

**AUDIT OF DIABETIC
KETOACIDOSIS
MANAGEMENT AT A
TERTIARY HOSPITAL IN
JOHANNESBURG,
SOUTH AFRICA**



UNIVERSITY OF THE
WITWATERSRAND,
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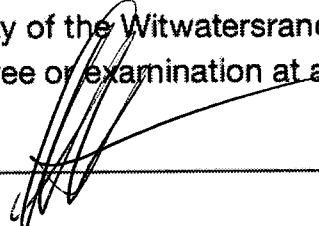
MASTERS OF MEDICINE

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1. ACCEPTANCE LETTER SAMJ

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To: Teresa Sumy Thomas

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Your Submission

30 October 2018 at 11:16

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1. MMED RESEARCH

Audit of Diabetic Ketoacidosis Management at a Tertiary Hospital in Johannesburg, South
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Abstract

Background. Continuous intravenous infusion (CII) of insulin is the preferred method of treating Diabetic Ketoacidosis (DKA) worldwide, especially in patients with severe DKA. There is limited evidence evaluating the low dose bolus intravenous (IV) insulin management of (DKA) out of the intensive care unit (ICU).

Objectives. To conduct an audit on patients admitted with DKA who were managed with IV bolus insulin at Chris Hani Baragwanath Academic Hospital (CHBAH) medical acute care unit (MACU) over a four month period to evaluate if this is an effective treatment modality, as well as assess patient, disease and management characteristics related to their admission.

Methods. A prospective cross-sectional cohort study was done interviewing 69 patients admitted with DKA from 1 September 2017 to 31 December 2017 and collecting relevant biochemical results from their hospital records. The current management protocol at CHBAH was observed, being insulin therapy administered hourly as 10 IU of insulin by the intravenous route. The time to resolution of DKA, complications and deaths were recorded.

Results. Our cohort was predominantly male (60.56%) with an average age of 36 years. (%). All patients were successfully treated with bolus IV insulin with an average time to resolution of 21 hours. DKA was categorised as mild (19.72%), moderate (50.7%) and severe (29.58). Most patients presented with raised inflammatory markers (64.79%) and some degree of renal impairment (>60%). Complications occurred in 9 patients (12.68%), 7 of which were related to the factor precipitating the DKA admission. No deaths occurred. The only factor predicting a longer time to resolution was severity, with an odd's ratio of 4.89 (CI 1.04-22.84, p 0.044).

Conclusion. Outcomes are favourable with IV bolus insulin being used as the treatment modality in patients with mild, moderate and severe DKA at CHBAH. Further studies are needed to corroborate these results in other centres.

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Conflicts of Interest

None.

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Author contributions

ST: Design, data collection, analysis, writing; SB: Conceptualisation of project, review of manuscript. NM: Conceptualisation of project, Review of manuscript

Audit of Diabetic Ketoacidosis Management at a Tertiary Hospital in Johannesburg, South Africa

Introduction

Diabetic ketoacidosis (DKA) is a serious manifestation of uncontrolled blood sugar that can occur in patients with Type 1 or 2 Diabetes Mellitus (DM). There are three cornerstones of therapy: intravenous (IV) fluids, insulin therapy and management of electrolytes. Treatment of DKA has shown many advances over the years. It is now clear that low dose insulin is as effective as high dose insulin in treating DKA, with a reduced rate of hypoglycaemia and hypokalaemia^[1]. It is also known that an initial IV insulin bolus may not be needed in the management of DKA as long as insulin therapy is started promptly at a dose of 0.14 IU/kg/hr^[2-3]. There are several ways to administer insulin therapy that have been evaluated: continuous IV infusion (CII) or bolus IV, subcutaneous (SC) or intramuscular (IM) insulin therapy. It is generally accepted that continuous IV infusion of insulin is the preferred method of treating DKA and has been incorporated worldwide into treatment protocols^[4]. Evidence evaluating different routes of administration of insulin are weak or low quality, and generally are consensus opinion^[5]. High quality randomised control trials (RCT's) are lacking and needed in this regard^[6]. There have only been five RCT's evaluating SC bolus management of DKA compared to CII and have found this to be an acceptable alternative in patients with mild to moderate DKA^[7]. Specifically, there is a paucity of evidence supporting the bolus IV insulin route.

The rationale behind evaluating the bolus insulin management of DKA stems from an anticipated cost and resource benefit in managing patients out of intensive care units (ICU's). CII's require flow regulators and constant monitoring of the infusion, both which are expensive and require a low nurse to patient ratio. With the use of bolus insulin administration, this offers the benefit of not requiring flow regulators which can save costs, and limit constant monitoring of the infusion which would be required in an ICU setting. Blood glucose could be checked hourly when insulin boluses are administered and decrease work load for nursing staff. Despite assumptions that bolus

insulin would result in a rapid peak and effect and subsequent absence of insulin during the remainder of the hour, clinically this does not seem to be so^[8].

The SEMDSA guidelines for the management of DKA released in 2017 state that insulin therapy should ideally be a CII in an ICU setting. Where ICU is not available or delayed, insulin should be administered by hourly IV or IM boluses, in order to decrease the incidence of hypoglycaemia^[9]. Literature to support the IV bolus administration of insulin include small trials done over 40 years ago, as well as the pharmacokinetic properties of insulin administered by different routes^[8,10-13]. These studies are difficult to apply to our current setting as some used much higher doses of insulin each hour and all contained very small sample sizes. This audit aims to fill a gap in literature, especially in the South African setting, where IV bolus low dose insulin can be used to treat patients with mild, moderate and severe DKA safely out of ICU.

Methods

Definitions

Diagnosis of DKA is by American Diabetes Association and SEMDSA guidelines^[9]: pH < 7.3 or bicarbonate < 18 mmol/L and blood ketonaemia. As serum ketones are not readily available, the presence of urine ketones are used as a surrogate marker.

Severity is classified by pH:

Mild: pH 7.25-7.3

Moderate: pH 7-7.24

Severe: pH < 7

Resolution of DKA is classified as resolution of acidosis (pH > 7.3, bicarbonate > 18 mmol/L) and ketonaemia (< 1 mmol/L). Similarly urine ketones (1+ or 0) were used due to resource constraints.

Objectives

The primary objective of this study was to determine if the IV insulin bolus method was effective in treating DKA. Secondly, we evaluated patient, disease and management characteristics in our cohort.

Setting

This audit was done at Chris Hani Baragwanath Academic Hospital (CHBAH), a tertiary hospital in Soweto serving a wide catchment area that is urban, semi-rural and rural. Patients with DKA are initially seen in the Emergency Department, where emergency measures are implemented once DKA is diagnosed (fluid bolus, insulin therapy commenced and correction of electrolyte disturbances). Internal medicine is then consulted and patients are transferred to either the Medical Acute Care Unit (MACU) or ICU as deemed appropriate by the admitting registrar. MACU was established in 2011 as a higher care unit with a nurse: patient ratio of 1:2 to 1:3 where acutely ill non-ventilated patients not can be managed until stable enough for transfer to a general medical ward. It is a 12 bedded unit with a nursing contingent of four to five nurses and covered by one medical registrar supported by his/her medical intern. Patients with DKA are a large portion of the pathology admitted to MACU, with an average of 26.67 patients admitted with DKA per month (See table 1).

Table 1. Number of DKA admissions August 2016 to January 2017	
Month	Number of DKA Admissions
August 2016	24
September 2016	36
October 2016	26
November 2016	27
December 2016	19
January 2017	28

DKA is managed by 10IU IV hourly insulin bolus therapy, with blood gases being done every 2-4 hours until resolution is achieved. Insulin is not administered if there is hypoglycaemia. IV fluids

(crystalloids) are administered and adjusted according to hourly fingerprick glucose readings and electrolytes, as monitored on serial blood gases.

