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Introduction

he numbers of people with diabetes mellitus (DM) is increasing. DM is one of the most common diseases globally, affecting 285,000,000 peoples in 2010 in the world. It is estimated that DM will affect 592,000,000 persons in 2035. In Iran, 8.43% of population aged 20 to 79 y (4395938 people) had DM in 2013[1].

Diabetic Ketoacidosis (DKA) is one of emergency conditions caused by acute hyperglycemia which may be associated with both type 1 and 2 diabetes, mostly type 1 and is the cause for 100,000 to 160,000 hospitalizations in US [2]. DKA is a life-threatening condition in which the severe insulin deficiency causes hyperglycemia, severe lipolysis, uncontrolled oxidation of fatty acids and ketone bodies (beta-hydroxy-butyrate, acetoacetate and acetone) formation. The process results in metabolic acidosis, dehydration and loss of body electrolytes [3].

The basic treatment of DKA is injection of rapid-acting regular insulin. Intravenous infusion of regular insulin is the preferred method of treatment until recovery from DKA. Then, the treatment is continued with subcutaneous injection of insulin. Intravenous regular insulin has short half-life as a few minutes, requires the infusion pump and is associated with hospitalization and nursing costs [4].

Glargine insulin is a long acting insulin which is injected subcutaneously once daily in patients with type 1 or 2 DM; its onset of action is about an hour and create a relatively stable concentration of insulin in 24 hours. Given these pharmacodynamics of glargine insulin, it seems that addition of this long acting insulin to standard regimen my facilitate the transition from intravenous infusion of insulin to subcutaneous injection in the recovery of patients with DKA.The British Diabetes Association (BDA) recommends that in DKA patients using long-acting insulin (glargine or Detemir) prior to DKA, must be continued with the same dosage in the phase of DKA [5].

Regarding the short half-life of intravenous insulin and risk of technical errors including transient pause of infusion pump which adversely affect the recovery process of DKA, it seems that adding long-acting insulin to the standard regimen of treatment can prevent these complications [6].

Aim of Work

**To evaluate the efficacy of adding insulin Glargine to IV regular insulin for managing patients diagnosed with DKA compared to regular insulin alone and to assess the following:**

1. Effect on Recovery from DKA
2. Amount of Insulin required to treat DKA
3. Impact on outcome such as ICU stay, incidence of complications, and mortality.

Diabetic Ketoacidosis in Adults

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iabetic ketoacidosis (DKA) remains a significant complication of diabetes in both the United States and around the world. Diabetic ketoacidosis remains a significant complication of diabetes worldwide with it is associated high rates of hospital admissions. Therefore, it becomes vital that the healthcare professional be able to manage the hyperglycemic crises associated with diabetes. Moreover, with increasing healthcare costs and a changing healthcare system, prevention of diabetic ketoacidosis remains essential [7].

Diabetic ketoacidosis primarily results from insulin deficiency and hyperglycemic hyperosmolar state (HHS) from severe insulin resistance. Both of the crises result in subsequent glucagon and counter-regulatory hormone excess from lack of suppression from insulin [8].

Normally, with elevated blood glucose, as occurs after a digested meal, there is production and release of insulin by the beta cells in the islets of Langerhans. With this surge of insulin, the production of new glucose is suppressed appropriately. Conversely, in a state of starvation, there is an increase in counter regulatory hormones such as glucagon in which stores are appropriately mobilized and glucose production increased. This is a catabolic state, which allows for sustenance in times when nutrition is not available [9].

Though management of diabetic ketoacidosis has followed a set algorithm for many years, there are exciting management alternatives on the horizon such as subcutaneous insulin administration for uncomplicated DKA patients. By understanding DKA, including its pathogenesis, presentation, treatment, and prevention, admissions may be decreased and length of stay shortened [10][11].

A- Definition and Incidence of DKA:

Diabetic ketoacidosis (DKA) is a metabolic derangement characterized by hyperglycemia, metabolic acidosis, and ketosis. DKA occurs in patients with diabetes who have a lack of circulating insulin relative to physiologic requirement, such as in type 2 diabetes mellitus (T2DM), or absolute depletion, such as in type 1 diabetes mellitus (T1DM), in the presence of increased counter-regulatory hormones (cortisol, growth hormone, epinephrine, and glucagon). The lack of adequate insulin can occur from medication noncompliance, infection, or a precipitating pathologic event, such as a myocardial infarction, that causes an increased metabolic demand for insulin [2].

The Centers for Disease Control and Prevention (CDC) United States Diabetes Surveillance System recently reported an increase in DKA episodes in the US between 2009 and 2014, with an average annual increase of 6.3%. DKA can occur at any age but primarily occurs in those aged younger than 30 years (36% incidence) and between 30 and 50 years (27% incidence). The highest incidence of DKA is for those aged between 11 and 15 years. In addition, girls and women and the immigrant population are at higher risk [12].

In the past, DKA had a fatality rate of 1% to 5%. Older adults and individuals who have comorbid risk factors are in the highest risk category. In recent years, however, the overall mortality of DKA has declined due to earlier detection and increased evidence-based management. In fact, the recent CDC US Diabetes Surveillance System report indicated that the mortality for DKA has decreased to 0.4% [13].

B- Pathogenesis of DKA:

In diabetic ketoacidosis (DKA), the balance between catabolism and anabolism is, in a sense, broken. With the lack of insulin, there is decreased storage of glucose, increased breakdown of glycogen stores, and increased synthesis of glucose in both the liver and kidney. To add to the overall hyperglycemic state, there is also a concomitant decreased utilization of glucose in peripheral tissues. The situation is complicated by the fact that in this more catabolic state there is breakdown of proteins to form new amino acids that in turn are used to build glucose [14].

Moreover, the risk of DKA increases with any increased stress state. In a so-called “stressed state,” there is a relative abundance of epinephrine and cortisol. Epinephrine acts to block the action of insulin and stimulates the release of glucagon. Growth hormone also has a similar role as epinephrine and cortisol. In a stressed state, such as infection, myocardial infarction, intoxication, pregnancy, or stroke there is an increased demand for insulin, but a diminished supply by the stress put on the pancreas [15].

While elevated blood glucose from the increased glycogenolysis and gluconeogenesis is certainly a major problem, the cornerstone of DKA lies in ketogenesis. Insulin is normally the most important regulator in production and utilization of ketones. Insulin will inhibit lipolysis and oxidation of free fatty acids. Insulin also increases oxidation of ketones in the peripheral tissues. Thus, there is both overproduction and underutilization of ketones in an insulin-deficient state [16].

Also, glucagon itself will stimulate hormone-sensitive lipase, which in turn mobilizes adipose stores and converts triglycerides to free fatty acids. These free fatty acids are then transported across the mitochondrial membrane, and they are eventually used for synthesis of ketones, namely in the form of acetoacetic acid, which is oxidized to form betahydroxybutyrate or decarboxylated to form acetone. Unfortunately, with ketone overproduction, peripheral tissues cannot utilize these molecules and ketosis predominates. Conversely, in HHS there is usually enough insulin to suppress ketogenesis, but not control blood sugars. In HHS, blood sugars are usually higher as ketoacidosis produces more severe symptoms and presentation is usually earlier [17].

**Symptoms of ketosis**

include nausea, vomiting, abdominal pain, and respiratory insufficiency. Increased ketone production results in the attempt for the body to buffer with bicarbonate. Because of this buffering, there is an increase in unmeasured anions that cause a gapped metabolic acidosis. Vomiting may induce a hidden alkalosis. Furthermore, with the pre-renal azotemia that ensues, there is retention of other acids besides ketoacids [18].

Many of the remaining problems with DKA are from the resultant osmotic diuresis. Elevated blood glucose shifts water into the extracellular compartment. However, the expansion of the extra-cellular compartment is short lived as the ability to reabsorb glucose at the level of the renal tubule is limited and osmotic diuresis occurs. Thus, glycosuria and polyuria result. Water losses are typically greater than electrolyte losses, and thus there is an increased serum osmolality. Polydipsia results from the hyperosmolarity after osmoreceptors are triggered in the brain. Many of the other symptoms may result from the pro-inflammatory state of DKA, and elevated cytokines have been documented during diabetic ketoacidosis. Sodium tends to be low secondary to the fact that glucose is osmotically active and will draw fluids into the extracellular space. Potassium is variable based on the degree of acidosis and the time of presentation of the DKA [19].

C- Precipitating Causes of Diabetic Ketoacidosis:

The two most common precipitating factors in the development of DKA are inadequate insulin therapy (whether omitted or insufficient insulin regimen) or the presence of infection. Other provoking factors include myocardial infarction, cerebrovascular accidents, pulmonary embolism, pancreatitis, alcohol and illicit drug use [20].

In addition, numerous underlying medical illness and medications that cause the release of counter regulatory hormones and/or compromise the access to water can result in severe volume depletion and hyperosmolar hyperglycemic state (HHS). Drugs such as corticosteroids, thiazide diuretics, sympathomimetic agents (e.g., dobutamine and terbutaline), and second-generation antipsychotic agents may precipitate DKA or HHS. Most recently, two new classes of medications have emerged as triggers for DKA. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) that are used for diabetes treatment have been implicated in the development of DKA in patients with both type 1 and type 2 diabetes [21].

On the other hand, anti-cancer medications that belong to classes of immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab can cause DKA as the initial presentation of type 1 diabetes.The propsed mechanism of immunotherapy induced hyperglycemai is an autoimmune process (insulitis). In young patients with type 1 diabetes, insulin omission due to fear of hypoglycemia or weight gain, the stress of chronic disease, and eating disorders, may contribute in 20% of recurrent DKA. Cocaine use also is associated with recurrent DKA [22].

Mechanical problems with continuous subcutaneous insulin infusion (CSII) devices can precipitate DKA; however, with an improvement in technology and better education of patients, the incidence of DKA have been declining in insulin pump users. There are also case reports of patients with DKA as the primary manifestation of acromegaly [23].

Increasing numbers of DKA cases have been reported in patients with Type 2 DM. Available evidence shows that almost 50 % of newly diagnosed adult African American and Hispanic patients with DKA have type 2 diabetes. These ketosis-prone type 2 diabetic patients develop sudden-onset impairment in insulin secretion and action, resulting in profound insulinopenia. Clinical and metabolic features of these patients include high rates of obesity, a strong family history of diabetes, a measurable pancreatic insulin reserve, and a low prevalence of autoimmune markers of β-cell destruction [24].

Aggressive management with insulin improves β-cell function, leading to discontinuance of insulin therapy within a few months of follow-up and 40% of these patients remain non-insulin dependent for 10 years after the initial episode of DKA. The etiology of acute transient failure of β-cells leading to DKA in these patients is not known, however, the suggested mechanisms include glucotoxicity, lipotoxicity, and genetic predisposition. A genetic disease, glucose-6-phosphate dehydrogenase deficiency, has been also linked with ketosis-prone diabetes [8].

