochemistry at admission**

Data are expressed as medians (interquartile ranges)

*Anion gap = Na⁺ - (Cl⁻ + HCO3⁻)*

### 3.9 Glasgow Coma Scale (GCS) at Admission

Patients in both the normal saline and Ringer’s lactate groups had a median GCS of 15 (14 -15) at admission.

### 3.10 Volume of initial resuscitation fluid received

Patients in the normal saline group received a median of 2800ml (2000 – 4200ml) of fluid over a median duration of 18.5 hours (9 – 25) compared to a median of 3000ml (2000 – 3000ml) of
fluid in the Ringer’s lactate group over a median duration of 17 hours (10 -24). There was no significant difference in the volume of initial resuscitation fluid received in the two groups (p=0.90).

### 3.11 Primary Outcome

#### 3.11.1 DKA Duration

The median duration of DKA in the normal saline group was 18.5 (9 - 25) hours compared to 17 (10 – 24) hours in the Ringer’s lactate group. There was no significant difference in DKA duration on comparison of the two fluid groups (p = 0.23).

Table 3.4 compares the duration of DKA when categorized into three time intervals. In the normal saline group, 7 (31.8%) patients resolved from DKA in less than twelve hours compared to 6 (33.3%) patients in the Ringer’s lactate group. Nine (40.9%) and 10 (55.6%) patients in the normal saline and Ringer’s lactate groups respectively resolved from DKA within 12 to 24 hours. In 6 (27.3%) patients in the normal saline group and 2 (11.1%) patients in the Ringer’s lactate group, the DKA took in excess of 24 hours to resolve. Comparing the two fluid groups by time category yielded no significant difference in DKA duration (p = 0.42).

<table>
<thead>
<tr>
<th>Duration of DKA by category</th>
<th>Normal Saline</th>
<th>Ringer’s Lactate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 22</td>
<td>N = 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 hours</td>
<td>7 (31.8)</td>
<td>6 (33.3)</td>
<td></td>
</tr>
<tr>
<td>12 – 24 hours</td>
<td>9 (40.9)</td>
<td>10 (55.6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 24 hours</td>
<td>6 (27.3)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.4 Duration of DKA by time categories

Data are expressed as number (%).

3.12 Secondary Outcomes

3.12.1 Biochemical Abnormalities during DKA Treatment

3.12.1.1 Hypernatraemia

Hypernatraemia was defined as any serum sodium level greater than 147mmol/L at any point during treatment. One (5.9%) patient in the normal saline group developed hypernatraemia compared to none in the Ringer’s lactate group (p=1.00).

3.12.1.2 Hyperchloraemia

Worsening hyperchloraemia, defined as a serum chloride level higher than the admission chloride, was a common occurrence and developed in 12 (85.7%) patients who received normal saline compared to 13 (86.7%) patients who received Ringer’s lactate (p=1.00). However, hyperchloraemia, defined as a serum chloride greater than 113mmol/L, developed in 1 (7.1%) patient in the normal saline group during therapy compared to 2 (13.3%) patients in the Ringer’s lactate group (p=1.00).

3.12.1.3 Worsening Acid-base status
Worsening pH was defined as any pH lower than the pH at admission at any point during therapy. Seven (31.8%) patients in the normal saline group had worsening pH compared to 6 (33.3%) patients in the Ringer’s lactate group (p=1.00). Worsening bicarbonate occurred in 4 (18.2%) patients who received normal saline compared to 2 (11.1%) patients who received Ringer’s lactate (p=0.67). A worsened base excess was a feature in 2 (9.1%) patients who received normal saline infusion and 2 (11.1%) patients who received Ringer’s lactate (p=1.00). The anion gap increased during therapy in 2 (15.9%) patients who received normal saline versus 3 (20%) patients who received Ringer’s lactate (p=1.00). There were no significant differences in the occurrence of acid-base abnormalities in the groups who received normal saline compared to Ringer’s lactate.

The data are illustrated in figure 3.4.
3.12.1.4 Hypoglycaemia

Two (9.1%) patients in the normal saline group developed hypoglycaemia (defined as a glucose level lower than 4mmol/L) while being treated for DKA versus none (0%) in the Ringer’s lactate group. The difference in the two fluid groups was non-significant (p=0.49).

