Role of Insulin Glargine in Early Phase of Treatment of Diabetic Ketoacidosis

Thesis

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CONTENTS

List of Abbreviations

Aao2.....Alveolar to arteriolar oxygen
ACE .....Angiotensin converting enzyme
ADA.....American Diabetes Association
BDA .....British Diabetes Association
BE .....Brain Edema
BMI.....Body mass index
CDC.....Center for Disease Control
CNS.....Central Nervous System\
CPT.....Carnitine Palmityle – Transferase
CRP .....C- reactive protein
CSII .....Continuous subcutaneous insulin infusion
CT .....Computerized tomography
CXR.....Chest X- ray
DCL .....Disturbed conscious level
DKA.....Diabetic ketoacidosis
DM.....Diabetes mellitus
DN.....Diabetic nephropathy
DR.....Diabetic retinopathy\
ECG.....Electrocardiogram
ESRD.....End stage renal disease
F-6-P .....Fructose- 6- phosphate
FFA.....Free fatty acid
GAD.....Glutamic acid decarboxylase
GDM.....Gestational diabetes mellitus
GFR .....Glomerular filtration rate

G-6-P ..... Glucose-6- phosphate
HHS ..... Hyperosmolar hyperglycemic state
HK ..... Hexokinase
HLA ..... Human leukocyte antigen
HMP ..... Hexose monophosphate
ICU ..... Intensive care unite
K..... Potassium
MRI ..... Magnetic resonant image
MSU..... Mid - stream urine.
Na..... Sodium
NGT ..... Normal glucose tolerance
PC ..... Pyruvate carboxylase
PEP ..... Phosphoenol pyruvate
PEPCK ..... Phosphoenol pyruvate carboxykinase
PFK..... Phosphofructokinase
PK ..... Pyruvate kinase
β-OHB ..... Beta-hydroxybutyrate
SOC ..... Standard of care
TIDM..... Type I diabetes mellitus
T2DM ..... Type 2 diabetes mellitus
TCA ..... Tricarboxylic acid
TG..... Triglycerides
WBC ..... White blood cell
µalb..... micro albuminuria

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Abstract

Background: Diabetic ketoacidosis (DKA) is a common cause of intensive care unit (ICU) admission, with high morbidity and mortality rates. 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. **Aim of the Work:** to investigate the effect of adding Insulin Glargine to the standard regimen of treatment of DKA on the recovery process of patients regarding the amount of intravenous insulin infusion and the duration of the patients' stay in the ICU. **Patient and Methods:** This randomized controlled study was conducted on 50 Egyptian individuals, in National Institute of Diabetes and Endocrinology & Ain Shams University Hospitals. 50 Patients with Diabetic Ketoacidosis diagnosed according to The American Diabetes Association criteria. All patients were divided into 2 groups according the protocol used for treatment: The first group including 25 patients treated only with the standard regimen of intravenous regular insulin infusion (0.1 unit/kg/hour). The second group including 25 patients treated with intravenous regular insulin (0.1 unit/kg/hour)+ Iv infusion of normal saline. **Results:** Added insulin Glargine resulted in a significantly shorter length of hospital stay, compared to SOC alone. The present study showed that insulin Glargine led to statistically significant less amount of insulin infused until resolution of DKA than the SOC alone. **Conclusion:** 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. Larger multi-centric trials are still needed to confirm our findings.

Key words: Insulin Glargine, Diabetic Ketoacidosis

INTRODUCTION

The number of people diagnosed with diabetes mellitus (DM) is increasing. DM is one of the most common diseases as it had affected about 285,000,000 persons in 2010 in the world. It is estimated that DM will be affecting 592,000,000 persons in 2035. ***(Raslova, 2010)***

Diabetic Ketoacidosis (DKA) is an emergency conditions that is caused by acute hyperglycemia which may be associated with both type 1 and 2 diabetes but mostly type 1.It is the cause for 10,000 to 160,000 diabetic patients' hospitalizations in US ***(Piva et al., 2007).***

DKA is a serious life-threatening condition in which the severe insulin deficiency causes hyperglycemia, severe lipolysis and oxidation of fatty acids and ketone bodies formation. The process causes metabolic acidosis, dehydration and loss of body electrolytes ***(Shankar et al., 2007a).***

The basic treatment of DKA is Intravenous infusion of Regular Insulin. It is the preferred method of treatment until recovery from DKA. Then, the treatment is continued with subcutaneous injection of insulin. Regular Insulin has a short half-life as a few minutes, so it requires the infusion pump and it is associated with hospitalization and nursing costs ***(American Diabetes Association, 2014).***

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 hour. ***(Goykhman et al., 2009).***

Given these pharmacodynamics of Glargine Insulin, it seems that addition of these long acting insulin to standard regimen might facilitate the transition from intravenous infusion of insulin to subcutaneous injection in the recovery of patients with DKA, so that the British Diabetes Association (BDA) recommends that in DKA patients using long-acting insulin (glargine or Detemir) prior to DKA, it must be continued with the same dosage in the phase of DKA ***(Barski et al., 2018).***

AIM OF THE WORK

The aim of this study is to investigate the effect of adding Insulin Glargine to the standard regimen of treatment of DKA on the recovery process of patients regarding the amount of intravenous insulin infusion and the duration of the patients' stay in the ICU.

DIABETIC KETOACIDOSIS IN ADULTS

Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes. The National Diabetes Surveillance Program of the Center for Disease Control (CDC) estimated that there were 120,000 hospital discharges for DKA in 2005 in the United States. It has been estimated that treatment of DKA episodes represent about one of every four health care dollars spent on direct medical care for adult patients with type 1 diabetes ***(Lakhtakia, 2010).***

The mortality for DKA before the discovery of insulin was greater than 90%. This was dramatically reduced in subsequent years to less than 50% and was further reduced to less than 20% with the incorporation of antibiotics and forced hydration. In the 1950s, the mortality of patients with DKA treated with high doses of insulin was reported to be less than 10% ***(Wang et al., 2008).***

In more recent years, the use of standardized written guidelines for therapy has resulted in a mortality rate less than 5%, with higher mortality observed in elderly subjects and in patients with concomitant life threatening illnesses ***(Centers for Disease Control and Prevention, 2014).***

In the last decade there has been significant improvement of survival among DKA patients in most developed countries and now mortality rates are reported to

be 1%. Improved health education of out-patient diabetics and introduction of hospital management guidelines of DKA might explain such an improvement of survival. ***(Umpierrez & Korytkowski, 2016).***

In this chapter, we reviewed the recent advances in our understanding of the development and complications of DKA in adults.

A- Definition and Incidence of DKA:

Diabetic ketoacidosis (DKA) is an extreme metabolic state caused by insulin deficiency. The breakdown of fatty acids (lipolysis) produces ketone bodies (ketogenesis), which are acidic. Acidosis occurs when ketone levels exceed the body's buffering capacity brain ***(Zabar, 2013).***

Data from the UK National Diabetes audit shows a crude one year incidence of 3.6% among people with type I diabetes mellitus (TIDM). In the UK nearly 4% of people with type 1 diabetes experience DKA each year, the number of DKA episodes per 100 patient years is 4.8, about 6% of cases of DKA occur in adults newly presenting with type 1 diabetes, and about 8% of episodes occur in hospital patients who did not primarily present with DKA ***(Misra, 2015).***

With regards to North America (USA and Canada), two long-term observational cohorts found that the