***Table 1 shows the prevalence of common precipitating causes of DKA [2].***

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Precipita-ting cause | Australia | Brazil | China | Indonesia | Korea | Nigeria | Spain | Syria | USA |
| New diagnosis of diabetes mellitus, % | 5.7 | 12.2 | NR | 3.3 | NR | NR | 12.8 | NR | 17.2–23.8 |
| Infection, % | 28.6 | 25.0 | 39.2 | 58.3 | 25.3 | 32.5 | 33.2 | 47.8 | 14.0–16.0 |
| Poor adherence to treatment, % | 40.0 | 39.0 | 24.0 | 13.3 | 32.7 | 27.5 | 30.7 | 23.5 | 41.0–59.6 |
| Other, % | 25.7 | 15.0 | 10.9 | 17.1 | 11.2 | 4.8 | 23.3 | 7.8 | 9.7–18.0 |
| Unknown, % | NA | 8.8 | 25.9 | 8.0 | 30.8 | 34.6 | NA | 20.9 | 3.0–4.2 |

D- Diagnosis of DKA:

The diagnosis of DKA is made based on the metabolic triad of high blood glucose (BG) levels (generally > 250 mg/dL), acidosis (pH < 7.3), and the presence of urine or serum ketones with an anion gap. Inpatient providers commonly rely on laboratory data to confirm DKA, whereas outpatient providers rely on history, presentation, BG levels, and urine ketones. The American Diabetes Association (ADA) consensus guidelines recommend assessment of severity of DKA based on mental status along with the laboratory parameters (table 2). This particular emphasis allows for safer triage of patients presenting to the emergency room to either the intensive care units or step-down units. Further, as per the US guidelines, patients with a bicarbonate level of 18 mmol/L can have mild DKA. This is included to recognize that DKA may be partially treated prior to presentation at the hospital. It should be noted that patients with DKA can have a wide range of acid-base disorders and may have a small anion gap despite increased beta-hydroxybutyrate concentrations. This subset of patients may be erroneously classified as having mild DKA if one was to look for just the anion gap [25].

***Table 2: Diagnosis of Diabetic Ketoacidosis***

|  |  |  |  |
| --- | --- | --- | --- |
| Diagnosis of Diabetic Ketoacidosis | | | |
| Variable | **Diabetic Ketoacidosis** | | |
| **Mild** | **Moderate** | **Severe** |
| Arterial pH | 7.25-7.3 | 7- < 7.24 | < 7.00 |
| Serum bicarbonate, mEq/L | 15-18 | 10- <15 | <10 |
| Urine ketones | Positive (trace or higher) | Positive | Positive |
| Serum ketones | Positive | Positive | Positive |
| Anion gap, mEq/L | >10 | >12 | >12 |
| Mental status | Alert | Alert/drowsy | Stupor/coma |

The UK guideline states that to make a diagnosis of DKA, a prior history of diabetes, regardless of glucose concentrations, although (a glucose >11 mmol/L (200 mg/dL) is specified), is sufficient diagnostic criteria. Due to the availability of testing of 3-beta-hydroxybutyrate testing at the bedside, measurement of serum ketones with a level >3 mmol/L has been suggested as part of the diagnostic criteria for ketoacidosis as opposed to using the urine ketones. Also, the UK guidelines state that using venous blood gas rather than arterial blood gas with a pH <7.3 or bicarbonte <15 should be used for diagnosis of acidosis. There are several advantages to the UK criteria. Approximately 10% of patients with DKA present with euglycemic DKA or with glucose levels below the thresholds set by the US guidelines [5].

Common presenting symptoms include abdominal pain and the classic triad of hyperglycemia symptoms: polydipsia, polyphagia, and polyuria. Physical examination findings can include any or all of tachycardia, hypotension, Kussmaul respirations, significant dehydration, or a change in mental status [26].

It is important to consider differential diagnoses of metabolic acidosis that may include lactic acidosis or hyperchloremic acidosis. Differential diagnoses for ketosis include starvation ketosis (dietary history, weight trends) or alcoholic ketoacidosis (alcohol consumption history), hyperemesis, isopropyl alcohol, or ketotic hypoglycemia [8].

Euglycemic DKA (euDKA), which occurs when the patient presents with acidosis and ketosis but has a glucose ≤ 200 mg/dL, has become an emerging concern. Causes of euDKA can include recent insulin administration, decreased caloric intake, substantial alcohol consumption, chronic liver disease, or rarely, glycogen storage issues. In addition, there have been increasing reports of euDKA caused by a new class of drugs for diabetes, sodium glucose cotransporter 2 (SGLT-2) inhibitors. In May 2015, the US Food and Drug Administration added a warning about the risk of DKA with use of these drugs. One study suggested that the risk of DKA for patients using SGLT-2 inhibitors was twice as high as those prescribed a dipeptidyl peptidase IV inhibitor, after controlling for other risk factors, although the risk of hospitalization was low [14].

The exact cause of this relationship is unknown, but several theories include reduced insulin doses when SGLT-2 is initiated, an increase in glucagon, or decreased excretion of ketone bodies. Other related factors may be mild infection, increased activity, reduced food intake, or insulin reduction or omission. Case reports of traditional and euDKA occurring while using SGLT-2 inhibitors has been shown in patients with T1DM and in those with T2DM. Many patients with euDKA present with nausea and vomiting but are misdiagnosed due to the lack of clear glucose elevation [27].

E- Diagnostic Workup:

Providers in outpatient settings where laboratory results are not readily available should rely on BG and ketone values for the initial diagnosis. BG values will typically be > 250 mg/dl, although up to 10% of patients in DKA may present with euDKA. For this reason, some experts argue that the cutoff BG value for diagnosing DKA should be decreased to 200 mg/dL [15]

Ketone measurement is an important diagnostic component and severity classification of DKA for patients in the outpatient setting. Urine ketones will test positive, although may be as minimal as “trace” ketones. Urine dipsticks measure acetoacetate (AcAc) and acetone but not β-hydroxybutyrate (β-OHB). Given this, the measurement of AcAc in the urine tends to underestimate the severity of DKA, because the ratio of AcAc to β-OHB can be 1:10 during ketoacidosis. Other limitations with urine ketone testing include lag time in change in urine ketones, difficulty obtaining urine from dehydrated patients, and subjective measurements by the patient. Many experts agree that measurement of blood or capillary ketones is preferred due to these limitations [19].

Some outpatient glucometers, measure β-OHB in addition to BG levels. Several of these types of monitoring systems are available on the market. These meters measuring capillary ketones have been shown to have high sensitivity, specificity, positive predictive value, and negative predictive value in identifying DKA compared with urine ketone testing. Patients with diabetes who have access to β-OHB meters may have reduced emergency department visits, time to recovery from DKA, and the potential for reduced costs. Currently, these systems are not widely used and are expensive but may be beneficial to consider for patients who are at risk for DKA [20].

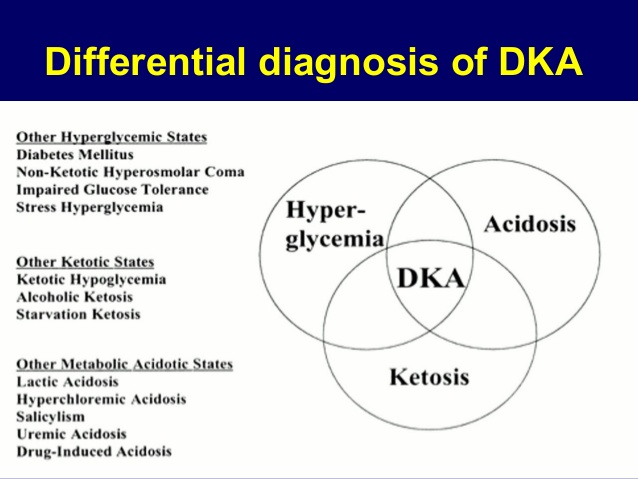
In the emergency department, initial recommended laboratory tests include a blood gas, electrolytes, complete blood count with differential, serum glucose, creatinine, serum or urine ketones, or both, and urinalysis. Any woman with child-bearing potential should receive a urine pregnancy test, and other diagnostic assessments should be done based on presenting symptoms, such as cardiac markers, electrocardiogram, urine drug screens, or blood cultures. If the patient requires hospital admission, a further workup may include tests such as chest x-ray imaging and an arterial blood gas. An anion gap (AG) should be calculated to assist in determining the severity of DKA [28].

F- Differential Diagnosis of DKA:

Patients may present with metabolic conditions resembling DKA or HHS. For example, in alcoholic ketoacidosis (AKA), total ketone bodies are much greater than in DKA with a higher β-OHB to acetoacetate ratio of 7:1 versus a ratio of 3:1 in DKA. The AKA patients seldom present with hyperglycemia [29].

It is also possible that patients with a low food intake may present with mild ketoacidosis (starvation ketosis); however, serum bicarbonate concentration of less than 18 or hyperglycemia will be rarely present. Additionally, DKA has to be distinguished from other causes of high anion gap metabolic acidosis including lactic acidosis, advanced chronic renal failure, as well as ingestion of drugs such as salicylate, methanol and ethylene glycol. Isopropyl alcohol, which is commonly available as rubbing alcohol, can cause considerable ketosis and high serum osmolar gap without metabolic acidosis. Moreover, there is a tendency to hypoglycemia rather than hyperglycemia with isopropyl alcohol injection [30].

Finally, patients with diabetes insipidus presenting with severe polyuria and dehydration, who are subsequently treated with free water in a form of intravenous dextrose water, can have hyperglycemia- a clinical picture that can be confused with HHS [31].

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***Figure (1): The differential diagnosis of DKA*** *(****Kitabchi and Nyenwe****,* ***2006****)*

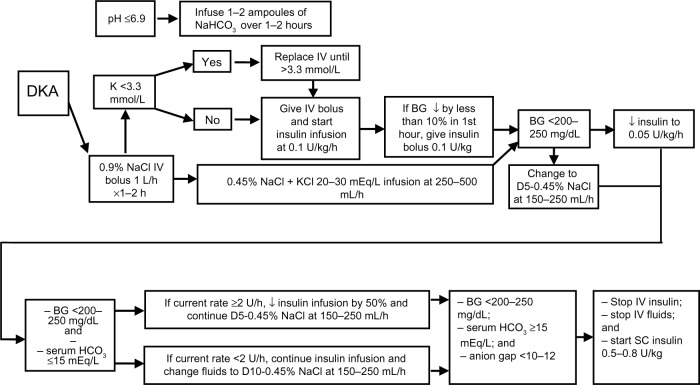
Management of Diabetic Ketoacidosis

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he therapeutic goals of DKA management include optimization of 1) volume status; 2) hyperglycemia and ketoacidosis; 3) electrolyte abnormalities; and 4) potential precipitating factors. The majority of patients with DKA present to the emergency room. Therefore, emergency physicians should initiate the management of hyperglycemic crisis while a physical examination is performed, basic metabolic parameters are obtained, and final diagnosis is made. Several important steps should be followed in the early stages of DKA management [26]:

1. Collect blood for metabolic profile before initiation of intravenous fluids;
2. Infuse 1 L of 0.9% sodium chloride over 1 hour after drawing initial blood samples;
3. Ensure potassium level of >3.3 mEq/L before initiation of insulin therapy (supplement potassium intravenously if needed);
4. Initiate insulin therapy only when steps 1–3 are executed.

The protocol for the management of patients with DKA is presented in **Figure 2**. It must be emphasized that successful treatment requires frequent monitoring of clinical and metabolic parameters that support resolution of DKA [22] (**Table 2**).