3.12.2 Duration of Hospitalization

Patients who received normal saline were hospitalized for a median of 4.5 (3-6) days while patients who received Ringer’s lactate were discharged after 5 (4-5) days. The difference in duration of admission between the two groups was not significant (p=0.825).

3.13 Summary of Results

The median time to resolution of DKA did not differ between the groups of patients who received normal saline and Ringer’s lactate. There were also no significant differences in the incidence of hypernatraemia, hyperchloremia, worsening acidosis or hypoglycaemia between the groups during treatment for DKA. The length of hospitalization did not differ in patients who received normal saline compared to patients who received Ringer’s lactate.
4.0 DISCUSSION

4.1 Discussion of results in relation to other studies

4.1.1 DKA Duration

In the current study, the median duration of DKA in patients who received normal saline was not significantly different to that of patients who received Ringer's lactate.

The time to resolution of DKA in both fluid groups in the current study was longer than that seen in previous studies. In a study comparing the efficacy of human insulin infusions compared to insulin analog infusions in patients with DKA, the time to resolution of DKA was 10.5 ± 6 hours in patients who received a human insulin infusion. The patients in the quoted study had a venous pH of 7.1 ± 0.2 and an anion gap of 22 ± 6 mEq/l at admission, indicating that the severity of DKA was not different from the patients in the current study sample. Another study comparing the efficacy of human insulin infusions compared to subcutaneous insulin aspart boluses in patients with DKA found that the time to resolution of DKA was 11 ± 3 hours in the group that received human insulin infusions. Again, the admission biochemical profile in the study sample was comparable to that in the current study. A possible reason for the longer duration of DKA in both fluid groups in the current study was the slower rate of fluid administration in relation to the rate recommended in other protocols for DKA management. This may have been due to the fact that patients who are nursed in busy casualty departments
or general wards often do not get the fluids as they are prescribed because of a lack of nursing care.

4.1.2 Biochemical Abnormalities

There were no significant differences in the development of biochemical abnormalities during treatment in patients who received normal saline or Ringer’s lactate in the current study.

While the effect of normal saline infusion has been compared to Ringer’s lactate infusion in healthy adults and in various other clinical scenarios including elective gynaecological surgery, elective abdominal aortic aneurysm repair and in renal transplantation, based on a literature search to date, the current study is the only study that compared the use of these intravenous infusion solutions in patients with DKA.

A previous double-blind crossover study comparing the effect of Hartmann’s solution and normal saline on healthy adult volunteers found that all patients developed a significant hyperchloraemia (>106mmol/L) that was sustained for more than 6 hours following the infusion of two litres of normal saline over an hour when compared to volunteers who received the same volume of Hartmann’s solution (p <0.001). Serum bicarbonate remained in the normal range but was significantly lower after normal saline than after Hartmann’s solution (p=0.008). The strong ion difference (SID), calculated by the equation $\text{SID} = [\text{Na}^+] + [K^+] - [\text{Cl}^-]$, decreased significantly in the normal saline group compared to the Hartmann’s solution group (p=0.008). This study did not report on patients’ serum pH.
A study comparing the effects of infusions of normal saline and Hartmann’s solution in patients undergoing elective gynaecological surgery\textsuperscript{19} found that only patients who received normal saline developed a significant acidosis (a pH reduction of 7.41 to 7.28) accompanied by a drop in serum bicarbonate (23.5 to 18.4 mmol/L) and anion gap (16.2 to 11.2 mmol/L) and a rise in serum chloride (104 to 115 mmol/L) within 2 hours of the infusion. Patients received a mean of 6000ml of normal saline over a mean of 135 (SD ± 23) minutes. In this study, the SID was calculated using the equation SID = [Na\textsuperscript{+}] + [K\textsuperscript{+}] – [Cl\textsuperscript{-}] – [lactate]. The decrease in SID was significantly larger in the group that received normal saline.

A double-blind randomized study examining the effects of infusions of either normal saline, Plasmalyte and Ringer’s lactate during kidney transplantation\textsuperscript{45} found that only patients who received normal saline had significant reductions in pH (7.44 to 7.36) and base excess (0.4 to -4.9) but did not develop acidosis. This was attributed to significant increases in serum chloride (104.2 ± 3.2 to 125.4 ± 3.7 mmol/L).