All patients age > 14 years admitted to CHBAH Internal Medicine department with a diagnosis of DKA during the period September to December 2017 were evaluated. Patients diagnosed with Hyperosmolar Hyperglycaemic State (HHS) were not included. In total, 70 patients were willing to participate in the study, and signed individual consent forms. Where a participant was aged 14-17 years, an assent form was signed. One patient was readmitted twice during the study period. All these patients were admitted to the MACU. Three patients relapsed back into DKA after initial resolution and transfer to the general medical wards. These patients were then transferred back to the MACU and time to resolution of the relapsed episode of DKA was recorded.

Demographic data (age, sex) for participants was obtained. Patients were interviewed about their past management of their diabetes; the facility accessed for care, historical DKA rate and recent treatment regimens, where known. Initial biochemical parameters were recorded on first medical contact, often being in the emergency department, prior to the initiation of DKA management. The initial blood glucose reading was ascertained from the first blood gas prior to initiation of DKA treatment. Where this was not calibrated, the finger prick glucose was recorded. The 'On Call Plus' glucometer is in use in MACU, which records blood glucose readings up to 33.3 mmol/L, thereafter recording as 'HI'. For statistical purposes, these readings were excluded from the data set as we could not ascertain the correct value above 33.3 mmol/L. We tried to identify the precipitant where possible as sepsis, non-compliance or other. Patients were asked where they would like to follow up following treatment and this was recorded. Patients were classified as Type 1 or 2 DM based on clinical judgement of the investigator looking at several factors (Previously known, age of onset, BMI, prior antibody testing, acanthosis nigricans or polycystic ovarian syndrome and family history of first degree relatives with DM). HbA1c was included if measured during current admission or if available from LABTRAK within the preceding 3 months. LABTRAK is the only laboratory information system that is utilised by medical staff to access patients results from any government hospital or clinic in South Africa.

Time to resolution of DKA was measured in hours as the time from the start of DKA treatment to cessation of insulin therapy as guided by the above SEMDSA criteria. Any complication or deaths were recorded. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (ref number M170551).

Results

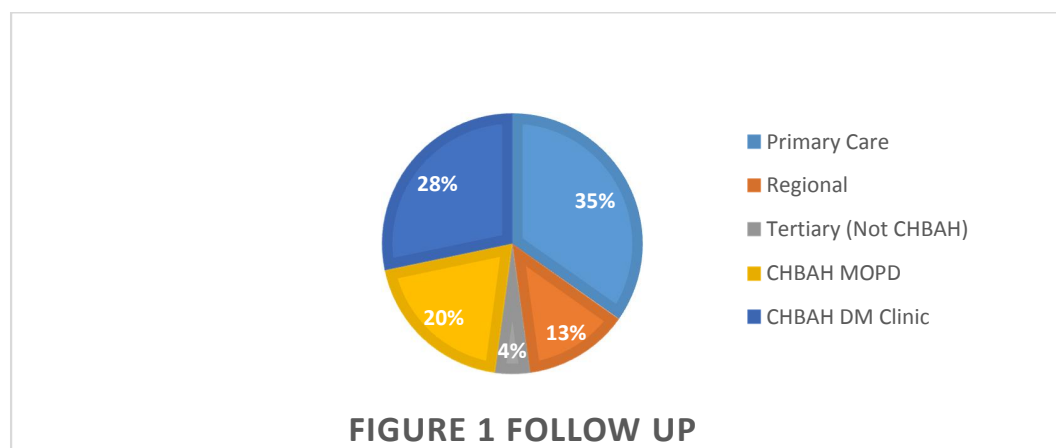
We audited 69 participants in this study during the study period, with 71 admissions. One patient aged 13 years was excluded from the study. The primary outcome was achieved in all participants, being that DKA was resolved in each subject using only insulin in the form of hourly IV boluses. There were no deaths, thus early survival in our cohort was 100%.

The average age of participants was 36 years (range 27 to 52 years old) with 60.56% male. Initial biochemistry is detailed in Table 2.

Table 2. Initial biochemistry pre-treatment		
Result	Mean/Median (IQ range or SD)	Reference range
Glucose	30 mmol/L (24-38.5)	3.6- 11.1 mmol/L
pH	7.14 (6.98-7.25)	7.35-7.45
Bicarbonate	8.6 mmol/L (6.9-13)	21- 28 mmol/L
Base Deficit	-20 mmol/L(13.3-24.5)	-4- 4 mmol/L
Potassium	5.1 mmol/L (1.41)	3.5-5.1 mmol/L
Urea	9 mmol/L (5.2-14.9)	2.1-7.1 mmol/L
Creatinine	118 µmol/L (91-182)	64-104 µmol/L
White cell count (WCC)	12.37 X10 ⁹ /L (8.69-21.06)	3.92-10.4 X10 ⁹ /L

C reactive protein (CRP)	13 mg/mL (4-31)	0-10 mg/mL
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Type 1 and 2 DM comprised 46.48% and 53.52% respectively. 38.03% of patients reported previous admissions of DKA, with an average of 2 episodes per participant within this group. The mean HbA1C measurement was 13.87% (SD 2.5), with values available from 62 participants. Severity was as follows, mild 19.72%, moderate 50.7% and severe 29.58%. The average time to resolution was 21 hours (13.5-29 hours). Excluding severe DKA, mild and moderate DKA had an average time to resolution of 20 hours. There were 32.39% of patients who were newly diagnosed with DM, with this episode of DKA as their index presentation. Of known patients with DM, past follow up for medication and monitoring is depicted in Figure 1. 47.85% of patients were previously following up at CHBAH, with the second largest proportion from primary health care clinics (34.78%). Of the three patients that relapsed with DKA, it took 8, 12 and 24 hours of further DKA treatment for complete resolution. No specific factors were identified to explain why these patients relapsed. One patients was readmitted twice after initial presentation with moderate and severe DKA respectively, non-compliance being the precipitant to each episode of DKA. This patient was extensively counselled and social services was consulted to assist the patient. The HbA1C at his last visit subsequently declined (16.6% to 9.1% measured after 3 months).



Forty nine patients could account for their previous treatment regimens, most being on twice daily insulin (see Figure 2). The majority of patients were issued follow up dates at CHBAH after discharge (74.65%).Precipitants were identified as sepsis (15.71%), non-compliance (47.14%) and

other/unknown (37.14%). Complications occurred in nine patients (12.68%). Most of these were related to initial septic precipitants, being surgical procedures aimed at source control. These included incision and drainage of a thumb abscess, axillary abscess and below knee amputation of a septic diabetic foot. Two patients had upper gastrointestinal bleeds during their admission. One patient who presented with severe DKA and a low Glasgow Coma Scale, developed an aspiration pneumonia which resolved with IV antibiotics. Two patients needed drainage of intraabdominal collections, one being a pigtail of a pyogenic liver abscess and the second a pigtail of a pancreatic pseudocyst. All of these patients recovered and were subsequently discharged from hospital.