***Figure (2): Workflow of management of adult DKA.***

*Abbreviations: BG, blood glucose; DKA, diabetic ketoacidosis; h, hour; IV, intravenous; SC, subcutaneous.*

***Table (3): Checklist of DKA management milestones***

|  |  |  |
| --- | --- | --- |
| □ Phase I (0–6 h) | □ Phase II (6–12 h) | □ Phase III (12–24 h) |
| □ Perform history and physical exam and order initial laboratory studies | □ Continue biochemical and clinical monitoring | □ Continue biochemical and clinical monitoring |
| □ Implement monitoring plan (biochemical and clinical) | □ Change isotonic fluids to hypotonic fluids if corrected Na normal/high | □ Adjust therapy to avoid complications |
| □ Give intravenous bolus of isotonic fluids | □ If glucose is <200–250 mg/dL, add dextrose to intravenous fluids | □ Address precipitating factors |
| □ Start insulin therapy (after fluids started and only if K >3.3 mmol/L) | □ Adjust insulin infusion rate as needed | □ If DKA resolved, stop intravenous insulin and start subcutaneous insulin |
| □ Consult diabetes team | □ Maintain K at 3.3–5.3 mmol/L range | □ Consult diabetes educator |

***Abbreviations:****DKA, diabetic ketoacidosis; h, hours.*

A- Fluid Therapy

Fluid loss averages approximately 6–9 L in DKA. The goal is to replace the total volume loss within 24–36 hours with 50% of resuscitation fluid being administered during the first 8–12 hours. A crystalloid fluid is the initial fluid of choice. Current recommendations are to initiate restoration of volume loss with boluses of isotonic saline (0.9% NaCl) intravenously based on the patient’s hemodynamic status. Thereafter, intravenous infusion of 0.45% NaCl solution based on corrected serum sodium concentration will provide further reduction in plasma osmolality and help water to move into the intracellular compartment. Hyperosmolar hyponatremia due to hyperglycemia is a frequent laboratory finding in DKA and is usually associated with dehydration and elevated corrected sodium concentrations [32].

The optimal rate of initial fluid administration was addressed in a prospective randomized controlled study in which patients were treated with either 500 mL/hour (h) or 1 L/h of isotonic fluid. There were no differences in the resolution of DKA, mortality, or complications. Most protocols call for an initial bolus of isotonic crystalloid solution (0.9% saline) at a starting rate of 15–20 mL/kg/h (1–1.5 L/h) for the first hour. Following the initial hydration, fluids can be administered at a decreased rate of 4–14 mL/kg/h. Tonicity of subsequent solution is dependent upon hydration status, electrolyte balance, and urine output. Rapid correction of serum sodium and, hence, serum osmolality by hypotonic fluids may carry an increased risk of cerebral edema. On the other hand, continuous isotonic fluid therapy in pediatric patients was found to have an increased risk of a non-anion gap hyperchloremic acidosis possibly leading to longer hospital stays due to erroneous diagnosis of persistent ketoacidosis [33].

 Accordingly, safe practice of fluid resuscitation in DKA patients includes provision of initial bolus of isotonic saline at 15–20 mL/kg/h followed by hypotonic saline solution (0.45% saline) at a rate of 4–14 mL/kg/h as long as the patient is hemodynamically stable and corrected serum sodium is normal to high. If a patient becomes hyponatremic based on corrected serum sodium, initiation of 0.9% saline at a rate of 150–250 mL/h is recommended until eunatremia is achieved. Replacement of the water deficit using high rates of intravenous fluids has not been studied in pediatric patient populations and, therefore, this approach cannot be recommended for the management of pediatric DKA [21].

Intravascular and extravascular volume resuscitation will decrease hyperglycemia by stimulating osmotic diuresis if renal function is not severely compromised and enhance peripheral action of insulin (insulin effects on glucose transport are decreased by hyperglycemia and hyperosmolarity). When glucose levels fall below 200–250 mg/dL, intravenous fluids should be switched to dextrose-containing 0.45% NaCl solution to prevent hypoglycemia, and/or insulin infusion rate should be decreased. Special considerations should be given to patients with congestive heart failure and chronic kidney disease. These patients tend to retain fluids; therefore, caution should be exercised during volume resuscitation in these patient groups. Urine output monitoring is an important step in patients with hyperglycemic crises [34].

B- Insulin Therapy:

Insulin administration is essential in DKA treatment because it promotes glucose utilization by peripheral tissues, diminishes glycogenolysis and gluconeogenesis, and suppresses ketogenesis. Intravenous infusion is a preferred route of insulin delivery in patients with DKA. Insulin infusion without initial volume resuscitation is not advised as it may only worsen dehydration. Insulin treatment has evolved from the use of high-dose insulin, with doses up to 100 U/h by various routes of administration, to lower doses in the range of 5–10 U/h. Some studies recommend an initial bolus of regular insulin of 0.1 U/kg followed by continuous insulin infusion. If plasma glucose does not fall by at least 10% in the first hour of insulin infusion rate, 0.1 U/kg bolus of insulin can be given once more while increasing rate of iv insulin infusion [35].

Of clinical significance is the phenomenon of hyperglycemia-induced insulin resistance; with reduction of glycemia, there can be a nonlinear decrease in insulin requirements. When plasma glucose reaches 200–250 mg/dL, the insulin rate can be decreased by 50% or to the rate of 0.02–0.05 U/kg/h (**Figure 2**) [36].

Clinical importance of the initial insulin bolus in the insulin management of DKA has been recently challenged in a study that compared efficacy and safety of two strategies of insulin infusion – with and without priming bolus. The authors found that there were no differences in outcomes between a group of patients who were treated with the infusion of regular insulin at a dose of 0.14 U/kg/h without administration of initial insulin bolus and a group of patients who were managed by the administration of priming insulin bolus of 0.07 U/kg followed by the continuous insulin infusion at 0.07 U/kg/h. The efficacy of the therapeutic approach with an insulin dose of 0.1 U/kg was not assessed in that study [37].

A more recent study showed no significant difference in incidence of hypoglycemia, rate of glucose change or anion gap, length of stay in the emergency department, or hospital stay in patients receiving an infusion rate of 0.1 U/kg/h with or without insulin bolus. No previous studies have compared clinical outcomes in pediatric DKA patients treated with and without priming insulin bolus; therefore, the use of priming bolus in pediatric DKA care is not recommended. The basis for use of a priming bolus stemmed from a study in patients with hyperosmolar hyperglycemic nonketotic diabetes, which suggested that an initial bolus could help correct the relative insulin resistance of DKA. As such, inconsistent results may have been due to patient variables such as absence of ketosis and/or presence of severe hyperglycemia. Current American Diabetes Association recommendations suggest one of the two above options for intravenous insulin therapy (with or without insulin bolus), considering a serum potassium >3.3 mEq/L [38].

As the majority of patients with DKA can rapidly become insulin sensitive following the administration of intravenous fluids and improvements in hyperglycemia. Therefore, to avoid hypoglycemia and rapid shifts of glucose and water between extracellular and intracellular compartments, the larger rates of insulin infusion should be reserved for obese and more insulin-resistant DKA patients. The administration of priming insulin bolus can be feasible in less insulin-resistant DKA patients initially presenting with extreme hyperglycemia [39].

The UK guideline recommends adjustment of insulin infusion depending on the rate of fall of glucose (3.0 mmol/h[54 mg/dL]) and serum ketones (0.5 mmol/h) with a corresponding rise in bicarbonate concentration of 3.0 mmol/L.The UK guideline also incorporates the new evidence to show that the continued use of long-acting basal insulin helps to prevent the rebound hyperglycemia seen when the intravenous insulin is stopped [6].

C- Potassium, Bicarbonate, and Phosphate Therapy:

Serum potassium should be closely monitored during DKA treatment. Insulin administration and correction of acidemia and hyperosmolality drive potassium intracellularly, resulting in hypokalemia that may lead to arrhythmias and cardiac arrest. If serum potassium decreases to <3.3 mEq/L during DKA treatment, insulin should be stopped and potassium administered intravenously. Small amounts of potassium (20–30 mEq/L) are routinely added to intravenous fluids when serum potassium is between 3.3 and 5.3 mmol/L. No replacement is needed for potassium levels >5.3 mmol/L [40].

Bicarbonate therapy is not indicated in mild and moderate forms of DKA because metabolic acidosis will correct with insulin therapy. The use of bicarbonate in severe DKA is controversial due to a lack of prospective randomized studies. It is thought that the administration of bicarbonate may actually result in peripheral hypoxemia, worsening of hypokalemia, paradoxical central nervous system acidosis, cerebral edema in children and young adults, and an increase in intracellular acidosis. Because severe acidosis is associated with worse clinical outcomes and can lead to impairment in sensorium and deterioration of myocardial contractility, bicarbonate therapy may be indicated if the pH is 6.9 or less. Therefore, the infusion of 100 mmol (two ampoules) of bicarbonate in 400 mL of sterile water mixed with 20 mEq potassium chloride over 2 hours, and repeating the infusion until the pH is greater than 7.0, could be recommended pending the results of future randomized controlled trials [21].

A whole-body phosphate deficit in DKA can average 1 mmol/kg. Insulin therapy during DKA will further lower serum phosphate concentration; 90% of patients were shown to have developed hypophosphatemia during infusion of insulin and fluids [41].

Previous studies [23] have failed to show any beneficial effect of phosphate replacement on the clinical outcomes in DKA. Phosphate replacement has actually been implicated in creating a state of severe hypocalcemia; however, careful phosphate replacement is indicated in patients with a serum phosphate concentration less than 1.0 mg/dL or in patients with a serum phosphate level between 1.0 and 2.0 mg/dL and cardiac dysfunction, anemia, or respiratory depression. Initial replacement strategy may include infusion of potassium phosphate at the rate of 0.1–0.2 mmol/kg over 6 hours, depending on the degree of phosphate deficit (10 mL of potassium phosphate solution for intravenous use contains 30 mmol of phosphorous and 44 mmol of potassium). Overzealous phosphate replacement may result in hypocalcemia; therefore, close monitoring of both phosphorous and calcium levels is recommended. Patients who have renal insufficiency and/or hypocalcemia may need less aggressive phosphate replacement [24].

D- Treatment of DKA in Severe Insulin Resistance:

Syndromes of severe insulin resistance (IR) include mutations of or autoantibodies to the insulin receptor and lipodystrophy. Diabetic ketoacidosis (DKA), although rare, can occur in these patients, even in the context of hyperinsulinemia, due to impaired insulin signaling. DKA can be extremely challenging to treat, and few clinicians are experienced or comfortable in using the high doses of insulin required [ 42] .

Insulin treatment in DKA has evolved from the use of high-dose insulin, up to 100 units/h, to lower doses of 5–10 units/h (0.1 units/kg/h) . However, low doses of insulin used in standard DKA protocols are not sufﬁcient for patients with severe IR. The unusually high doses of insulin required for DKA in severe IR raise safety concerns for providers not experienced with severe IR. This highlights the importance of aggressive management of DKA in severe IR, including high-dose insulin, ﬂuids, bicarbonate, and treatment of underlying infection. Cooperation between critical care physicians and endocrinologists is essential fo rsafe and effective management.[26,35]

E- Metabolic Treatment Targets:

Serial measurements (every 2–4 hours) of metabolic parameters are required to monitor therapy and then confirm resolution of DKA. DKA is resolved when 1) plasma glucose is <200–250 mg/dL; 2) serum bicarbonate concentration is ≥15 mEq/L; 3) venous blood pH is >7.3; and 4) anion gap is ≤12. In general, resolution of hyperglycemia, normalization of bicarbonate level, and closure of anion gap is sufficient to stop insulin infusion. Venous pH is adequate to assess the degree of acidosis with consideration that it is 0.02–0.03 lower than arterial blood. If plasma glucose is <200 mg/dL but bicarbonate and pH are not normalized, insulin infusion must be continued and dextrose-containing intravenous fluids started. The latter approach will continue to suppress ketogenesis while preventing hypoglycemia [43].