While a significant number of patients who received normal saline and Ringer’s lactate in the current study developed worsening hyperchloraemia, none became acidotic. This may be attributed to the much slower rate of normal saline infusion in the current study compared to the studies described above. In addition, serum urea and electrolytes were only measured 4-hourly in the current study and the transient hyperchloraemia may have been missed.
4.2 Strengths and weaknesses of the current study

4.2.1 Strengths

- First study comparing crystalloid solutions in DKA

  Based on published literature, this is the first study comparing the use of normal saline and Ringer’s lactate as initial resuscitation fluid in patients with DKA.

- The study is inclusive of the various South African ethnic groups

  Few studies have characterized DKA in the South African population. The current study sample includes Black, White, Coloured and Indian patients with Type 1 diabetes mellitus and DKA in South Africa.

4.2.2 Weaknesses and difficulties

- Randomization

  It was difficult to randomize patients to a particular fluid group in this study. The initial plan was to randomize patients to fluid groups by computer-generated selection of numbers as they arrived in casualty. It came to my attention when the study was underway that the casualty officers consulted the endocrine unit regarding patients in DKA only after they had started an intravenous infusion. As a result, for the remainder of the study, casualty officers ‘randomized’ patients to a specific fluid group. Patients continued to receive the same infusion fluid and data were collected as in a prospective observational study.
- Lack of study nurse

The lack of a budget meant that a dedicated study nurse could not be employed to admit patients and perform investigations timeously. The intern and rotating medical registrars who were responsible for admissions as well as ward patients were relied upon to admit and manage patients after hours. As a result, all patients did not always have their investigations at standardized time intervals.

- Sample size

The study sample size was relatively small. A power analysis was not used to calculate the minimum sample size required to detect a difference in biochemical abnormalities before the study commenced.

- Selection bias

Patients in DKA who were admitted to the Intensive Care Unit (ICU) from casualty were not included in this study. Similarly, patients who deteriorated in the endocrine ward and required admission to ICU were withdrawn from the study. Therefore, conclusions regarding this more severely ill subset of patients cannot be drawn. There was no mortality in the patients studied but no conclusions regarding the overall mortality of patients in DKA admitted to Charlotte Maxeke Johannesburg Hospital may be drawn from this study.
• Potassium replacement

It was difficult to accurately determine and quantify potassium replacement from patients’ nursing notes. As a result, it was not possible to compare potassium in the two fluid groups even though the study protocol listed it as one of the outcome measures.

4.3 Interpretation of the study findings

Since neither normal saline nor Ringer’s lactate conferred a benefit in time to resolution of DKA or in the occurrence of biochemical abnormalities, either infusion solution may be safely used as initial fluid resuscitation in DKA.

Although hyperchloraemia occurred frequently in both patients who had received normal saline and Ringer’s lactate, none of the patients developed a hyperchloraemic acidosis at the rate of fluid administration that was used in this study.

4.4 Unanswered Questions

4.4.1 Safety of infusion solutions in patients with baseline electrolyte abnormalities

4.4.1.1 Hyperkalaemia

Patients with hyperkalaemia at admission were excluded from the study because of the potential danger of Ringer’s lactate administration causing further hyperkalaemia.

Furthermore, a limitation of the study was the difficulty in accurately quantifying the potassium replacement received during DKA treatment from patients’ files. As a result,
this study is not able to address the concern of Ringer’s lactate infusion causing hyperkalaemia in patients who present with initial hyperkalaemia in DKA.

4.4.1.2. Hyperchloraemia

Similarly, patients with baseline hyperchloraemia were excluded from the study due to the possibility of normal saline aggravating the hyperchloraemia. This study is unable to determine the safety of normal saline in patients who present with initial hyperchloraemia.

4.4.2. Lactate

Lactate levels were not routinely measured at admission and during treatment for DKA. Therefore this study is unable to assess whether Ringer’s lactate causes hyperlactatemia in patients who receive Ringer’s lactate infusions for the initial treatment of DKA.

4.4.3. Possible danger of hyperchloraemic metabolic acidosis

Since none of the patients in this study developed hyperchloraemic acidosis, the current study is not able to examine the clinical consequences of the development of hyperchloraemic metabolic acidosis as a result of normal saline administration in patients with DKA. Previous studies have attempted to answer this question.