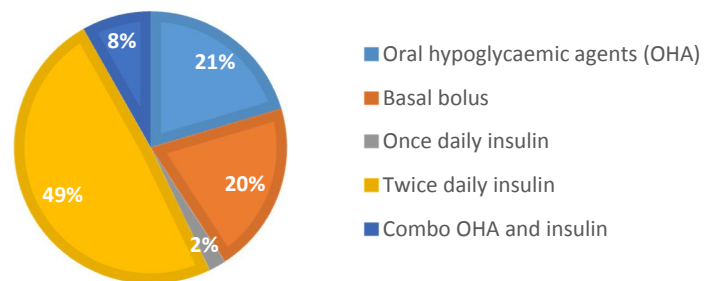


FIGURE 2 PREVIOUS MEDICATION REGIMEN

Time to resolution was divided into less than and greater than 24 hours to determine which factors influenced a longer time to recovery of DKA. This was chosen as the median time was 21 hours, thus it was evaluated which patients took longer than a day (24 hours) to recover. Logistic regression showed an association between only severity of DKA and time to resolution, with an odds ratio of 4.89 (CI 1.04-22.84, p 0.044). No other factors significantly influenced duration of treatment. No correlation was found between the inflammatory markers CRP and WCC, both individually above the normal range in 64.79% of cases despite no identifiable sepsis in the majority of admissions (90.14%), likely elevated as a result of the acidosis. Most patients presented with renal impairment, with urea and creatinine deranged in 60.56% and 64.79% of cases respectively. No patients required dialysis.

Discussion

Managing DKA by IV insulin boluses as opposed to a continuous infusion has been incorporated into protocols in South Africa and overseas, even though the evidence is based on low quality evidence^[8,14]. This audit shows that IV boluses of low dose insulin can be successfully used to treat DKA, regardless of severity. Our primary objective was to prove that this method was effective, and thus there is a need to define what efficacy means in this context. There was no mortality in our cohort, as opposed to other DKA studies done in Africa. South African studies quote a mortality rate of 7.5% and 6.8% over a 2 and 12 month period respectively for hyperglycaemic emergencies (DKA and HHS)^[15,16]. Mortality statistics for the rest of the African subcontinent are estimated at over 25%^[17]. Managing severe DKA with reduced mortality out of ICU would be a great advantage and cost benefit to any hospital.

Time to resolution could be evaluated as a function of efficacy. Our average time to resolution was 21 hours, slightly longer than most other studies, in which different insulin treatment regimens were used. Studies with similar biochemical inclusion criteria showed a mean time to resolution of 17 hours, 18.7 hours and 19.85 hours. CII was employed for the first two studies and subcutaneous bolus injections for the last^[18,19,20]. A Cochrane review evaluating subcutaneous bolus IV insulin reported a time to resolution of 11 hours looking at 5 RCT's^[21]. This study, however, only evaluated participants with mild to moderate DKA. Analysis of our data showed that severe DKA was correlated with a longer time to resolution, and this could be an explanation for the shorter time to resolution observed in the previous study. There are notable differences to our sample for the aforementioned studies, they were performed in first world settings, demographics were different, children were included as participants, insulin analogues were used sometimes as opposed to human insulin and patients were mostly managed in an ICU setting. It is, however, not clear whether time to resolution has any impact on improved clinical outcomes, thus this can't be necessarily used to prove efficacy until further studies are performed^[5].

The number of DKA admissions per month of 26.67 are similar historically to previous studies in South Africa, Groote Schuur Hospital 1991 and CHBAH 1986^[22,23]. Zouvanis et al evaluated severe DKA admissions (pH<7.25 which equates to moderate and severe DKA in our study) at an academic hospital in Johannesburg^[16]. The majority of patients were aged>40 years, as opposed

to our average of 36 years. The proportion of newly diagnosed patients with DM (31%) was similar to our data, as was the portion of type 1: type 2 DM. An identifiable precipitant was present in two thirds of participants in keeping with our data, however with infection being more common than non-compliance. There were no deaths in the DKA group.

The majority of patients in our sample presented with moderate DKA, some degree of renal impairment and a large majority showing an initial potassium reading that was at the upper limit of normal or high (NHLS range 3.5-5.1 mmol/L). This increased potassium does not represent total body potassium, but instead diminished renal tubular secretion, in addition to hydrogen-potassium shifts across the cellular membrane^[24]. Inflammatory markers were raised in the majority of patients, not always correlating with the presence of sepsis. Acidosis was likely the cause of this.^[25]

Low dose insulin given as an IV bolus hourly has been found to be just as effective as pharmacological (high dose) doses in one study with 9 participants^[26]. The main clinical benefit observed is the reduced rates of hypokalaemia and hypoglycaemia. Fisher et al randomised 15 patients each to hourly IV, SC or IM bolus of 7 IU of insulin, observing no difference after 8 hours in rates of decline of glucose or serum ketones^[11]. Similarly Clumeck et al administered low dose insulin at 5 IU IV hourly in 19 patients with DKA^[8]. Once glucose had reached 13.9 mmol/L, insulin was changed to SC six hourly doses, regardless if ketonaemia had resolved. Once again, to highlight, very small numbers were used in these landmark studies.

Insulin given intramuscularly has unpredictable absorption and may accumulate in tissues resulting in delayed hypoglycaemia^[9]. It may also be unacceptable to the patient as injections are painful and need to be administered several times. Umpierrez et al proved that insulin analogues given as a CII or subcutaneously are equally effective compared to regular human insulin, which must be balanced against their increased cost and lesser availability^[27,28]. SC insulin is a reasonable alternative to treat patients with mild to moderate DKA. Human insulin, as used effectively in this

audit, has the advantage over insulin analogues in a lower income country such as South Africa, in that it is readily available and would have a cost advantage.

Limitations

There were several limitations to this study. A large portion of data was self-reported by patients, and this could lead to recall bias. Determination of the type of diabetes did not include Type 3 (pancreatic) DM as this was not evident clearly from patient history, past clinical diagnoses or notes in a lot of cases. CHBAH is a very busy hospital and complete adherence to DKA protocol by doctors and nurses could not be ensured, and perhaps an audit of this is needed. Blood gases were sometimes not done at precise 2-4 hour intervals as recommended and this could affect time to resolution. Excluded blood glucose values, seven out of 71, resulted in a minimally underestimated mean initial blood glucose. DKA was successfully treated in all patients, thus Kaplan-Meier survival analysis could not be performed as stated in the study protocol.

Conclusion

This audit is the first of its kind in South Africa that shows that the IV bolus insulin management of DKA is a safe and feasible way to manage this condition. This method can be used in patients with severe DKA out of ICU. It is effective, in that all patients with DKA resolved and there was no mortality in our cohort. No complications related to bolus insulin administration was observed. A longer time to resolution was observed but this does not necessarily correlate with increased complications or efficacy of the treatment regimen.

This study could serve as a platform to influence other health centres in South Africa to employ this route of insulin administration. Further audits could strengthen evidence for its use. Large RCT's are needed to compare all routes of administration of insulin and provide clear data on the preferred method.

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2. PROTOCOL

AUDIT OF DIABETIC
KETOACIDOSIS MANAGEMENT AT
A TERTIARY HOSPITAL IN
JOHANNESBURG, SOUTH AFRICA

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INTRODUCTION

Diabetes Mellitus (DM) is a complex disease of abnormal carbohydrate metabolism resulting in high blood sugar levels for a prolonged period. It is a growing epidemic worldwide and a topic of extensive and diverse research. It is estimated that 90% of people with diabetes mellitus have type 2 and the remaining 10% consists mainly of type 1 and gestational diabetes (1). Type 1 DM is as a result of pancreatic beta cell destruction, usually autoimmune and hence resultant insulin deficiency(2), whereas type 2 DM is mediated by insulin resistance(1). Both types of diabetes can cause multisystemic complications in the long term. If one manages the disease well, through good lifestyle and pharmacological support, one can delay the onset of complications(1).

Untreated and poorly controlled diabetes, on the other hand can be fatal at times. The World Health Organisation (WHO) estimates diabetes mellitus as one of the top ten causes of death worldwide for the last six years and this is on the increase, with an average of 1.6 million deaths estimated in 2015 compared to one million in the year 2000(3). Glycated haemoglobin (HbA1C) can be measured to give an indication of blood sugar control over the prior three months. The target in newly diagnosed patients with no cardiovascular risk is <7% for good glycaemic control(4). The leading cause of death in diabetes is cardiovascular disease, followed by cerebrovascular disease and renal disease(5). These are long term consequences of poorly managed diabetes.