F- Insulin Therapy after Resolution of DKA:

When the patient is able to tolerate oral intake and DKA is resolved, transition to subcutaneous insulin must be initiated. It is common to see transition from intravenous to subcutaneous insulin using sliding scale insulin only. This strategy as a sole approach should be discouraged, as it cannot provide the necessary insulin requirement in patients recovering from hyperglycemic crisis and β-cell failure. Patients should be given intermediate (neutral protamine Hagedorn) or long-acting insulin (detemir or glargine) 2 hours before termination of intravenous insulin to allow sufficient time for the injected insulin to start working. It is also feasible to begin administration of long-acting insulin while the patient continues to receive intravenous insulin therapy. In one prospective randomized study, insulin glargine was given at a dose of 0.25 U/kg to subjects with severe hyperglycemia, including patients with DKA, within 12 hours after initiation of intravenous insulin. The authors found that once-daily subcutaneous insulin glargine administered during intravenous insulin infusion prevents future rebound hyperglycemia without an increased risk of hypoglycemia [6].

When a patient resumes oral intake, studies recommend the addition of short-acting insulin for prandial glycemic coverage. The regimen containing both long-acting and short-acting insulin is called a basal-bolus insulin regimen; it provides physiological replacement of insulin. If a patient used insulin prior to admission, the same dose can be restarted in the hospital. Insulin-naïve patients require insulin at a total dose of 0.5–0.8 U/kg/day divided as 50% basal insulin and 50% prandial insulin before each meal [26].

G- Complications:

Hypoglycemia is the most frequent complication of DKA and can be prevented by timely adjustment of insulin dose and frequent monitoring of blood glucose levels. Hypoglycemia is defined as any blood glucose level below 70 mg/dL. If DKA is not resolved and blood glucose level is below 200–250 mg/dL, decrease in insulin infusion rate and/or addition of 5% or 10% dextrose to current intravenous fluids can be implemented (**Figure 2**). When DKA is resolved, strategies to manage hypoglycemia will depend on whether or not the patient is able to maintain oral intake. For patients who are able to drink or eat, ingestion of 15–20 g of carbohydrates, eg, four glucose tablets, 6 ounces of orange or apple juice, or “regular” soda, is advised. In patients who are nil by mouth, unable to swallow, or have an altered level of consciousness, administration of 25 mL of 50% dextrose intravenously or 1 mg glucagon intramuscularly, if no intravenous access is present, is recommended. Blood glucose should be rechecked after 15 minutes; only if the glucose level is <70 mg/dL should the above steps be repeated [44].

Non-anion gap hyperchloremic metabolic acidosis frequently develops during DKA treatment and is believed to occur due to urinary losses of ketoanions, which are needed for bicarbonate regeneration, and preferential reabsorption of chloride in proximal renal tubule secondary to intensive administration of chloride-containing fluids. This acidosis usually resolves spontaneously in a few days and should not affect the treatment course. Cerebral edema due to rapid reduction in serum osmolality has been reported in young adult patients. This condition is manifested by appearance of headache, lethargy, papillary changes, or seizures, with mortality rates reaching 70%. Mannitol infusion and mechanical ventilation should be used to treat this condition. Rhabdomyolysis is another possible complication due to hyperosmolality and hypoperfusion. Pulmonary edema can develop from excessive fluid replacement in patients with chronic kidney disease or congestive heart failure [24].

I

Insulin Glargine and Diabetic Ketoacidosis

n January 1922, Banting, Best, Collip and MacLeod succeeded in purifying insulin from beef pancreas to treat children dying from type 1 diabetes. On 11 January 1922, Leonard Thompson, a 14-year-old boy with diabetes, who lay dying at the Toronto General Hospital, was given the first injection of insulin. However, the extract was so impure that Thompson suffered a severe allergic reaction, and further injections were cancelled. Over the next 12 days, James Collip worked day and night to improve extract, and a second dose was injected on the 23 January. This was completely successful, not only in having no obvious side-effects, but in completely eliminating the glycosuria sign of diabetes [45]

**Types of Insulin:**

**Rapid-acting insulin**, begins to work about 15 minutes after injection, peaks in about 1 hour, and continues to work for 2 to 4 hours. Types: Insulin glulisine, insulin lispro, and insulin aspart.

**Regular or Short-acting insulin** usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from 2 to 3 hours after injection, and is effective for approximately 3 to 6 hours.

**Intermediate-acting insulin** generally reaches the bloodstream about 2 to 4 hours after injection, peaks 4 to 12 hours later, and is effective for about 12 to 18 hours. Types: NPH*.*

**Long-acting insulin** reaches the bloodstream several hours after injection and tends to lower glucose levels up to 24-hours or longer. Types: degludec, detemir, and glargine*.*

**Ultra Long-Acting** reaches the blood stream in 6 hours, does not peak, and lasts about 36 hours. Types: glargine u-300.

**Premixed insulin** reaches bloodstream after 5-60 min. with dual peak and is effective for about 18 hours.

**Inhaled insulin** begins working within 12 to 15 minutes, peaks by 30 minutes, and is out of your system in 180 minutes. Types: Technosphere insulin-inhalation system (Afrezza) (46)

***Table (4): Pharmacokinetics and pharmacodynamics of subcutaneous insulin preparations***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Insulin | Onset of action | Time to peak | Duration | Timing of dose |
| Regular | 30–60 min | 2–3 h | 8–10 h | 30–45 min before meal |
| Aspart | 5–15 min | 30–90 min | 4–6 h | 15 min before meal |
| Glulisine | 5–15 min | 30–90 min | 5.3 h | 15 min before meal |
| Lispro | 5–15 min | 30–90 min | 4–6 h | 15 min before meal |
| NPH | 2–4 h | 4–12 h | 12–18 h | Twice a day |
| Detemir | 2 h | No peak | 12–24 h | Once or twice a day |
| Glargine | 2 h | No peak | 24 h | Once a day |

***Abbreviations:****h, hours; min, minutes; NPH, neutral protamine Hagedorn.*

Insulin Glargine was the first long-acting insulin analog produced by recombinant DNA technology, approved for use by the US FDA in April 2000 and by the European Agency for the Evaluation of Medicinal Products in June, 2000. It has become the most widely used insulin in the USA owing to its long duration of action without a pronounced peak. The principal advantage of insulin Glargine over neutral protamine Hagedorn (NPH) insulin is in a lower frequency of hypoglycemic reactions, thus affording improved safety. It is used in both type 1 and type 2 diabetes, usually as a single daily dose. In type 2 patients, it is often the first insulin introduced as a single daily dose [47].

Although, the preferred protocol for the management of DKA is intravenous infusion. However, intravenous regular insulin has a short half-life and requires an infusion pump. Long-acting insulin, such as Glargine, has an onset of action is about an hour and is stable for 24 hours. Given the duration of action of glargine, it seems that adding long-acting insulin to standard therapy improves the recovery of the patients [3].

A- Biochemistry of Insulin Glargine:

Insulin Glargine (A21-Gly-B31-Arg-B32- Arg- human insulin), a long-acting insulin analog produced by recombinant DNA technology using Escherichia coli plasmid DNA. It was approved for clinical use by the US FDA in April 2000 and by the European Agency for the Evaluation of Medicinal Products in June 2000 [48].

The structure of insulin Glargine differs from that of human insulin by glycine substitution for an asparagine at position A21, and addition of arginine to the carboxyl terminal of the B chain at positions B31 andB32. These amino acid modifications change the isoelectric point of the molecule closer to neutral (from pH 5.4 to 6.8), making the molecule more soluble within the acidic environment of the vial but insoluble at the neutral pH of the injection site .When injected subcutaneously, insulin Glargine forms micro precipitates at the injection site, greatly slowing its absorption. Zinc (30 pg/mL) added to the insulin Glargine formulation further stabilizes the molecule and helps delay absorption time. As a result of delayed absorption, the duration of effect of insulin Glargine is prolonged[49].

* **Pharmacokinetics and bioavailability**

Pharmacokinetic and pharmacodynamic studies have been performed in nondiabetic volunteers and in patients with type 1 and type 2 diabetes. The onset of action of insulin Glargine is about 1.5 h. The insulin serum concentration/time profile is relatively constant over 18 h, with a slow decrement in the time period of 20 – 24 h [50].

In contrast to NPH human insulin and lente insulin, there is no pronounced peaking of insulin concentration with insulin Glargine. The duration of action of insulin Glargine is similar whether injected in the abdomen, deltoid or thigh. There is no accumulation of insulin Glargine after multiple injections over 12 days. There is less variability in absorption of insulin Glargine than of ultralente insulin. A direct comparison trial demonstrated less variability of glucose values with Glargine rather than ultralente as basal insulin treatment [51].

When Glargine and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular insulin was observed. The total bioavailability of the mixture was also slightly decreased compared with separate injections of Glargine and regular human insulin. In a study by Kaplan et al., 14 pediatric patients with type 1 diabetes were allowed to premix Glargine with lispro or aspart insulin in order to decrease their total number of injections to two a day. Although the mixtures turned cloudy, no complaints of increased pain or injection difficulties were reported, and no changes occurred in HbA1c or in short-term glycemic profile [52].

In a study by Fiallo-Scharer et al., 55 children mixed insulin Glargine with a rapid acting insulin analogue. Data was collected for 6 months before and 6 months after the insulin mixing began. Data from a control group of 55 children who did not mix the insulins were collected at similar intervals. After 6 months of study, HbA1c values were equivalent for the control and test groups (8.54% and 8.61% respectively) [53].

B- Possible Adverse Effects of Insulin Glargine:

1. **Mitogenic potential**

Insulin is a known growth factor with mitogenic effects. It is thought that the mitogenic effect of insulin is mediated through insulin-like growth factor (IGF-1) receptor stimulation. Mitogenic stimulation of insulin analogs is related to residence time on the receptor, dissociation rate and other factors such as receptor internalization and the degree of phosphorylation of signaling proteins [54].

Insulin Glargine has a 60% lower binding affinity to the insulin receptor and 1.5 times faster dissociation than does human insulin. However, it has a 6.5 times increased binding affinity for the IGF-1 receptor. In a crossover study by Slawik et al. in 2005, serum IGF-1 concentrations were higher during insulin Glargine treatment compared with NPH insulin in patients with type 1 diabetes. Despite these findings, insulin Glargine does not reveal significantly different mitogenic effects compared with regular insulin in human breast epithelial and carcinoma cells [55].

An in vivo study performed in mice and rats showed no increase in the incidence of mammary gland tumors using insulin Glargine at doses of 2 – 12.5 mcg/kg [29]. IGF-1 signaling plays a role in regulation of vascular endothelial growth factor dependent retinal neovascularisation. There is a known relationship between elevated IGF-1 levels and diabetic retinopathy. The higher affinity of insulin Glargine for the IGF-1 receptor raised concern about possible progression of retinopathy in diabetes mellitus patients treated with Glargine [56].

Analysis of four randomized trials comparing ophthalmologic examinations and fundus photographs in insulin-Glargine-treated patients with NPH-insulin-treated patients did not resolve these concerns. Therefore, a large 5-year comparison trial was initiated in 2017 type 2 diabetic patients randomized to either insulin Glargine or NPH insulin. Sequential fundus photographs in this population showed no difference in three-step progression of retinopathy between the two insulin groups, thereby alleviating previous concerns [57].

1. **Pregnancy and embryotoxicity**

Insulin Glargine is rated as a Pregnancy Category C drug. Limited studies in animals do not suggest effects on fertility or embryogenesis. There are no well-controlled clinical studies of the use of insulin Glargine in pregnant women. There have been several case reports in which Glargine was used for the treatment of diabetes during pregnancy. These reports indicate that, compared with NPH insulin, Glargine results in improved glycemic control without any nocturnal hypoglycemia [58].