A double-blind study by Waters et al\textsuperscript{20} randomized patients undergoing aortic reconstruction surgery to receive either normal saline or Ringer’s lactate to determine if the metabolic acidosis and changes in serum osmolarity following normal saline infusion influenced patient outcome.
The patients who received normal saline developed a hyperchloraemic acidosis and lower base deficits and required more bicarbonate therapy during the operation to achieve predetermined measurements of base deficit (-5mEq/l). However, the acidosis resulted in no apparent change in outcome in terms of death, post-operative complications, ventilator time nor length of hospital stay.

Scheingraber et al who randomized 24 women to receive either normal saline or Ringer’s lactate during elective gynaecological surgery\textsuperscript{19} found that pH dropped significantly from a mean of 7.41 to 7.28 in the group that received normal saline accompanied by a significant increase in chloride from a mean of 104mmol/L to 115mmol/L. Despite the hyperchloraemic acidosis, the authors concluded that, in the setting that they described, pH values more than 7.20 do not seem to have any major pathophysiologic implications.

Base excess defines the metabolic component of an acid-base disorder. While base excess is the amount of strong acid in millimoles required to titrate 1 litre of arterial blood to a pH of 7.4, the base deficit is the amount of base in millimoles required to do the same. The reference range for base excess is typically -3 to +3; a positive number indicating an excess of base and a negative number indicating a deficit. The trauma literature suggests that base deficit, a measure of the degree and duration of poor perfusion, is an independent predictor of mortality in critically ill patients.\textsuperscript{48} Brill studied 75 trauma patients admitted to a surgical ICU and found, interestingly, that the 37 patients who had a pure hyperchloraemic acidosis had a lower mortality (10.8%) than patients with a base deficit due to a high anion gap acidosis (34.2%)
showing that a hyperchloraemic acidosis doesn’t carry the same poor prognosis as inadequate perfusion.49

To date, there is no direct evidence that hyperchloraemic acidosis from excessive use of normal saline is harmful to patients. Despite the lowered pH and increased chloride, no studies have shown that this impacts on clinical outcome. It is likely that this mild acidosis is well-tolerated in patients.

4.4.4 Treatment of hyperchloraemic acidosis

The question of whether hyperchloraemic acidosis requires any specific treatment remains unanswered. Taylor et al carried out a retrospective chart review in paediatric intensive care units and found a high incidence of hyperchloraemia that coincided with the period of greatest fluid administration in patients treated for DKA. The authors of this study do not advocate a change in established fluid regimens for DKA, but rather the recognition that resolution of acidosis in DKA may be masked by hyperchloraemia. It is suggested that simultaneous measurement of anion gap, base deficit and plasma chloride be performed to overcome this.

Apart from the study comparing the use of normal saline and Ringer’s lactate in gynaecological surgery19 where the authors advised treating hyperchloraemic acidosis to a base excess close to zero, the literature does not suggest that hyperchloraemic acidosis requires any specific treatment. A change of infusion solution to a fluid containing less chloride would be prudent to prevent worsening acidosis.
4.5. Future research

Larger randomized controlled studies are required to address the research gaps identified above.
5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

As Awad points out, the search for a truly physiological crystalloid has been ongoing for 150 years. No intravenous solution in our current armamentarium is ideal. Clinicians should be aware of the constituents of intravenous solutions and should be cognisant of the fact that various crystalloid solutions impact electrolyte and acid-base balance in different ways. While it has been recognized that an ideal crystalloid solution would resemble the electrolyte content of plasma, this solution is not yet a reality. Indeed, “a fresh look at crystalloid formulae is overdue”.

Although some authors are of the opinion that there is no longer any room for the use of ‘unphysiological’ normal saline and discourage its use, saline continues to be widely used. In this study, neither normal saline nor Ringer’s lactate conferred a benefit in time to resolution of DKA or in the occurrence of biochemical abnormalities and suggests that either fluid is suitable for resuscitation in DKA.

5.2 Recommendations

5.2.1 Rate of Fluid administration

The average water loss in a patient with DKA is in the order of 5 to 10 litres or 100 ml/kg. The aim is to replace half of this fluid deficit during the first 12 hours of presentation and the
remainder in the next 12 – 16 hours. The ADA consensus statement advocates initial fluid resuscitation to begin at 15 – 20 ml/kg/hr or 1 – 1.5 litres in the first hour and subsequent fluid resuscitation at a rate of 250 – 500 ml/hr. The patients in this study received considerably less intravenous resuscitation than recommended - a median of 2.8 litres over a median DKA duration of 18.5 hours in the normal saline group and 3 litres over 17 hours in the Ringer’s lactate group. Considering that increased osmolarity impairs insulin action, it is likely that DKA duration would have been reduced with more aggressive fluid resuscitation. This warrants more attention in the future management of patients in DKA at Charlotte Maxeke Johannesburg Academic Hospital.