There are acute and chronic complications of diabetes. Acutely, patients can become unwell and present with an altered mental state caused by uncontrolled (high or low) blood glucose. High glucose may culminate in two serious clinical states, namely diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). DKA is more common than HHS. Both of these present with hyperglycaemia and may present with coma. Although both these conditions present with dehydration and high glucose, there are several differences to distinguish them. DKA presents with acidosis (ketoacids) associated with moderate to severe dehydration, caused by an osmotic diuresis as a result of the high glucose. HHS on the other hand, presents with a much higher glucose values than DKA, but does not have significant acidosis, rather an increase in serum osmolality and profound dehydration. For the purposes of my study, I would like to focus on management of patients with DKA.

Diabetic emergencies do result in a large portion of death worldwide and need to be recognised and treated appropriately. Prevalence data for hyperglycaemic emergencies in South Africa is very scanty. D J Pepper et al estimated an admission rate of 25.6% with a mortality rate of 7.5% in a secondary level hospital in Cape Town(6). Overall mortality is higher in developing compared to developed countries. Death estimates in Tanzania and Kenya are 25 and 33% respectively(7). Thus, effective DKA management has the ability of reducing mortality. In my audit, I would like to evaluate how the hyperglycaemic crisis DKA is managed at Chris Hani Baragwanath Academic Hospital (CHBAH), looking at various parameters in patient management. CHBAH, amongst a few other hospitals in Johannesburg, is unique compared to the majority of hospitals in South Africa, in that we utilise bolus intravenous human insulin to manage patients with DKA in a higher care setting. The rationale behind this regimen is many-fold. Infusion pumps are costly and not readily available. In addition, infusion of fluids and medication out of ICU is via flow regulators that are crude measures of infusion rate, thus not always reliable. These are difficult to monitor adequately in a busy admission unit such as in CHBAH and correct insulin administration cannot be guaranteed. Bolus insulin is a practical alternative for these reasons. My primary objective in this study is to evaluate if this method is effective in the management of DKA.

No such audit has been conducted at CHBAH before. In fact, to my knowledge, there are no published studies worldwide to date evaluating the effectiveness of low dose intravenous (IV) bolus insulin to manage DKA, either independently or compared to subcutaneous or continuous IV insulin. Thus, this audit is necessary in South Africa. Although diabetes is not curable, its complications DKA are both treatable and preventable.

PREVALENCE

In 2016, it was estimated by the World Health Organisation that there are 422 million adults living worldwide with diabetes mellitus. This number is on the increase and expected to double by 2030(8). These are staggering statistics. The greatest increase thus far has been noted in low and middle income countries, South Africa being one of them. This parallels an increase in urbanisation and nutritional shift, with more saturated fats and sugars being consumed. Prevalence statistics are largely guesstimates. South Africa ranks number 91 in global prevalence trends in 2016 for diabetes mellitus(9).

The latest data from the International Diabetes Federation suggests that 7% of our population are living with diabetes; which equates to 3.85 million South Africans in 2015(10). This is in contrast to a figure of 4.5% released in 2010(10); thus a greater than 150% increase. There remains a significant portion who are undiagnosed and a large number of these patients, may presents with hyperglycaemic crises (DKA and HHS).

It is estimated that 60-80% of South African patients with diabetes mellitus die before the age of 60(10). Leading causes of death in adults with diabetes include ischaemic heart disease, cerebrovascular disease and chronic kidney disease as stated earlier, whereas DKA is the leading

cause of death in children, adolescents and young adults less than 24 years of age(11). It is estimated that half of deaths from DKA occur in patients who are newly diagnosed with the disease. Prompt and effective recognition and management of DKA and HHS has the potential of altering mortality greatly. At CHBAH, initial treatment is often started in an emergency/casualty setting and patients are subsequently referred to the Internal Medicine Department for ongoing management and monitoring. This is done preferably in a high care setting.

CHBAH is the third largest hospital in the world(12). Large numbers of patients with DKA are admitted monthly to CHBH. This is a table depicting the amount of patients admitted over a recent six month period:

MONTH	NO OF DKA ADMISSIONS
AUGUST 2016	24
SEPTEMBER 2016	36
OCTOBER 2016	26
NOVEMBER 2016	27
DECEMBER 2016	19
JANUARY 2017	28

BACKGROUND AND REASON FOR STUDY

As mentioned earlier, diabetic emergencies consist of hyperglycaemic crises and hypoglycaemia. Hyperglycaemic crises are sub-classified biochemically as either DKA or HHS, usually but not exclusively occurring with type 1 and 2 diabetes respectively. Both require fluids and insulin as the backbone of treatment and can be successfully treated within hours or days depending on the severity at presentation. DKA can be briefly defined as a serious metabolic derangement characterised by hyperglycaemia, acidosis and ketonaemia that is potentially life threatening. DKA can be classified as mild, moderate or severe by the pH 7.25-7.3, 7-7.24 and <7 respectively. DKA is said to be resolved when the ketoacidosis has improved, this is indicated by a pH>7.3 and bicarb>15.(13)

For the purpose of my study, I will be looking at patients with DKA alone. I would like to embark on this audit of DKA's managed at CHBH, looking at admissions to the wards and high care area (named 'MACU'- Medical Acute Care Unit at CHBAH) as a checkpoint of our care of this emergency and to evaluate if the bolus IV insulin method is effective to treat DKA, while at the same time evaluating patient and disease factors. These factors include demographics, laboratory investigations, precipitants leading to admission, complications and success of treatment including duration of DKA, length of hospital stay, and length of high care stay.

There are three main endpoints in DKA management i.e. insulin administration, fluid management and electrolyte replacement. Traditionally insulin has been given as a continuous IV infusion (recommended at 0.14units/kg/hour by SEMDSA)(13). There is much research to support the continuous infusion and it is established as a successful form of treatment. In 1976, Kitabchi et al performed a randomised controlled trial establishing that a low dose continuous insulin infusion was effective in treating DKA compared to high dose insulin, with less side effects (hypoglycaemia and hypokalaemia)(14). Many studies have since reproduced this result.(15, 16)

Newer studies are emerging evaluating whether bolus insulin given subcutaneously or intramuscularly is just as effective. The American diabetes association published a study in 2004 comparing bolus subcutaneous insulin to continuous IV infusion(17) No difference in outcome

was found between the two and it was concluded that subcutaneous insulin is a safe alternative to the conventional infusion method. Similarly Ersoz H.O et al and George A Edwards et al found similar results(18, 19) There are no studies available, to my knowledge, evaluating the efficacy of bolus IV insulin compared to subcutaneous or continuous infusion routes.

The SEMDSA 2012 guidelines for diabetes management recommend ten units hourly IV boluses for the management of DKA(13). This is based on the above stated hourly rate calculated for a 70 kilogram patient. This recommendation is largely extrapolated from the known physiological effects of insulin and research in this regard is largely lacking.

Concerns regarding hourly IV bolus of insulin include the rapid peak and short half life of intravenous short acting insulin. There is an almost immediate peak following administration and thereafter a rapid decline. The half life of insulin is about 10-12 minutes. This could mean that in the hourly IV bolus management of DKA, insulin is only active for the first quarter of the hour after the bolus is given. Our experience in treating patients with DKA does not show this. Plasma half life does not equate to physiological effect. One of the main outcomes in this study is to document this and show the effectiveness of IV bolus insulin in treating DKA.