In a study by Price et al., 32 pregnant women with diabetes treated with insulin Glargine during their pregnancy were compared with a control group treated with intermediate-acting human insulin. There was no significant difference between the birth weights of babies or neonatal morbidity in the two groups [59].

1. **Allergy and injection site pain**

Allergy to human recombinant insulin is rare and reported for < 1% of patients. Symptoms are local and appear a few minutes after the injection (indurations, pruritus, and burning sensation at insulin injection sites). Pain resulting from injections has a potential influence on the acceptance, and thus on the success, of insulin treatment. Systematic investigation in humans has suggested that individuals perceive more pain during subcutaneous injection of acidic solutions than neutral solutions [60].

Insulin Glargine, unlike other insulins, is injected as an acidic solution (pH 4). In clinical studies in adult patients, there was a higher incidence of injection-site pain with insulin Glargine versus NPH insulin, but the pain was usually mild and did not result in discontinuation of therapy [61].

C- Indications for Insulin Glargine:

Insulin Glargine is a long-acting insulin with an essentially peakless release of insulin from the subcutaneous site of injection. Therefore, it mimics the underlying basal secretion of insulin from the pancreas in the nonfed state. Insulin Glargine is typically administered in the evening to maintain insulin levels overnight and impact on fasting plasma glucose levels. The two indications for insulin Glargine use are: i) to provide a basal insulin level in type 1 diabetes; and ii) to supplement basal insulin production in type 2 diabetes [47].

Advantages of insulin Glargine compared with NPH insulin

The most important advantage of insulin Glargine over NPH insulin is reduction in the risk of hypoglycemia, primarily at night. This advantage derives from the very flat pharmacokinetic profile of insulin Glargine and has been demonstrated in multiple studies in type 1 diabetic patients [62].

Fulcher showed that Glargine is superior to NPH in improving HbA(1c) and FBG levels during intensive insulin therapy in patients with type 1 diabetes and is associated with less severe nocturnal hypoglycemia. Rosenstock showed that insulin Glargine has not only a lower risk of nocturnal hypoglycemia but also less weight gain compared with NPH insulin [63].

Chaterrjee et al. found no difference in hypoglycemia in type 1 diabetic patients treated with insulin Glargine compared with those treated with NPH insulin [64].

Results in children are similar to those in adult patients. The most common regimen used in pediatric patients is the basal-bolus regimen in which long-acting insulin is used as the basal insulin and rapid-acting insulin is used to cover meals. A study by Herwig et al. evaluating the efficacy of Glargine in pediatric patients failed to show lower HbA1c level compared with NPH insulin, but fasting blood glucose concentrations decreased significantly in subjects receiving Glargine, with lower incidence of hypoglycemia [65].

Most studies concluding superiority of insulin Glargine over NPH insulin have been done using NPH twice daily. There are suggestions that NPH insulin given three times daily with premeal rapid-acting insulin may provide the same overlapping, relatively peakless result as obtained with Glargine, but HbA1c improvement appears to be superior with insulin Glargine [66].

D- The Role of Insulin Glargine in DKA:

On resolution of DKA and cessation of intravenous insulin infusion, rebound hyperglycaemia is a major issue. Once an intravenous infusion is ceased its duration of action is only minutes, whilst the onset of basal subcutaneous insulin is 1–2 h and thus overlap of the two is an integral component of successful transition [6].

In 2007, a small study (n = 75) investigating the optimal insulin dose for transition from IV insulin infusion to subcutaneous insulin glargline, randomized patients to receive either 40%, 60%, or 80% of their total daily insulin requirement, calculated from the rate of insulin infused during the last 6 h of their insulin infusion, as insulin glargine. The study concluded that insulin glargine administered at 80% of the total daily insulin requirement resulted in the highest percentage of capillary blood glucose level within target glycaemic range of 4.4–8.3 mmol/L within the initial 24 h after transition [67].

A prospective randomised trial compared multidose insulin regimens demonstrated that split mixed insulin (NPH plus regular insulin) and basal bolus insulin regimen (glargine and glulisine) offered similar glycaemic control though basal bolus regimen was associated with a lower rate of hypoglycaemic events (15 vs. 41%) [68].

The ADA 2009 consensus statement recommend patients normally on subcutaneous insulin should be recommenced on their usual dose if this was typically adequate for glycaemic control, In patients with new onset diabetes, a multi-dose insulin regimen should be started at a dose of 0.5-0.8 U/kg per day, including regular or rapid-acting and basal insulin until an optimal dose is established [33]

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O

Patients & Methods

ur study was a prospective controlled study on 300 patients admitted to the ICU of National Institute of Diabetes and Endocrinology from the period of January 2018 to September 2018 with diagnosis of DKA based on ADA[25] criteria which is :

* 1. RBS ≥250 mg/dl
  2. serum bicarbonate level ≤18 mmol/lit
  3. PH <7.3
  4. The presence of ketone bodies in blood and urine.
  5. High anion gap metabolic acidosis.

We aimed to evaluate the effect of insulin Glargine as addition therapy to standard care of patients with DKA aiming to assess the following:

1) Impact on the Recovery from DKA:

a) amount of insulin required

b) Time required till recovery

2) Effect on different outcome parameters such as:

a) Length of ICU stay time

b) Incidence of complications

c) impact on Mortality

Inclusion Criteria:

* Patients with the diagnosis of DKA based on ADA guidelines criteria requiring admission to ICU
* Age above 18 years with consent to participate in this study.

Exclusion Criteria:

* Patients who refuse to sign the consent for the study.
* Progressive renal or hepatic failure.
* Pregnancy.
* New onset diabetes.
* Patient who received Glargin insulin within 12 hours prior to admission.

**Ethical Statement**

We confirm that the present study run in concordance with international ethical standards and applicable local regulatory guidelines. The study does not have any physical, psychological, social, legal, economic, or any other anticipated risks to study’s participants. The study conserves participants’ privacy. Investigators are responsible for keeping the security of the data. We also confirm that the participants’ data were not used for any other purpose outside this study. Personal data (e.g. Name, Contact info) were not entered in our data entry software to conserve the participants' privacy.

***All patients included in our study were subjected to the following:***

1. Written informed conscent
2. Full medical history taking
3. Full Clinical Examination, Body Weight and BMI measurement and calculation.

4-Cause of admission to ICU and presumed predisposing factor for DKA were clearly documented

5- Routine Labs and investigations on admission to ICU. (as Complete blood count, renal chemistry, full liver profile, coagulation profile, inflammatory indices, ECG, chest x-ray)

6- All 300 patients enrolled in our study were diagnosed with DKA according to ADA guidelines which were based on:

* a) Blood sugar ≥250 mg/dl
* b) Serum bicarbonate ≤18 mmol/lit,
* c) PH <7.3, and presence of ketone bodies in urine .
* d)Anion gap and ketone bodies in blood couldn’t be assessed due to limited laboratory kits availability.

7- Capillary Blood Sugar will be measured every hour (by Accu-CHEK Performa blood glucose meter) after admission and until recovery from DKA.

8- Arterial Blood Gases will be taken (GEM Premier 3000 system) every 4 hours after admission till DKA resolves.

9- Urinary ketone bodies will be assessed by urinary dipstick (Mission Expert urinalysis Reagent strips) every 4 hours after admission till DKA resolves.

10- Serum Electrolytes” Na+ & K+” will be measured every 12 hours after admission until discharge from ICU*.*

11- Patients enrolled in our study were subdivided into two groups with 150 patients each based on the management protocol for DKA: following:

1. *Group 1:* are patients with DKA who will be treated with only intravenous regular insulin(insulin Actrapid produced by NovoNordisk company) infusion , initiation by a start dose of 0.1unit/kg B.Wt. as Iv bolus followed by 0.1 u/kg/hr. iv continuous infusion as per ADA guidelines for management of DKA .Insulin infusion rate was adjusted hourly according to fluctuation of measured blood glucose levels targeting a decrease by 50-75 mg/dl/hr.
2. Group 2: are patients diagnosed with DKA who will be treated with subcutaneous injection of Glargine insulin (insulin Lantus produced by Sanofi company) in addition to standard intravenous regular insulin infusion protocol. Initiation dose of Glargine insulin was 0.3unit/kg given subcutaneously within 3 hours of starting IV Regular Insulin infusion as per protocol. Standard regular insulin protocol was initiated as a dose of regular insulin 0.1u/kg B.Wt. given as an IV bolus followed by 0.1 unit/kg/min iv continuous infusion adjusted hourly based on measured random blood glucose levels.

12- Fluid replacement would be the same in both groups: as per BDA guidelines for resuscitation and fluid management Initial fluid replacement of choice is 0.9 % sodium chloride. If patient SBP < 90 mmHg 1000 cc 0.9 % Nacl over 20-30 min (iv bolus) with reassessment of circulatory status after it. Once SBP is 90 mmHg or over .Rate of IV fluids adjusted to :

0.9% NaCl 1L 1000ml given over 1st hour

0.9% NaCl 1L with KCl. 1000ml over next 2 hours

0.9% NaCl 1L with KCl 1000ml over next 2 hours

0.9% NaCl 1L with KCl 1000ml over next 4 hours

0.9% NaCl 1L with KCl 1000ml over next 6 hours and continues till DKA recovery, Changed to 0.45% NaCl if serum Na level ≥145 mmol/L. When blood glucose level reached 250 mg/dl or less 0.9% NaCl was changed to glucose 5%.

13- Potassium Replacement protocol: based on BDA according to serum K level

* Over 5.5 mmol/ l: no correction was needed
* 3.3 to less than 5.5 mmol/l: 20-30 mEq K was to each liter of IV fluid to keep serum K at 4-5 mmol/l
* Less than 3.3: 40mEq KCl given over 1 hour until serum K ≥ 3.3 mmol.

13- All patients will be monitored after the start of treatment protocols on an hourly basis during their ICU stay until DKA is treated to avoid rebound hyperglycemia which was defined as blood sugar > 180 mg/dl up to 24 hours after discontinuation of regular insulin, and hypoglycemia which was defined as blood sugar <70 mg/dl.

14-Capillary blood sugar was monitored on an hourly basis for all patients with DKA until recovery, insulin infusion was adjusted as per protocol Insulin infusion rate was adjusted hourly according to fluctuation of measured blood glucose levels targeting a decrease by 50-75 mg/dl/hr. If blood glucose level is not falling by 50-75 mg/dl insulin dose doubled. Once glucose concentrations reached 250 mg/dl insulin dose decreased to the half.

15-All patients will be observed from their day of ICU admission until ICU discharge to evalutethe following outcome parameters:

a) Recovery from DKA which was determined by:

* Plasma glucose level <200-250
* Venous blood PH >7.3
* Serum bicarbonate concentration ≥15 mEq/L
* Absence of ketone bodies in urine

b) Amount of regular insulin required for each patient enrolled in our study during the treatment period until recovery from DKA.

c) Amount of Glargine insulin given for each patient during the study period.

d) Incidence of complications during treatment period such as hypoglycemia, hypokalemia or rebound hyperglycemia

e) Length of ICU stay

f) Incidence of mortality.

16- All data collected was secured to ensure patient confidentiality

17- **Statitistical analysis:** SPSS-24 win software used for statistical analysis. The collected data were analysed using descriptive statistical methods including frequency, percent and average ± SD. The comparisons between the study groups were made by using Chi-square test or Fisher's exact test for comparison of qualitative variables and independent t-test for quantitative variables. The normal distribution of data was assessed by Kolmogorov Simonov test. The p-values less than 0.05 were considered as significant.