5.2.2 Recognition of hyperchloraemic acidosis

Hyperchloraemic acidosis secondary to intravenous fluid use is an important condition to detect in patients with DKA. If missed, it may prompt an unnecessary increase in the rate of the offending fluid administration. It should be emphasized to junior staff that rotate through the endocrine ward that recovery from DKA should be monitored not only by means of glucose, base excess and pH but also by measurement of the anion gap. A high anion gap acidosis suggests that the patient is still ketotic and requires further treatment of DKA whereas a normal anion gap acidosis suggests the presence of hyperchloraemic acidosis.

5.2.3 Hyperkalaemia

The current study excluded a patient with initial hyperkalaemia and the study was not able to address the concern that Ringer’s lactate may worsen the hyperkalaemia. Until this question is
answered, it is important to note that if Ringer’s lactate is used in this scenario, close monitoring of serum potassium is prudent.

5.2.4 Guidelines for fluid resuscitation in patients with DKA

Following the outcome of this study, it is recommended that the current guidelines for the management of DKA in adult patients at Charlotte Maxeke Johannesburg Academic Hospital continue to recommend that both normal saline and Ringer’s lactate are appropriate and safe choices for the initial resuscitation of patients in DKA.
REFERENCES


29. Hartman AF, Darrow DC. Chemical changes occurring in the body as the result of certain diseases. III. The composition of the plasma in severe diabetic acidosis and the changes taking place during recovery. *J Clin Invest* 1928;6(2):257-76.


APPENDIX A

ETHICS CLEARANCE CERTIFICATE
APPENDIX B

PATIENT INFORMATION SHEET

My name is Dr Daksha Jivan and I am a consultant at the Johannesburg Hospital in the Division of Endocrinology.

I am currently involved in a research study entitled “A comparison of the use of normal saline versus Ringer’s lactate in the fluid resuscitation of diabetic ketoacidosis”. The purpose of my study is to compare which fluid – Ringer’s lactate or normal saline - is the better drip to use in patients who present, like you, in diabetic ketoacidosis, that is, a coma due to severely high sugar levels.

You may not remember that you were admitted to hospital because you were very ill. I got permission from your family to enrol you in my study and collect your information while you were recovering.

I would now like to request your permission to use the data we have collected on you for the study.

There are 2 different types of intravenous fluids that may be used when patients develop coma due to increased glucose levels – normal saline or Ringer’s lactate. At the moment, either fluid may be used but we are not sure which fluid is the better one to use in this situation. I will be looking at all patients that come to hospital in a diabetic coma. By using computer-generated randomisation, half of these patients will receive normal saline and the other half will receive Ringer’s lactate. We will do blood tests regularly (one to four-hourly) as we would normally do when patients are admitted in a diabetic coma. By comparing the blood results of patients receiving the two different types of fluid while they are recovering from the coma, we hope to find which patients had better outcomes.

If you decide that you would not like to be a part of this study, it will not affect the further medical treatment that you will receive or your future access to health care.

If you decide to participate in this study and agree that I can use your information when writing up my study, you will be asked to sign a consent form to confirm that you understand. Your personal details will always be kept confidential.

If you have any questions, please do not hesitate to ask me.
PATIENT INFORMED CONSENT

- I hereby confirm that the study doctor, Dr D Jivan, has informed me about the clinical study to compare two different intravenous fluids (fluids by drip) used in the treatment of the condition that I presented with (diabetic ketoacidosis).

- I agree that the information collected during my stay in hospital will be kept strictly confidential and may be anonymously used in a study report.

Patient:  
Signature:  
Date and Time:

___________________  _____________  ______________

Doctor:  
Signature:  
Date and Time:

___________________  _____________  ______________

Witness:  
Signature:  
Date and Time:

___________________  _____________  ______________
APPENDIX C

RELATIVE INFORMATION SHEET

My name is Dr Daksha Jivan and I am a consultant at the Johannesburg Hospital in the Division of Endocrinology.

I am currently involved in a research study entitled “A comparison of the use of normal saline versus Ringer’s lactate in the fluid resuscitation of diabetic ketoacidosis”.