There are currently no published studies comparing IV bolus insulin to subcutaneous or continuous IV insulin infusion, and no studies proving that IV bolus insulin is effective in the management of DKA, despite national recommendations. Several studies have compared subcutaneous bolus insulin to continuous infusion and have shown no difference in effect and no serious added side effects or mortality. All of these studies have included less than 50 study participants (45, 20, 36, 20 respectively)(17, 18, 20, 21) with mild to moderate DKA. Severe DKA managed in an intensive care setting have been excluded from the studies. A Cochrane review in 2016 evaluated these studies and considered them low quality evidence as the total number of studies were few, and they all had small number of study participants(22). Good quality data is needed to show that intravenous bolus insulin is effective.

Bolus insulin is theoretically more cost effective as no infusion pumps are needed and patients can be safely managed out of ICU setting, and this is more pertinent in resource poor settings where both infusion pumps and ICU are not available. In addition, intravenous insulin offers the potential advantage of less pain and discomfort for the patients of hourly intramuscular injections. In a

patient managed with subcutaneous bolus therapy, IV access would have already been established for fluids, therefore no additional costs are incurred when embarking on this method.

I would like to evaluate patient knowledge of their medication, type of treatment and to ascertain the patients' primary care facility. These parameters may well be a target to decrease admissions with DKA.

This will be a benchmark study that can be expanded upon at a later stage to increase the number of patients evaluated. In this way, we can evaluate if we fall in line with global standards of DKA care.

OBJECTIVES

The main objective of this prospective analysis is to evaluate if the IV bolus insulin management is effective in treating DKA in a South African population at CHBAH.

The secondary parameters I would like to evaluate are:

1. Patient demographics (age, sex)
2. Type of diabetes (1,2)
3. Recent HbA1c (if known)
4. Historical DKA readmission rate
5. Admission laboratory parameters (glucose, bicarbonate, pH, base excess, urea, creatinine, white cell count, C reactive protein)
6. Severity (mild/moderate/severe)
7. Time to resolution of DKA
8. Level of outpatient care prior to admission (i.e. primary/regional/tertiary)
9. If known to CHBAH diabetic clinic
10. Precipitants (if established)
11. Newly diagnosed/ known diabetes mellitus

12. Patient knowledge of prior pharmacological management (By regimen- basal bolus, once daily, twice daily or combination of insulin and oral therapy)

13. Deaths

(Please see attached data collection sheet.

STUDY DESIGN

DKA is defined by the American Diabetic Association (ADA) as a triad of hyperglycaemia, acidosis and ketonaemia, these figures being $\text{pH} < 7.3$, $\text{bicarb} < 18$ and serum ketones positive (betahydroxybutyrate). The current CHBAH DKA protocol for insulin therapy includes the following(23):

1. Administer insulin only after potassium is known to be above 3.5mmol/l
2. 10 units insulin stat, then 5-10 units/hour as intravenous boluses.
3. Aim to reduce glucose by 5mmol/l per hour, the dose of insulin can be doubled to achieve this

Thus my inclusion criteria would be patients meeting the above definition, with ketones measured by urine dipstick as serum ketone measurement is not readily available. I am only including patients admitted to ward 20 (admission ward) or MACU. Adult and adolescent patients above the age of 14 are included in keeping with the age managed by internal medicine at CHBAH.

Exclusion criteria include patient managed by subcutaneous or continuous insulin infusion for any reason, as well as those managed outside ward 20 or MACU.

I wish to collect data over a four month period (August to November 2017) and aim for at least 50 patients. Data will be collected from patient records i.e. patient file, outpatient card and MACU high care flow sheet and additional information needed will be obtained by interviewing the patient or relatives.

Time to resolution of DKA will be from the time DKA protocol is initiated until the following parameters are achieved (pH >7.3 and bicarb>15) with cessation of the bolus intravenous insulin. Treatment will be deemed effective if the above criteria are achieved.

The type of diabetes will be established by looking at various factors including age of onset, BMI, presence or absence of acanthosis nigricans and polycystic ovarian syndrome suggesting insulin resistance, if antibody testing for autoimmunity has been done, family history of diabetes in first degree relatives and presence of other autoimmune disease. All this information shall be put together and the patient will be categorised as Type 1 or 2 as best as possible clinically. This is not a precise scientific method, however it reflects how diabetes is often classified in clinical practice, especially when specific tests such as antibody testing are not readily available.**Statistical analysis**Frequencies will be determined for categorical variables (e.g disease severity) whereas descriptive statistics such as median and interquartile ranges will be determined for continuous measures (e.g investigation tests). The proportion of patients presenting with DKA will be determined as well as the number resolving. Time to resolution of DKA will be determined using the Kaplan-Meier logrank test (stratified by socio-demographic measures). Factors associated with DKA resolution will be determined through logistic regression where independent covariates will include socio-demographic variables and clinical measures. All statistical analysis will be performed in STATA 14.

ETHICAL CONCERNS AND POTENTIAL PROBLEMS

The current standard of care is being evaluated and no additional intervention is performed on patients, thus no ethical concerns are anticipated. Patients' personal details including names and contact details shall not appear in the study. An informed consent form will be signed by each participant to have their medical information included in the study. Should a patient be too ill to sign consent, a family member will be able to sign on his/her behalf.

Potential problems include poor note keeping by attending physicians and nursing staff; limiting the data collected. I will attempt to curtail this by collecting additional history myself. Patients will

remain in the general medical wards for at least a day after discharge from MACU, thus even if I am not at hospital on the weekends, information can still be collected retrospectively a day or two later.

Collecting information about previous DKA episodes may be limited as this relies on a patient's memory, as well as their understanding of what DKA is. If hospital records are available i.e. notes in the outpatient card regarding previous DKA admissions, this will be a concrete way of obtaining this information. The diabetic educators have been recording every diabetic admission over the last 20 years, so this may improve the efficacy of the previous admission data.

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APPENDIX

1. Data collection sheet
2. Consent form

3.1 DATA COLLECTION SHEET

[illegible][illegible]

3.2 INFORMED CONSENT

PARTICIPANT INFORMATION DOCUMENT

Study title: AUDIT OF DIABETIC KETOACIDOSIS MANAGEMENT AT A TERTIARY HOSPITAL IN JOHANNESBURG, SOUTH AFRICA

GOOD DAY

My name is Dr Teresa Sumy Thomas and I am doing research on diabetes. This is in fulfilment of my Master's degree in the field of Internal Medicine. I want to study the complications of diabetes, specifically when very high sugar levels lead to increased acid levels in the body (diabetic ketoacidosis). I am trying to evaluate how best to treat this condition.

I am inviting you/ your child to participate in this study.

I would like to ask you questions about your diabetes- how it was treated before, why you have come to hospital now and also to see how your current condition is being treated in hospital. I will do this by looking at your blood results including sugar levels. This will give us information about whether you are getting better, as well as what has caused this complication. I ask that you try answer these questions as honestly as possible. This will take about 20-30 minutes. I will not disrupt your care in hospital in any way. You will be involved in the study until your current complication has improved.

Risks: There are no risks in being involved in this research.

Benefits: You will not directly benefit from the study, however this is an important way to help medical professionals understand the treatment of diabetes and help you and other patients with diabetes feel better.

This study will run over a four month period from September to December 2017.

Participation is voluntary. You will not be penalized and your care will not be affected if you choose not to participate in the research. You can at any time choose to withdraw your participation, with no penalties or risks.

If you are admitted to ICU, you will no longer be able to participate in the research.

If you are too ill to sign a consent form initially, a first degree relative is allowed to consent on your behalf. Once you are well enough, you can choose to continue or discontinue your involvement in the study.

For patients aged 14-17 years, a parent/guardian may consent on your behalf.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the WITS Human Research Ethics Committee (Medical).