O

Results

ur study was conducted on 300 patients admitted to the ICU of National Institute of diabetes and Endocrinology with proven diagnosis of DKA from period 1/2018 to 9/2018 aiming to evaluate the effectiveness of insulin Glargine on early recovery of patients with DKA when added to standard protocol of DKA management.

**Patients enrolled in our study were subdivided into two groups:**

***Group A:*** included 150 patients who received additional insluin glargine to standard therapy to treat DKA

***Group B:*** included 150 patients with the diagnosis of DKA and received standard therapy with regular insulin.

**Our results will be presented as follows:**

***A) Study group demographics***

**1) Group A**: Glargine insulin group receiving insulin glargine as add on to SOC.

In this group, 150 patients were included with mean age of 29 years median 24. They included 75 males (50 %) and 75 females (50%) with mean weight of 65.7 kg. ±11.2 and height 168.3 Cm. ±7.6 cm.

***Table (5): Patient demographics of study group receiving Insulin Glargine in addition to SOC.***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Age   1. Mean +SD 2. Median (IQR) | 29 +11.5  24 (20 -30) | |
| Gender  Male  Female | 75  75 | 50  50 |
| Weight (Kg)   1. Mean +SD 2. Median (IQR) | 65.7 +11.21  66 (57.75 -72) | |
| Height (cm)   1. Mean +SD 2. Median (IQR | 168.3 +7.6  169 (162 -174) | |

***Figure (3): Gender distribution in Insulin Glargine group***

**2) Group B:** standard of care group receiving IV. Regular insulin only.

In this group, 150 patients were included with mean age of 28.4 year median 25. They included 69 males (40 %) and 81 females (54%) with mean weight of 65.1 kg. ±11.1 and mean height 168.2 Cm. ±7.9 Cm.

***Table (6): Patients demographics of study group in Standard of care group***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Age   1. Mean +SD 2. Median (IQR) | 28.4 +11.5  25 (20 -31) | |
| Gender  Male  Female | 69  81 | 46  54 |
| Weight (Kg)   1. Mean +SD 2. Median (IQR) | 65.1 +11.1  63 (56 -71) | |
| Height (cm)   1. Mean +SD 2. Median (IQR | 168.2 +7.9  168 (162 -174.25) | |

***Figure (4): Gender distribution in Standard grou***

***B) Type of diabetes, onset and predisposing factors in study population:***

**1) Group A:** All patients in this group were diagnosed with diabetes with mean onset 7.8 years ± 5.05. They included 128 patients diagnosed to have type 1 DM (85.3 %) and 22 patients diagnosed with type 2 DM (14.7 %).

In this group of patients several factors predisposed to DKA which indicated their ICU admission where 78 patients had infection (52%) , 59 patients with poor compliance to insulin (39.3 %) ,11 patients had inappropriate dosage of insulin treatment(7.3 %) , and 2 patients had stress factor precipitating such as Acute coronary syndrome (1.3 %) .

***Table (7): Type, onset and predisposing factors of DKA in Insulin Glargine group***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Type of DM   1. T1DM 2. T2DM | 128 (85.3%)  22 (14.7%) | |
| Onset of DM in years   1. Mean +SD 2. Median (IQR) | 7.8+5.05)  7(4-11) | |
| Predisposing factors   * Infection * Inappropriate dosage * Poor Compliance * Stress | 78  11  59  2 | 52.0  7.3  39.3  1.3 |

***Figure (5): Type of DM distribution in Insulin Glargine group***

**2) Group B**: All patients in this group were diagnosed with diabetes with mean onset 7.2 years ± 5.2. They included 127 patients diagnosed to have type 1 DM (84.7 %) and 23 patients diagnosed with type 2 DM (15.3 %).

in this group of patients several factors predisposed to DKA which indicated their ICU admission where 89 patients had infection (59.4%) 47 patients with poor compliance to insulin (31.3%), 10 patients had inappropriate dosage of insulin (6.7 %) , and 4 patients had stress factors (2.7%) .

***Table (8): shows Type, onset of DM and the predisposing factors in standard of care group***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Type of DM   1. T1DM 2. T2DM | 127 (84.7%)  23 (15.3%) | |
| Onset of DM in years   1. Mean +SD 2. Median (IQR) | 7.2+5.2  6(3-10.75) | |
| Predisposing factors   * Infection * Inappropriate dosage * Poor Compliance * Stress | 89  10  47  4 | 59.4  6.7  31.3  2.7 |

***Figure (6): Type of DM distribution in Standard group***

**C) Amount of insulin required to control DKA in study population:**

**1) Group A:** in this group, patients received 2 types of insulin, regular insulin with mean units required 106.3 ± 37.8, and Glargine insulin with mean units 22.8 ± 9.3.

***Table (9): Shows total amount of insulin given in Insulin Glargine group***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Amount of Insulin Glargine |  | |
| * Mean (SD) | 22.8 +9.3 | |
| * Median (IQR) | 20 (17 -24) | |
| Amount of Regular Insulin |  | |
| * Mean (SD) | 106.3 +37.8 | |
| * Median (IQR) | 102.5 (42.5 -189) | |

**2) Group B**: in this group only, regular insulin was used with mean units 139 ± 48.9

***Table (10): Shows total amount of insulin given in standard of care group***

|  |  |  |
| --- | --- | --- |
| **Variables** | **Patients (N =150)** | |
| No | % |
| Amount of Regular Insulin |  | |
| * Mean (SD) | 139.4 (48.9) | |
| * Median (IQR) | 128 (63.5 -253) | |

**D) Incidence of complications in study population:**

**1) Group A** : in this group , 15 patients had rebound hyperglycemia ( 10%), 12 patients had hypoglycemic episodes (8%) , hypokalemia in 17 patients (11.3%) , AKI in 10 patients (6.7 %) ,hepatic dysfunction in 4 patients ( 2.7%), unstable angina in 2 patients (1.3%) , and only 1 patient had either CVS ,fits, or TIA .

*Table (11): The rate of complications in Insulin Glargine group*

|  |  |  |
| --- | --- | --- |
| **Complications** | **Patients (N =150)** | |
| No | % |
| * Rebound Hyperglycemia | 15 | 10.0 |
| * Hypoglycemia | 12 | 8.0 |
| 1. Hypokalemia | 17 | 11.3 |
| 1. AKI | 10 | 6.7 |
| 1. Hepatic Dysfunction | 4 | 2.7 |
| 1. Unstable angina | 2 | 1.3 |
| 1. CVS | 1 | 0.7 |
| 1. Fits | 1 | 0.7 |
| 1. TIA | 1 | 0.7 |

*Figure (7): The rate of complications in Insulin Glargine group*

**2) Group B**: in this group , 20 patients had rebound hyperglycemia ( 13.3%), 14 patients had hypoglycemic episodes (9.3%) , hypokalemia in 18 patients (12%) , AKI in 13 patients (8.7 %) ,CVS in 5 patients (3.3 %) hepatic dysfunction in 3 patients ( 2%), unstable angina in 2 patients (1.3%).

*Table (12): The rate of complications in Standard group*

|  |  |  |
| --- | --- | --- |
| **Complications** | **Patients (N =150)** | |
| No | % |
| * Rebound Hyperglycemia | 20 | 13.3 |
| * Hypoglycemia | 14 | 9.3 |
| * Hypokalemia | 18 | 12 |
| * AKI | 13 | 8.7 |
| * CVS | 5 | 3.3 |
| * Hepatic dysfunction | 3 | 2 |
| * Unstable angina | 2 | 1.3 |

***Figure (8): The rate of complications in Standard group***

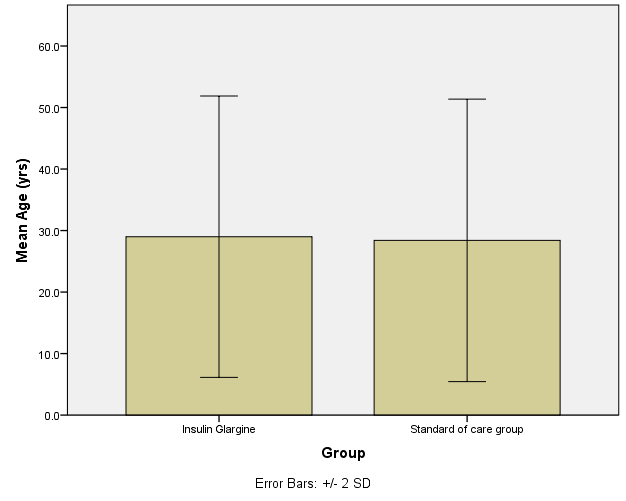
E) Comparison between both study groups as regards to different outcome parameters:

***1) Demographics:***

**a) Age**: In our study comparing both groups regarding age, there was no statistically significant difference with p-value 0.654.

***Table (13): Shows the difference in Age according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Age |  |  |  |  |
| -Mean +SD | 29 +11.5 | 28.4 +11.5 | -.689 | 0.654 |
| -Median (IQR) | 24 (20 -30) | 25 (20 -31) |



***Figure (9): Age distribution in Insulin Glargine and Standard groups***

**b) Gender**: regarding gender there was no statistically significant difference between both groups with p-value 0.488.

***Table (14): Shows the difference in gender according to type of therapy***

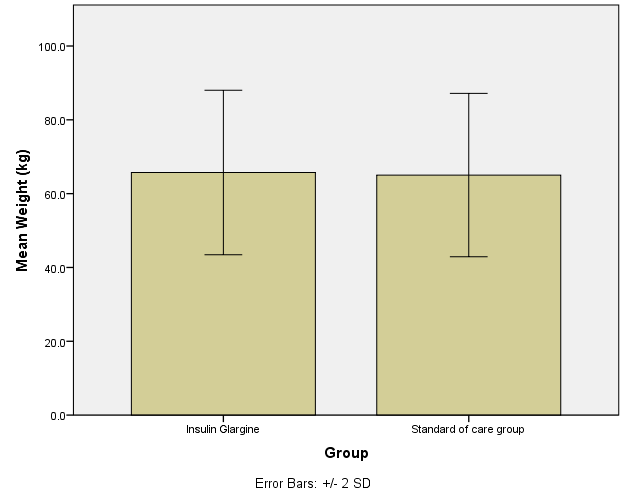
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Group | | DM treatment | | P- value |
| **IG** | **SOC** |
| Male | No. | 75 | 69 | 0.488 |
| % | 50.0% | 46.0% |
| Female | No. | 75 | 81 |
| % | 50.0% | 54.0% |
| Total | No. | 150 | 150 |
| % | 50.0% | 50.0% |

***Figure (10): Gender distribution in insulin Glargine and Standard group***

**c) Weight**: comparing both groups regarding weight there was no statistically significant difference between both groups with p-value 0.58**.**

***Table (15): Shows the difference in Weight according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Weight |  |  |  |  |
| -Mean (SD) | 65.7 (11.21) | 65.1 (11.1) | 0.541 | 0.58 |
| -Median (IQR) | 66 (57.75 -72) | 63 (56 -71) |

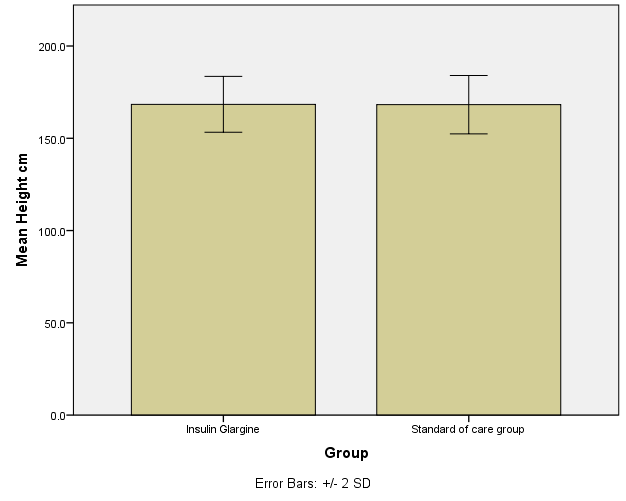


***Figure (11): Weight distribution in Insulin Glargine and Standard groups***

**d) Height**: in our study, regarding height there was no statistically significant difference between both groups with p-value 0.298.