I would like to invite your relative to be a part of this study but he/she is too ill to give me permission right now. I would like to request your permission on his/her behalf to enter him/her into the study. The purpose of my study is to compare which fluid – Ringer’s lactate or normal saline - is the better drip to use in patients who present in diabetic ketoacidosis, that is, a coma due to severely high sugar levels.

There are 2 different types of intravenous fluids that may be used when patients develop coma due to increased glucose levels – normal saline or Ringer’s lactate. At the moment, either fluid may be used but we are not sure which fluid is the better one to use in this situation. I will be looking at all patients that come to hospital in a diabetic coma. By using computer-generated randomisation, half of these patients will receive normal saline and the other half will receive Ringer’s lactate. We will do blood tests regularly (one to four-hourly) as we would normally do when patients are admitted in a diabetic coma. By comparing the blood results of patients receiving the two different types of fluid while they are recovering from the coma, we hope to find which patients had better outcomes.

If you decide that your relative should not be a part of this study, it will not affect the further medical treatment that they will receive or their future access to health care. If you wish to withdraw your relative from the study at any time, simply inform me of your decision to do so.

If you agree to your relatives’ participation in this study, you will be asked to sign a consent form.

When your relative recovers enough to understand, I will ask for his/her permission to use the information I have collected in the study. Their personal details will always be kept confidential.

If you have any questions, please do not hesitate to ask me.
RELATIVE INFORMED CONSENT

- I hereby confirm that the study doctor, Dr D Jivan, has informed me about the clinical study to compare two different intravenous fluids (fluids by drip) used in the treatment of diabetic ketoacidosis.

- I agree that the information collected during my relative’s stay in hospital will be kept strictly confidential and may be anonymously used in a study report.

Relative: ____________________________ Signature: ____________________________ Date and Time: ____________________________

Doctor: ____________________________ Signature: ____________________________ Date and Time: ____________________________

Witness: ____________________________ Signature: ____________________________ Date and Time: ____________________________
APPENDIX D

PROTOCOL FOR THE MANAGEMENT OF DKA
# APPENDIX E

## DATA COLLECTION SHEET

<table>
<thead>
<tr>
<th>Date of Admission:</th>
<th>Date of Discharge:</th>
<th>Patient No.:</th>
<th>Fluid:</th>
</tr>
</thead>
<tbody>
<tr>
<td>/ / 200</td>
<td>/ / 200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History:</th>
<th>Duration of DM</th>
<th>Current Meds:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitant of DKA:</td>
<td>Previous DKAs</td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>Y   N</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Y   N</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Y   N</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examination:</th>
<th>Ht - cm</th>
<th>Wt - kg</th>
<th>BMI -</th>
<th>Waist - cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>PR</td>
<td>Temp</td>
<td>GCS</td>
<td></td>
</tr>
<tr>
<td>Neuropathy:</td>
<td>Fundoscopy:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment &amp; Progress:</th>
<th>Other Investigations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(CXR, ECG, CTB, etc)</td>
</tr>
</tbody>
</table>

<p>| Fluids received: | |
|------------------| |</p>
<table>
<thead>
<tr>
<th>DATE:</th>
<th>TIME:</th>
<th>HGT</th>
<th>GCS</th>
<th>Lab Glu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME:</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>CO₂</th>
<th>Urea</th>
<th>Creat</th>
<th>Alb</th>
<th>CCa</th>
<th>Mg</th>
<th>PO₄</th>
<th>WCC</th>
<th>Hb</th>
<th>Plts</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME:</th>
<th>pH</th>
<th>HCO₃</th>
<th>BE</th>
<th>AG</th>
<th>Ketones</th>
<th>HbA1c</th>
<th>Uric acid</th>
<th>Chol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME:</th>
<th>ESR</th>
<th>Lactate</th>
<th>TG</th>
<th>CRP</th>
<th>CK</th>
<th>HDL</th>
<th>LDL</th>
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<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME:</th>
<th>Urine MAC</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
### APPENDIX F

**NATIONAL HEALTH LABORATORY SERVICE**

**CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL**

**NORMAL LABORATORY REFERENCE RANGES**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>136 – 145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.5 – 5.1</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98 – 107</td>
</tr>
<tr>
<td>CO(_2) (mmol/L)</td>
<td>23 – 29</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>2.1 – 7.1</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>49 – 90</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7</td>
</tr>
</tbody>
</table>