If results are published, may lead to individual / cohort identification.

If you have any questions about this study please contact –
Dr Teressa Sumy Thomas 0119330000

If you have any complaints about this study please contact–

Zanele Ndlovu 0117171252 (Administrator of WITS Human Research Ethics Committee-Medical)

Prof Cleaton-Jones 0117172301 (Chairperson of WITS Human Research Ethics Committee-Medical)

Informed Consent

TITLE OF THE RESEARCH PROJECT: AUDIT OF DIABETIC KETOACIDOSIS
MANAGEMENT AT A TERTIARY HOSPITAL IN JOHANNESBURG, SOUTH AFRICA

Declaration by participant

By signing below, I agree to take part in this research study

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

Signed at (*place*) on (*date*) 2017.

.....
Signature of participant

.....
Signature of witness

Declaration by investigator

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above

- I did/did not use an interpreter. *(If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) on (*date*) 2017.

.....
Signature of investigator

.....
Signature of witness

Declaration by interpreter

I (*name*) declare that:

- I assisted the investigator (*name*) to explain the information in this document to (*name of participant*) using the language medium of.....
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) on (*date*)

.....
Signature of interpreter

.....
Signature of witness

ASSENT FORM

Good day

Project Title: **AUDIT OF DIABETIC KETOACIDOSIS MANAGEMENT AT A TERTIARY HOSPITAL IN JOHANNESBURG, SOUTH AFRICA**

My name is Dr Teressa Sumy Thomas. I am doing some research on Diabetes and would like you to be involved in this research.

I am doing a research study about Diabetes and what the best way is to manage diabetes when it becomes complicated by a very high blood sugar. A research study is a way to learn more about diseases. If you decide that you want to be part of this study, you will be asked to answer a few questions about your diabetes and how it has been managed so far.

There are some things about this study you should know. I am collecting information about your stay in hospital and how the doctors are managing you while you are sick. You have come into hospital with a very high blood sugar and it has affected your body by causing an increased amount of acid (diabetic ketoacidosis). I would like to monitor how long it takes to treat this high acid level and look at your blood results to see how else this high sugar has affected you.

Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. You will not directly benefit from this research, but this information will help us to better treat many you and many other children and adults that have a similar problem to you.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents/guardians know about the study too.

If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

(Sign your name here)

(Date)

(Name of researcher)

(Date)

4. PLAGIARISM DECLARATION



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Dr Sumy Thomas _____ (Student number: 0501135E _____)
am a student registered for the degree of _____ Internal Medicine (FCP)/ MMED _____
in the academic year 2019

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____

A handwritten signature in black ink, appearing to read 'Sumy Thomas', written over a horizontal line.

Date: 18/03/2019

5. TURNITIN ASSESSMENTS

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by Denise Nicholson

Submission date: 25-Jul-2018 08:11AM (UTC+0200)

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File name: 4c-b939-4350-8225-7a158756d54e_Sumy_DKA_write_up_-_turnitin.docx
(72.35K) **Word count:** 3081

Character count: 16532

Audit of Diabetic Ketoacidosis Management at a Tertiary Hospital in Johannesburg, South Africa

Introduction

Diabetic ketoacidosis (DKA) is a serious manifestation of uncontrolled blood sugar that can occur in type 1 or 2 diabetes mellitus (DM). There are three cornerstones of therapy: intravenous (IV) fluids, insulin therapy and management of electrolytes. Treatment of DKA has shown many advances over the years. It is now clear that low dose insulin is as effective as high dose insulin in treating DKA, with a reduced rate of hypoglycaemia and hypokalaemia^[1]. It is also known that an initial IV insulin bolus may not be needed in the management of DKA as long as insulin therapy is started promptly at a dose of 0.14 IU/kg/hr^[2-3]. There are several ways to administer insulin therapy that have been evaluated: continuous IV infusion (CII) or bolus IV, subcutaneous (SC) or intramuscular (IM) insulin therapy. It is generally accepted that continuous IV infusion of insulin is the preferred method of treating DKA and has been incorporated worldwide into treatment protocols^[4]. Evidence evaluating different routes of administration of insulin are weak or low quality, and generally are consensus opinion^[5]. High quality randomised control trials (RCT's) are lacking and needed in this regard^[6]. There have only been five RCT's evaluating SC bolus management of DKA compared to CII and have found this to be an acceptable alternative in patients with mild to moderate DKA^[7]. Specifically, there is a paucity of evidence supporting the bolus IV insulin route.

The rationale behind evaluating the bolus insulin management of DKA stems from an anticipated cost and resource benefit in managing patients out of intensive care units (ICU's). CII's require flow regulators and constant monitoring of the infusion, both which are expensive and require a low nurse to patient ratio. With the use of bolus insulin administration, this offers the benefit of not requiring flow regulators which can save costs, and limit constant monitoring of the infusion which would be required in an ICU setting. Blood glucose could be checked hourly when insulin boluses are administered and decrease work load for nursing staff. Despite assumptions that bolus insulin would result in a rapid peak and effect and subsequent absence of insulin during the remainder of the hour, clinically this does not seem to be so^[8].

The SEMDSA guidelines for the management of DKA released in 2017 state that insulin therapy should ideally be a CII in an ICU setting. Where ICU is not available or delayed, insulin should be administered by hourly IV or IM boluses, in order to decrease the incidence of hypoglycaemia^[9]. Literature to support the IV bolus administration of insulin include small trials done over 40 years ago, as well as the pharmacokinetic properties of insulin administered by different routes^[8,10-13]. These studies are difficult to apply to our current setting as some used much higher doses of insulin each hour and all contained very small sample sizes. This audit aims to fill a gap in literature, especially in the South African setting, where IV bolus low dose insulin can be used to treat patients with mild, moderate and severe DKA safely out of ICU.

Methods

Definitions

Diagnosis of DKA is by American Diabetes Association and SEMDSA guidelines^[9]: pH < 7.3 or bicarbonate < 18 mmol/L and blood ketonaemia. As serum ketones are not readily available, the presence of urine ketones are used as a surrogate marker.

Severity is classified by pH:

1 Mild: pH 7.25-7.3

Moderate: pH 7-7.24

2 : pH < 7

6 Resolution of DKA is classified as resolution of acidosis (pH > 7.3, bicarbonate > 18 mmol/L) and ketonaemia (< 1 mmol/L). Similarly urine ketones (1+ or 0) were used due to resource constraints.

4 The primary objective of this study was to determine if the IV insulin bolus method was effective in treating DKA. Secondly, we evaluated patient, disease and management characteristics in our cohort.

Setting

This audit was done at Chris Hani Baragwanath Academic Hospital (CHBAH), a tertiary hospital in Soweto serving a wide catchment area that is urban, semi-rural and rural. Patients with DKA are initially seen in the Emergency Department, where emergency measures are implemented once DKA is diagnosed (fluid bolus, insulin therapy commenced and correction of electrolyte disturbances). Internal medicine is then consulted and patients are transferred to either the Medical Acute Care Unit (MACU) or ICU as deemed appropriate by the admitting registrar. MACU was established in 2011 as a higher care unit with a nurse: patient ratio of 1:2 to 1:3 where acutely ill non-ventilated patients not can be managed until stable enough for transfer to a general medical ward. It is a 12 bedded unit with a nursing contingent of four to five nurses and covered by one medical registrar supported by his/her medical intern. Patients with DKA are a large portion of the pathology admitted to MACU, with an average of 26.67 patients admitted with DKA per month (See table 1).