***Table (16): Shows the difference in Height according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Height |  |  |  |  |
| * Mean +SD | 168.2 +7.9 | 168.3 +7.6 | 0.164 | 0.298 |
| * Median (IQR) | 168 (162 -174.25) | 169 (162 -174) |



***Figure (12): Height distribution in Insulin Glargine and Standard groups***

**2) Type, onset of DM and Predisposing factors:**  Regarding type of DM there was no statistically significant difference between both groups with p-value 0.87 in our study.

***Table (17): Shows the difference in DM type according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Group | | DM Type | | P- value |
| **IG** | **SOC** |
| T1DM | No. | 128 | 127 | 0.87 |
| % | 85.3% | 84.7% |
| T2DM | No. | 22 | 23 |
| % | 14.7% | 15.3% |
| Total | No. | 150 | 150 |
| % | 100% | 100% |

***Figure (13): DM type distribution in insulin Glargine and Standard group****.*

In our study, regarding onset of diabetes there was no statistically significant difference between both groups with p-value 0.319.

***Table (18): Shows the difference in onset of diabetes according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Onset of diabetes |  |  |  |  |
| * Mean (SD) | 7.8 (5.05) | 7.2 (5.2) | 0.999 | 0.319 |
| * Median (IQR) | 7 (4 -11) | 6 (3 -10.75) |

There was no statistically significant difference between both groups as regard for the predisposing factors for developing DKA p-value 0.273.

***Table (19): Shows the difference in predisposing factors according to type of therapy***

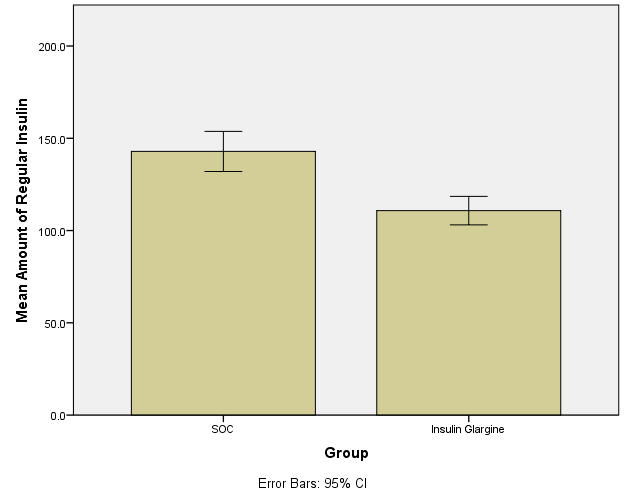
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Group | | DM Type | | P- value |
| **IG** | **SOC** |
| Infection | No. | 78 | 89 | 0.273 |
| % | 52.0% | 59.4% |
| Inappropriate dosage | No. | 11 | 10 |
| % | 7.3% | 6.7% |
| Poor Compliance | No. | 59 | 47 |
| % | 39.3% | 31.3% |
| Stress | No. | 2 | 4 |
| % | 1.3% | 2.6% |
| Total | No. | 150 | 150 |
| % | 100% | 100% |

*Figure (14): Predisposing factors in Insulin Glargine and Standard groups*

**3) Insulin requirement to control DKA**: regarding needs for regular insulin till recovery from DKA there was statistically significant difference between booth groups, patients in insulin Glargine group received significantly lower amounts of regular insulin units (mean 106.3 ±37.8 vs. 139.4±48.9) p-value < 0.001.

***Table (20): Shows the difference in Amount of Regular Insulin according to type of therapy***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Amount of Regular Insulin | | | | |
| * Mean +SD | 106.3 +37.8 | 139.4 +48.9 | 4.778 | <0.001 |
| * Median (IQR) | 102.5 (42.5 -189) | 128 (63.5 -253) |

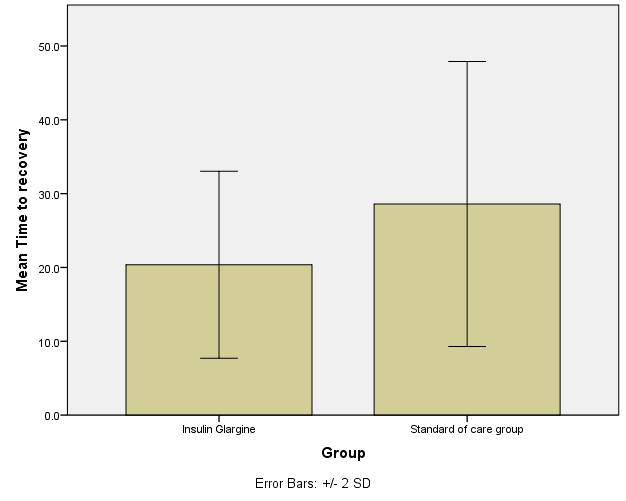


***Figure (15): Amount of insulin in Insulin Glargine and Standard groups***

**4) Time to recovery from DKA:** comparing both groups regarding time of recovery (in hours) from DKA between both groups Glargine insulin group had significantly lower time to recovery from DKA (mean time 20.4 hrs ±6.3 vs. 28.6 hrs ±9.6).

***Table (21): Shows the difference in time to recovery according to type of therapy in hours***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| Time to recovery | |  |  |  |
| * Mean +SD | 20.4 +6.3 | 28.6 +9.6 | -8.726 | <0.001 |
| * Median (IQR) | 20 (15 -24) | 26.5 (22 -32) |

****

***Figure (16): Time to recovery in Insulin Glargine and Standard groups***

**5) Incidence of complications:** comparing both groups regarding rate of complications as rebound hyperglycemia, hypoglycemia, and hypokalemia there was no statistically significant difference in rate of complications between both groups (p value 0.362, 0.168, 0.858 respectively).

***Table (22): Shows the difference in rate of complications according to type of therapy***

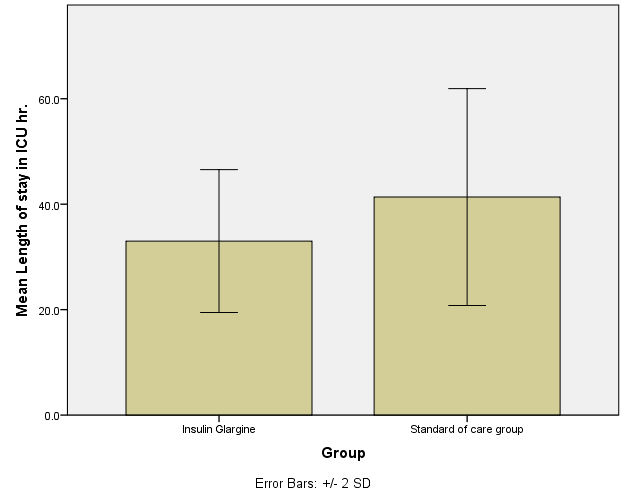
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **IG** | | **SOC** | | **P-values** |
| **Percentage** | **NO.** | **Percentage** | **NO.** |
| **Rebound hyperglycemia** | 10 % | 15 | 13.3 % | 20 | 0.362 |
| **Hypoglycemia** | 8 % | 12 | 9.3 % | 14 | 0.168 |
| **Hypokalemia** | 11.3 % | 17 | 12 % | 18 | 0.858 |
| **AKI** | 6.7 % | 10 | 8.7 % | 13 | 0.514 |
| **Hepatic dysfunction** | 2.7 % | 4 | 2 % | 3 | 0.702 |
| **CVS** | 0.7 % | 1 | 3.3 % | 5 | 0.09 |
| **Unstable angina** | 1.3 % | 2 | 1.3 % | 2 | 0.99 |
| **Fits** | 0.7 % | 1 | 0 % | 0 | 0.316 |

***Figure (17): Rate of complications in insulin glargine and standard grou***

**6) Length of ICU stay:** comparing both groups regarding length of ICU stay glargine insulin group had significantly lower length of ICU stay (mean 33hrs ± 6.8 vs. 41.4hrs ± 10.5) with p-value < 0.001 .

***Table (23): Shows the difference in Length of ICU stay according to type of therapy in hours***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | IG | SOC | Independent t test | P-value |
| LOS in hours |  |  |  |  |
| * Mean +SD | 33 +6.8 | 41.4 +10.5 | -8.308 | <0.001 |
| * Median (IQR) | 32 (28 -37) | 39 (35 -45) |



***Figure (18): LOS in ICU in Insulin Glargine and Standard groups****.*

Discussion

D

iabetic ketoacidosis (DKA) is a common cause of intensive care unit (ICU) admission, with high morbidity and mortality rates. The current body of evidence shows that DKA is still the main cause of death in children and adolescents with type 1 diabetes mellitus (T1DM) and it results in long-term sequelae in 10-25% of survivals[69]. However, with the introduction of insulin, the mortality rates from DKA showed a dramatic decrease to reach 2-5% [70].

Recently, a growing body of evidence has suggested that adding insulin Glargine to the standard regimen may facilitate the transition from an intravenous infusion of insulin to subcutaneous injection in the recovery of patients with DKA. [71]

Our study was a prospective controlled study on 300 patients admitted to the ICU of National Institute of Diabetes and Endocrinology from the period of January 2018 to September 2018 with diagnosis of DKA based on ADA criteria which is :

* 1. RBS ≥250 mg/dl
  2. serum bicarbonate level ≤18 mmol/lit
  3. PH <7.3
  4. The presence of ketone bodies in urine.

We aimed to evaluate the effect of insulin Glargine as addition therapy to standard care of patients with DKA aiming to assess the following:

1) Recovery from DKA: a) amount of insulin required

b) time required till recovery

2) Effect on outcome: a) ICU stay time

b) complications

Both groups were comparable in terms of baseline characteristics such as age, gender, and weight, height onset and type of DM and the predisposing factor for DKA .there was no statistically significant difference between them .

Regarding time of recovery it was found that GI group recover earlier than SOC with mean time to recover 20.4±6.3 hr. vs. 28.6±9.6 hr respectively That was statistically significant with P-value <0.001.

In agreement with these findings, **Shankar and colleagues** had studied the effect of subcutaneous administration of insulin glargine on the rate of resolution of acidosis and intravenous insulin infusion requirement in children with moderate and severe diabetic ketoacidosis .71 children included in his study, The patients were divided into two groups based on whether they received or did not receive insulin glargine (0.3 units/kg) within the ﬁrst 6h of treatment .He founded The children in the glargine group had a faster correction of acidosis which was 12.4±2.9 hrs in Glargine group vs 17.1±6.2 hrs in control group which was statistically significant with P-value <0.001. [72]

In concordance with these findings**, Houshyar and colleagues** performed a randomized clinical trial conducted on 40 patients with DKA to investigate the effects of insulin Glargine on the recovery of patients with DKA. Experimental group was given 0.4U/kg of GI within three hours of initiation of IV insulin infusion the mean duration of acidosis correction time and recovery from DKA was 13.77±6.10 and 16.91±6.49 h in the intervention and control groups respectively (p-value=0.123). It wasn’t statistically significant. [71]

In line with these findings, **Andrade-Castellanos and colleagues** performed a systematic review and meta-analysis on four studies (135 participants during hospital follow-up) to evaluate adding subcutaneous insulin Glargine to SOC protocol with IV regular insulin alone in patients with DKA. Insulin glargine subcutaneous dose ranged from 0.25 to 0.4 U/kg, which was administered between the first 2, 3, 6 and 12 hr of having initiated the insulin IV infusion, to subsequently continue with a subcutaneous dose every 24 h until DKA resolution .The pooled results in three studies showed that subcutaneously administered insulin glargine, in addition to the SOC, significantly reduces the time to resolution of DKA [73].

**Doshi and colleagues** conducted a randomized controlled trial on 40 patients, divided inot 2 groups, to determine the efficacy of coadministration of subcutaneous insulin Glargine in combination with intravenous insulin for treating them. This was a prospective, randomized, controlled trial comparing coadministration of insulin glargine and IV insulin (experimental) with IV insulin (standard care control). Additionally, the experimental group was given sc. insulin glargine within 2 hours of diagnosis. Upon closure of anion gap, patients in the control group were subsequently transitioned to long-acting insulin. In the study group, IV insulin was discontinued and long-acting sc. insulin was reinstituted 24 hours after initial introduction. The primary outcome of time to closure of anion gap was compared between groups. Results showed that the estimated mean time to closure of anion gap was 10.2 hours in the experimental group and 11.6 hours in the control group (p-value = 0.63). But it was statistically insignificant [74]

In contrary to these findings, **Harrison and colleagues** in retrospectivestudy to evaluate if the practice of administering subcutaneous glargine during intravenous insulin is associated with an increased risk of hypoglycemia, hypokalemia, or other complications in children with DKA. Patients were divided into distinct groups: those with preexisting T1D, and those with new-onset T1D. In each group, children who received glargine ≥ 4 hours before discontinuation of intravenous insulin infusion (G+group) were compared with those who received glargine ≤ 2 hours, or no subcutaneous insulin, before cessation of infusion (G− group). These time thresholds were chosen to ensure a detectable overlap in the insulin action of glargine with the insulin infusion in the G+ group, based on glargine pharmacokinetics. Results showed that (G+group) had increase in duration of acidosis. in pre-existing T1D group duration of acidosis was 10.9 hrs in (G+ group) compared to 6.6 hrs in (G− group) P-value 0.002. In new onset T1D group it was 8.1 hrs in (G+ group) compared to 5.9 hrs in (G− group) P-value 0.06 [75]

In our study, total amount of intravenous insulin infusion was much lower in GI group than in SOC group with mean requirements 106.3 vs. 139.4 units respectively. That was statistically significant with P-value <0.001.

In agreement with these findings , **Shankar and colleagues ,** in there study had founded that the total amount of intravenous insulin required was signiﬁcantly higher in the standard group than in the glargine group 43±31.6 u in glargine group vs 89.4±68.8 u in control group That was statistically significant with P-value (p=0.026).[72]

**Houshyar and colleagues**, in there study founded that the mean dosage of RI until recovery from DKA was 84.8±45.6 in the intervention and 116.5±91.6 units in control groups . it was much less in intervention group with (p-value=0.17) [71]

In the present study, we used the length of ICU stay as the primary outcome parameter. Our analysis showed that added insulin Glargine resulted in a significantly shorter length of ICU stay, compared to SOC alone with total time 33±6.8 vs. 41.4±10.5 hrs. respectively. That was statistically significant with P-valu < 0.001.

**Shankar and colleagues** had founded that There was no statistically signiﬁcant difference in total length of stay in the hospital between the two groups (3.2±1.0days in the glargine group vs 3.72±1.06days in the standard insulin group) despite a trend towards shorter stay in the glargine group [72].

**Houshyar and colleagues**, in their study founded that the mean The mean duration of hospitalization was 5.1±1.88 days in intervention and 5.9±2.19 days in control group (p-value=0.225).it was much less in intervention group but his data was statistically insignificant.[71]

In contrary to our findings, in **Doshi and colleagues** study the secondary outcome parameter was hospital length of stay (LOS) it was adjusted for age, etiology. The estimated mean hospital LOS was 3.9 days in the experimental group and 4.8 days in the control group (p-value = 0.66). Though the authors reported that coadministration of Glargine in combination with an insulin infusion in the acute management of DKA is feasible, it did not result in a statistically significant shorter length of hospital stay [74].

***E)*** Regarding incidence of complications there was no increase in rate of hypoglycemia, hypokalemic episodes rates between both groups.

In concordance with that in **Houshyar and colleagues** study there was no siginficant increase in rate of hypokalemia between both groups .Hypokalemia occurred in three patients in intervention and four patients in control groups .[71]

In agreement with this finding, **Doshi and colleagues, in** their study**,** Rate of hypoglycemia was compared between both groups. There were no hypoglycemic episodes during iv insulin infusion in either group. There were three asymptomatic hypoglycemic measurements in two control subjects (68, 62, and 58 mg/dl) during the 12 h of postinfusion follow-up and none in the intervention group. the authors reported that coadministration of Glargine in combination with an insulin infusion in the acute management of DKA didn’t increased rate of hypoglycemia.[74]

In a controlled multicenter and open-label trial done by **Umpierrez GE and collegues**, To compare the safety and efficacy of insulin analogs and human insulins both during acute intravenous treatment and during the transition to subcutaneous insulin in patients with diabetic ketoacidosis (DKA) they randomly assigned patients with DKA to receive intravenous treatment with regular or glulisine insulin until resolution of DKA. After resolution of ketoacidosis, patients treated with intravenous regular insulin were transitioned to subcutaneous NPH and regular insulin twice daily (*n* \_ 34). Patients treated with intravenous glulisine insulin were transitioned to subcutaneous glargine once daily and glulisine before meals (*n* \_ 34). Results showedThere were no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA between intravenous treatment with regular and glulisine insulin. After transition to subcutaneous insulin, there were no differences in mean daily blood glucose levels, but patients treated with NPH and regular insulin had a higher rate of hypoglycemia (blood glucose <70 mg/dl). Fourteen patients (41%) treated with NPH and regular insulin had 26 episodes of hypoglycemia and 5 patients (15%) in the glargine and glulisine group had 8 episodes of hypoglycemia (p-value 0.03). this study indicated that after resolution of DKA, transition to subcutaneous glargine once daily and glulisine before meals resulted in similar glycemic control but in a lower rate of hypoglycemic events than treatment with NPH and regular insulin twice daily.These findings indicate that a basal bolus insulin regimen with glargine and glulisineis safer and should be preferred over NPH and regular insulin after the resolution of DKA. [68]

In contrary of our finding, in **Harrison and colleagues** studyrate of hypokalemia in (G+group) which was defined as serum potassium level <3.5 mmol/L it was was compared between study groups. In pre-existing T1D group, rate was 25% in (G+group) vs. 19% in (G−group) with P-value 0.5. In new onset T1D group hypokalemai rate was 71% in (G+group) vs. 47% in (G−group) with P-value 0.1. He stated tha hypokalemia occurred more frequently in(G+group) this data was statistically insignificant. Regarding hypoglycemia there was no significant increase in risk of hypoglycemia. Their study showed that Co-administration of glargine early in the course of DKA treatment is well tolerated and convenient for discharge planning. [75].

In our study, in 24 hours after discontinuation of iv insulin infusion at least one reading of blood glucose level ≥180 mg/dl (rebound hyperglycemia) in 20 patients in standard group vs. 15 patients in control group. this difference was not statistically significant with p-value 0.362. This is attributable to long half-life of GI and continuation of its effect for many hours after discontinuing of RI.

In agreement with this finding in **Houshyar and colleagues** study Occurrence of blood glucose level >8.3 mmol/l (150 mg/dl) in first 24 hours after discontinuation of the insulin infusion (rebound hyperglycemia). Averagely, in 1.4±1.04 samples (35% of four checked samples) in intervention group and in 2.05±0.94 samples (51% of four checked samples), it was statistically significant with (p-valu=0.046).[71]

The addition of insulin Glargine to regular insulin appears to be well-tolerable as well. **Hsia and colleagues** in prospective randomized controlled study 61 patients with known type1 or type2 DM on iv insulin infusion divided into two groups. 32 patients in the intervention group received daily injections of 0.25u/kg bodyweight of insulin Glargine sc. Within 12 hr of initiating iv insulin infusion. The primary outcome of this study was to compare the rates of rebound hyperglycemia between the conrol group and the intervention group after iv insulin infusion is discontinued. Results showed that Overall, 29 subjects in the control group (93.5%) had at least one glucose value above 180 mg/dl during the 12-hrs follow-up period. This was significantly greater than the rate of rebound hyperglycemia in the intervention group(10 subjects or 33.3%,) with P-vaue <0.001 .He approved that once daily sc. Insulin glargin administered during iv insulin infusion is a safe method to prevent future rebound hyperglycemia without increased risk of hypoglycemia [6].

The exact causes of this discrepancy between our findings and this report are unclear. However, it can be attributed the difference in administrated doses of insulin Glargine, study’s methodology, or patients’ characteristics.

In summary, in our study subcutaneous insulin Glargine coadministration with regular insulin results in a shorter length of hospital stay and less amount of infused insulin in DKA patients admitted to ICU.

Conclusion

S

ubcutaneous insulin Glargine co-administration with regular insulin results in a shorter length of ICU stay and less amount of infused insulin in DKA patients admitted to ICU, without increasing risk of hypokalemia or hypoglycaemic episodes. Nevertheless, further large-scale studies are still needed to confirm our findings.

Recommendation & Limitation

W

e acknowledge that the present study has some limitations. The sample size of the present study was relatively small which may affect the generalizability of our findings for type 2DM patients. In addition. The patients were not followed after hospital charge as well .So a Larger multi-centric trial is still needed to confirm our findings for type 2 patients suffering from DKA .

Summary

D

iabetic Ketoacidosis (DKA) is a potentially fatal metabolic disorder presenting as a common cause of intensive care unit admission. The disorder can have significant mortality if misdiagnosed or mistreated.

The main features of DKA are hyperglycemia, metabolic acidosis with a high anion gap and heavy ketonuria.

Insulin Glargin is along-acting basal insulin analogue shows no plasma insulin peaks. Insulin glargin was reported to be safe and effective to be added to the standard protocols of DKA management giving the advantage of reducing time of recovery of DKA patients and facilitate the transition from intravenous insulin infusion to subcutaneous injection, with no increase in risks of hypoglycemia, nor hypokalemia.

Our study was prospective controlled trial conducted on 300 patients admitted to the ICU of National Institute of diabetes and Endocrinology with proven diagnosis of DKA from period 1/2018 to 9/2018 aiming to evaluate the effectiveness of insulin glargin on early recovery of patients with DKA when added to standard protocol of DKA management compared to regular insulin alone .

***Our study showed the following results:***

There was no statistically significant difference between both groups regarding age, gender, weight, and height p value 0.654,0.488, 0.58, 0.298 respectively.

There was no statitistically significant difference between both groups as regards type of diabetus, onset of diabetes or predisposing factors for DKA, p value: 0.87, 0.319, 0.273respectively

There was a statistically significant difference between both groups regarding insulin required to control DKA, p value <0.001 favoring the insulin glargine group.

There was a statistically significant difference between both groups regarding time to recovery from DKA, p-value <0.001 favoring the insulin glargine group.

There was no a statistically significant difference between both groups regarding incidence of complications during DKA management as hypoglycemia, hypokalemia and rebound hyperglycemai, p-value (0.168, 0.858, 0.362) respectively.

There was a statistically significant difference between both groups regarding total time of ICU stay ,p-value <0.001 favoring the insulin glargine group.

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