Table 1. Number of DKA admissions August 2016 to January 2017	
Month	Number of DKA Admissions
August 2016	24
September 2016	36
October 2016	26
November 2016	27
December 2016	19
January 2017	28

DKA is managed by 10IU IV hourly insulin bolus therapy, with blood gases being done every 2-4 hours until resolution is achieved. Insulin is not administered if there is

hypoglycaemia. IV fluids (crystalloids) are administered and adjusted according to hourly fingerprick glucose readings and electrolytes, as monitored on serial blood gases.

All patients age > 14 years admitted to CHBAH Internal Medicine department with a diagnosis of DKA during the period September to December 2017 were evaluated. Patients diagnosed with Hyperosmolar Hyperglycaemic State (HHS) were not included. In total, 70 patients were willing to participate in the study, and signed individual consent forms. Where a participant was aged 14-17 years, an assent form was signed. One patient was readmitted twice during the study period. All these patients were admitted to the MACU. Three patients relapsed back into DKA after initial resolution and transfer to the general medical wards. These patients were then transferred back to the MACU and time to resolution of the relapsed episode of DKA was recorded.

Demographic data (age, sex) for participants was obtained. Patients were interviewed about their past management of their diabetes; the facility accessed for care, historical DKA rate and recent treatment regimens, where known. Initial biochemical parameters were recorded on first medical contact, often being in the emergency department, prior to the initiation of DKA management. The initial blood glucose reading was ascertained from the first blood gas prior to initiation of DKA treatment. Where this was not calibrated, the finger prick glucose was recorded. The 'On Call Plus' glucometer is in use in MACU, which records blood glucose readings up to 33.3 mmol/L, thereafter recording as 'HI'. For statistical purposes, these readings were excluded from the data set as we could not ascertain the correct value above 33.3 mmol/L. We tried to identify the precipitant where possible as sepsis, non-compliance or other. Patients were asked where they would like to follow up following treatment and this was recorded. Patients were classified as Type 1 or 2 DM based on clinical judgement of the investigator looking at several factors (Previously known, age of onset, BMI, prior antibody testing, acanthosis nigricans or polycystic ovarian syndrome and family history of first degree relatives with DM). HbA1c was included if measured during current admission or if available from LABTRAK within the preceding 3 months. LABTRAK is the only laboratory information system that is utilised by medical staff to access patients results from any government hospital or clinic in South Africa.

Time to resolution of DKA was measured in hours as the time from the start of DKA treatment to cessation of insulin therapy as guided by the above SEMDSA criteria. Any complication or deaths were recorded. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (ref number M170551).

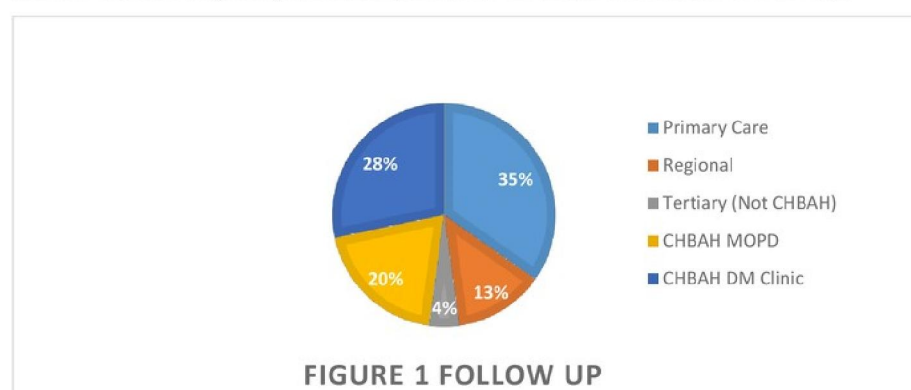
Results

We audited 69 participants in this study during the study period, with 71 admissions. One patient aged 13 years was excluded from the study. The primary outcome was achieved in all participants, being that DKA was resolved in each subject using only insulin in the form of hourly IV boluses. There were no deaths, thus early survival in our cohort was 100%.

The average age of participants was 36 years (range 27 to 52 years old) with 60.56% male. Initial biochemistry is detailed in Table 2.

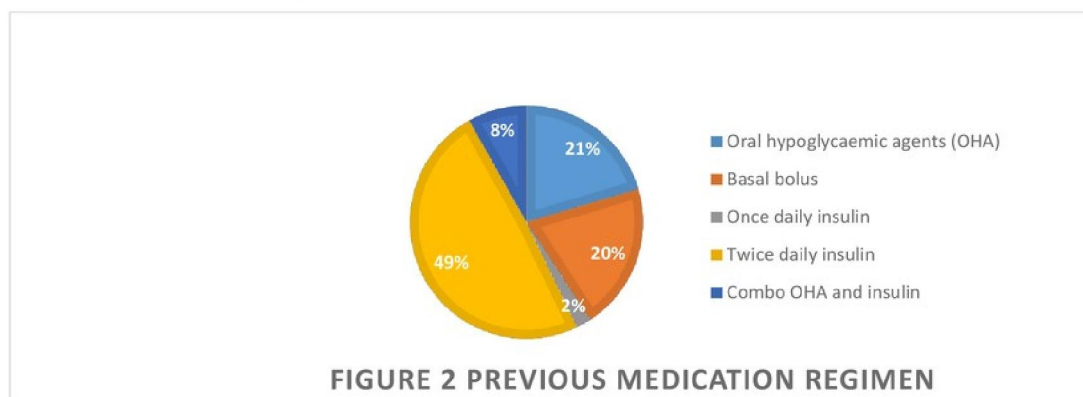
Table 2. Initial biochemistry pre-treatment		
Result	Mean/Median (IQ range or SD)	Reference range
Glucose	30 mmol/L (24-38.5)	3.6- 11.1 mmol/L
pH	7.14 (6.98-7.25)	7.35-7.45
Bicarbonate	8.6 mmol/L (6.9-13)	21- 28 mmol/L
Base Deficit	-20 mmol/L(13.3-24.5)	-4-6 mmol/L
Potassium	5.1 mmol/L (1.41)	3.5-5.1 mmol/L
Urea	9 mmol/L (5.2-14.9)	2.1-7.1 mmol/L
Creatinine	118 µmol/L (91-182)	64-104 µmol/L
White cell count (WCC)	12.37 X10 ⁹ /L (8.69-21.06)	3.92-10.4 X10 ⁹ /L
C reactive protein (CRP)	13 mg/mL (4-31)	0-10 mg/mL

Type 1 and 2 DM comprised 46.48% and 53.52% respectively. 38.03% of patients reported previous admissions of DKA, with an average of 2 episodes per participant within this group. The mean HbA1C measurement was 13.87% (SD 2.5), with values available from 62 participants. Severity was as follows, mild 19.72%, moderate 50.7% and severe 29.58%. The average time to resolution was 21 hours (13.5-29 hours). Excluding severe DKA, mild and moderate DKA had an average time to resolution of 20 hours. There were 32.39% of patients who were newly diagnosed with DM, with this episode of DKA as their index presentation. Of known patients with DM, past follow up for medication and monitoring is depicted in Figure 1. 47.85% of patients were previously following up at CHBAH, with the second largest proportion from primary health care clinics (34.78%). Of the three patients that relapsed with DKA, it took 8, 12 and 24 hours of further DKA treatment for complete resolution. No specific factors were identified to explain why these patients relapsed. One patient was readmitted twice after initial presentation with moderate and severe DKA respectively, non-compliance being the precipitant to each episode of DKA. This patient was extensively counselled and social services was consulted to assist the patient. The HbA1C at his last visit subsequently declined (16.6% to 9.1% measured after 3 months).



Forty nine patients could account for their previous treatment regimens, most being on twice daily insulin (see Figure 2). The majority of patients were issued follow up dates at CHBAH

after discharge (74.65%). Precipitants were identified as sepsis (15.71%), non-compliance (47.14%) and other/unknown (37.14%). Complications occurred in nine patients (12.68%). Most of these were related to initial septic precipitants, being surgical procedures aimed at source control. These included incision and drainage of a thumb abscess, axillary abscess and below knee amputation of a septic diabetic foot. Two patients had upper gastrointestinal bleeds during their admission. One patient who presented with severe DKA and a low Glasgow Coma Scale, developed an aspiration pneumonia which resolved with IV antibiotics. Two patients needed drainage of intraabdominal collections, one being a pigtail of a pyogenic liver abscess and the second a pigtail of a pancreatic pseudocyst. All of these patients recovered and were subsequently discharged from hospital.



Time to resolution was divided into less than and greater than 24 hours to determine which factors influenced a longer time to recovery of DKA. This was chosen as the median time was 21 hours, thus it was evaluated which patients took longer than a day (24 hours) to recover. Logistic regression showed an association between only severity of DKA and time to resolution, with an odds ratio of 4.89 (CI 1.04-22.84, p 0.044). No other factors significantly influenced duration of treatment. No correlation was found between the inflammatory markers CRP and WCC, both individually above the normal range in 64.79% of cases despite no identifiable sepsis in the majority of admissions (90.14%), likely elevated as a result of the acidosis. Most patients presented with renal impairment, with urea and creatinine deranged in 60.56% and 64.79% of cases respectively. No patients required dialysis.

Discussion

Managing DKA by IV insulin boluses as opposed to a continuous infusion has been incorporated into protocols in South Africa and overseas, even though the evidence is based on low quality evidence^[8,14]. This audit shows that IV boluses of low dose insulin can be successfully used to treat DKA, regardless of severity. Our primary objective was to prove that this method was effective, and thus there is a need to define what efficacy means in this context. There was no mortality in our cohort, as opposed to other DKA studies done in Africa. South African studies quote a mortality rate of 7.5% and 6.8% over a 2 and 12 month period respectively for hyperglycaemic emergencies (DKA and HHS)^[15,16]. Mortality statistics for the rest of the African subcontinent are estimated at over 25%^[17]. Managing severe DKA with reduced mortality out of ICU would be a great advantage and cost benefit to any hospital.

Time to resolution could be evaluated as a function of efficacy. Our average time to resolution was 21 hours, slightly longer than most other studies, in which different insulin treatment regimens were used. Studies with similar biochemical inclusion criteria showed a mean time to resolution of 17 hours, 18.7 hours and 19.85 hours. CII was employed for the first two studies and subcutaneous bolus injections for the last^[18,19,20]. A Cochrane review evaluating subcutaneous bolus IV insulin reported a time to resolution of 11 hours looking at 5 RCT's^[21]. This study, however, only evaluated participants with mild to moderate DKA. Analysis of our data showed that severe DKA was correlated with a longer time to resolution, and this could be an explanation for the shorter time to resolution observed in the previous study. There are notable differences to our sample for the aforementioned studies, they were performed in first world settings, demographics were different, children were included as participants, insulin analogues were used sometimes as opposed to human insulin and patients were mostly managed in an ICU setting. It is, however, not clear whether time to resolution has any impact on improved clinical outcomes, thus this can't be necessarily used to prove efficacy until further studies are performed^[5].

The number of DKA admissions per month of 26.67 are similar historically to previous studies in South Africa, Groote Schuur Hospital 1991 and CHBAH 1986^[22,23]. Zouvanis et al evaluated severe DKA admissions (pH<7.25 which equates to moderate and severe DKA in our study) at an academic hospital in Johannesburg^[16]. The majority of patients were aged>40 years, as opposed to our average of 36 years. The proportion of newly diagnosed patients with DM (31%) was similar to our data, as was the portion of type 1: type 2 DM. An identifiable precipitant was present in two thirds of participants in keeping with our data, however with infection being more common than non-compliance. There were no deaths in the DKA group.

The majority of patients in our sample presented with moderate DKA, some degree of renal impairment and a large majority showing an initial potassium reading that was at the upper limit of normal or high (NHLS range 3.5-5.1 mmol/L). This increased potassium does not represent total body potassium, but instead diminished renal tubular secretion, in addition to hydrogen-potassium shifts across the cellular membrane^[24]. Inflammatory markers were raised in the majority of patients, not always correlating with the presence of sepsis. Acidosis was likely the cause of this.^[25]

Low dose insulin given as an IV bolus hourly has been found to be just as effective as pharmacological (high dose) doses in one study with 9 participants^[26]. The main clinical benefit observed is the reduced rates of hypokalaemia and hypoglycaemia. Fisher et al randomised 15 patients each to hourly IV, SC or IM bolus of 7 IU of insulin, observing no difference after 8 hours in rates of decline of glucose or serum ketones^[11]. Similarly Clumeck et al administered low dose insulin at 5 IU IV hourly in 19 patients with DKA^[8]. Once glucose had reached 13.9 mmol/L, insulin was changed to SC six hourly doses, regardless if ketonaemia had resolved. Once again, to highlight, very small numbers were used in these landmark studies.

Insulin given intramuscularly has unpredictable absorption and may accumulate in tissues resulting in delayed hypoglycaemia^[9]. It may also be unacceptable to the patient as injections are painful and need to be administered several times. Umpierrez et al proved that insulin analogues given as a CII or subcutaneously are equally effective compared to regular human insulin, which must be balanced against their increased cost and lesser availability^[27,28]. SC insulin is a reasonable alternative to treat patients with mild to moderate DKA. Human insulin, as used effectively in this audit, has the advantage over insulin analogues in a lower income country such as South Africa, in that it is readily available and would have a cost advantage.

Limitations

There were several limitations to this study. A large portion of data was self-reported by patients, and this could lead to recall bias. Determination of the type of diabetes did not include Type 3 (pancreatic) DM as this was not evident clearly from patient history, past clinical diagnoses or notes in a lot of cases. CHBAH is a very busy hospital and complete adherence to DKA protocol by doctors and nurses could not be ensured, and perhaps an audit of this is needed. Blood gases were sometimes not done at precise 2-4 hour intervals as recommended and this could affect time to resolution. Excluded blood glucose values, seven out of 71, resulted in a minimally underestimated mean initial blood glucose. DKA was successfully treated in all patients, thus Kaplan-Meier survival analysis could not be performed as stated in the study protocol.

Conclusion

This audit is the first of its kind in South Africa that shows that the IV bolus insulin management of DKA is a safe and feasible way to manage this condition. This method can be used in patients with severe DKA out of ICU. It is effective, in that all patients with DKA resolved and there was no mortality in our cohort. No complications related to bolus insulin administration was observed. A longer time to resolution was observed but this does not necessarily correlate with increased complications or efficacy of the treatment regimen.

This study could serve as a platform to influence other health centres in South Africa to employ this route of insulin administration. Further audits could strengthen evidence for its use. Large RCT's are needed to compare all routes of administration of insulin and provide clear data on the preferred method.

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**6. ETHICS
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R14/49 Dr Teresa Thomas

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CLEARANCE CERTIFICATE NO. M170551

NAME: Dr Teresa Thomas
(Principal Investigator)
DEPARTMENT: Internal Medicine
Chris Hani Baragwanath Academic Hospital

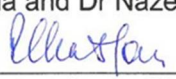
PROJECT TITLE: Audit of Diabetic Ketoacidosis Management at a
Tertiary Hospital in Johannesburg, South Africa

DATE CONSIDERED: 26/05/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Sindeep Bhana and Dr Nazeer Mohamed

APPROVED BY: 
Professor P. Cleaton-Jones Chairperson, HREC (Medical)

DATE OF APPROVAL: 14/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____

Date _____

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