COMPARISON BETWEEN DIFFRENT INSULIN PROTOCOLS IN TREATMENT OF CRITICALLY ILL PATIENT

ESSAY

Submitted by:
Dr/ Mohamed Diaa El-Deen Mohamed Abd-Elaziz
M.B.B.CH

In partial fulfillment of Master Degree in intensive care medicine

Supervised by

Prof.Dr.SAMIR ABD ELRAHMAN ELSEBAEY
Professor of anesthesia &critical care
Ain Shames university

Dr.MAHMOUD AHMED ABDEL HAKIM
Lecturer of anesthesia &critical care
Ain Shames university

٢٠١٣

Contents

List of Abbreviations

Amp	Ampoule
B.G	Blood glucose
Cl	Chloride
D.K.A	Diabetic ketoacidosis
D٥٠	Dextrose ٥٠ %
D٥W	٥٪ dextrose in water
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
FDA	Food and Drug Administration
GIP	glucose dependent insulin tropic polypeptide
GKI	glucose, potassium and insulin
GLP	glucagons like peptide
H.H.S	Hyperglycemic hyperosmolar diabetic coma
I.C.U	Intensive care unit
I.D.D.M	Insulin dependent diabetes mellitus
I.V	Intra venous
K	Potassium
KCL	Potassium chloride
Mg	Magnesium
N.S	Normal saline
Na	Sodium

Nacl	Sodium chloride
S.C	Subcutaneous
T.P.N	total parenteral nutrition
VISEP	Volume Substitution and Insulin Therapy in Severe Sepsis study

List of tabels

List of figures

INTRODUCTION

An optimal target for glucose control in ICU patients remains unclear. This prospective randomized controlled trial compared the effects on ICU mortality of intensive insulin therapy (IIT) with an intermediate glucose control .In a recent randomized controlled trial, lowering blood glucose levels to ٨٠–١١٠ mg/dl improved clinical outcomes in critically ill patients. In that study, the insulin infusion protocol (IIP) used to normalize blood glucose levels provided valuable guidelines for adjusting insulin therapy. In our hands, however, ongoing expert supervision was required to effectively manage the insulin infusions. This work describes our early experience with a safe, effective, nurse-implemented IIP that provides detailed insulin dosing instructions and requires minimal physician input ***(Preiser et al.,*** ٢٠٠٩***)***

Control of blood glucose (BG) in critically ill patients is considered important, but is difficult to achieve, and often associated with increased risk of hypoglycemia. We examined the use of a computerized insulin dosing algorithm to manage hyperglycemia with particular attention to frequency and conditions surrounding hypoglycemic events **(*Bagshaw, et al.* ٢٠٠٩***)***

The recent publication of the results of an aggressive approach to the treatment of hyperglycaemia in critically ill patients, and a rekindling of interest in the use of an infusion of glucose insulin and potassium as adjunctive therapy in a diverse group of patients with cardiovascular disease, warrants a review of the multiple effects of insulin and a review of laboratory and clinical studies*. (Thomas Solano, et al.* ٢٠٠٤ *)***

Chapter ١

Physiology & pathophysiology of diabetes& different methods of insulin administration

Types of Diabetes

Disorder arising from the loss of insulin action is ٤ types:
*Insulin. dependent.(IDDM).....١٠٪ (Juvenile onset) occurs when the pancreas no longer produces any or very little insulin.
*Non-insulin dependent.....٩٠٪ (Adult onset) occurs when the pancreas does not produce enough insulin or when the body does not use the insulin that is produced effectively.
*Gestational diabetes
*Diabetes insipidus ***(light p. et al٢٠٠٨)***

Risk Factors

Although the causes of diabetes are unknown, there are several factors that can increase the risk of developing diabetes.
For Type ١ diabetes, risk factors include:
Race/ethnicity (diabetes is more prevalent in people of Aboriginal, African and Latin-American descent); and family history of diabetes.
For Type ٢ diabetes the risk factors include:
age (over ٤٥ years old);
obesity (the number of people with diabetes in an unhealthy weight range is double that found in the population without diabetes);gave birth to a large baby (over ٤,٠ kg/٩ lbs.); and a previous diagnosis of impaired glucose tolerance

(light p. et al ٢٠٠٨***)***

Control of insulin release

Stimulants (insulin secretagogues)
Glucose
Amino acids
Fatty acids (acute NOT chronic)
Sulphonylureas

Inhibitors

Somatostatin

Sympathetic activation (alpha-٢ ARs on beta-cells)

Decreased blood glucose

Mechanisms of Insulin Action

Binds to insulin receptor Dimerizes and tyrosine kinase activity increased…leads to:

Autophosphorylation of receptor Phosph-

orylation of targetproteins ***(light p.et al*** ٢٠٠٨***)***

Cellular mechanisms of insulin action

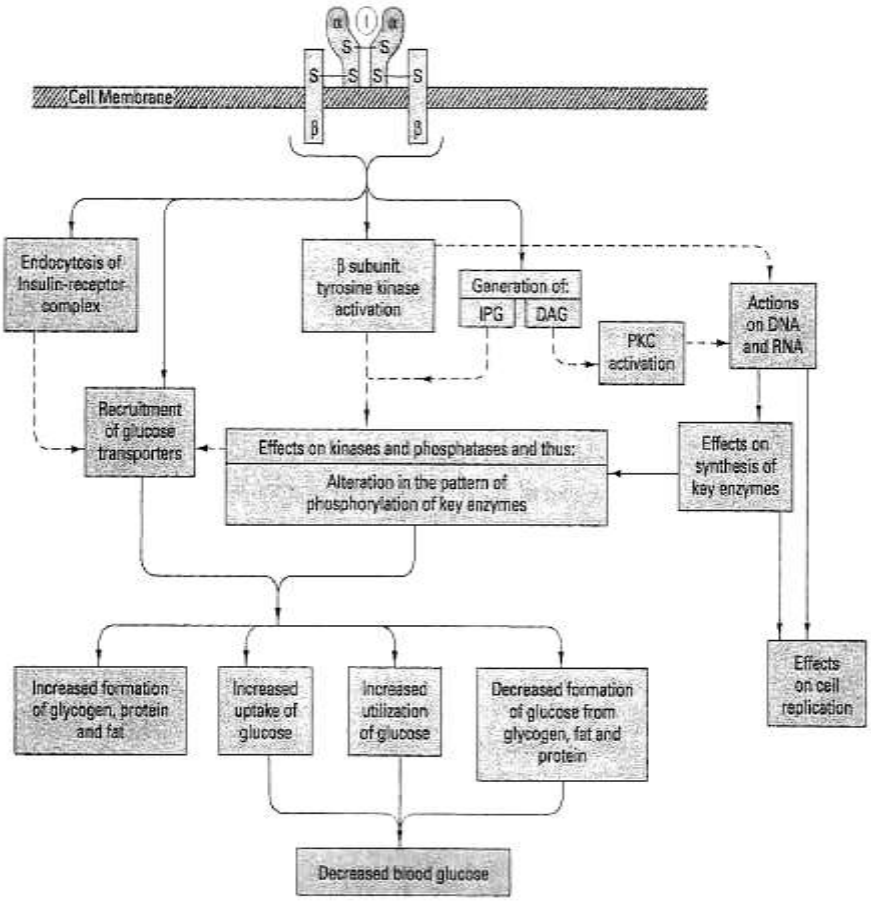

figure ١

****The Pathophysiology of Diabetes**

Pathophysiology of diabetes Involves a Defective Amplification of the Late-Phase Insulin Response to Glucose by Glucose-dependent Insulinotropic Polypeptide

Glucagons like peptide-١ (GLP-١) &glucose dependen insulinotropic polypeptide (GIP) are insulinotropic incretin hormones secreted from the intestine in response to ingestion of a mixed meal. Together, they are responsible for the so-called incretin effect, i.e. the enhanced plasma insulin secretion after oral vs. iv administration of glucose .Type ٢ diabetic patients are characterized by an impaired incretin effect Recently, we presented data showing near-normal GIP secretion but reduced postprandial concentrations of total and intact, biologically active GLP-١ in typical obese, insulin-resistant, type ٢ diabetic patients, which might explain part of the impaired incretin effect in type ٢ diabetes Furthermore, previous studies have indicated that GLP-١ is strongly insulinotropic in patients with type ٢ diabetes mellitus, whereas the effect of GIP is much weaker or absent . The GIP defect particularly involves a defective amplification of the late-phase plasma insulin response to glucose by GIP . This defect could be determined separately from the general pancreatic β-cell dysfunction in diabetes mellitus by using the preserved response to GLP-١ as a measure of β-cell function to allow quantification of the defective responsiveness to GIP. Further studies revealed a similar, defective response to GIP in first-degree relatives of type ٢ diabetic patients, indicating that the defect might be genetically determined. To analyze this more closely, we now studied the β-cell responsiveness to GIP of five groups of diabetic patients, with completely different etiology. The patients underwent hyperglycemic clamps (١٥ mm) with or without a continuous infusion of an incretin hormone to provide a prolonged stimulation of the β-cell, to estimate both early- and late-phase plasma insulin and C-peptide responses to the incretin hormones .(***Vilsboll T,etal***٢٠٠١

)

Different methods of insulin administration
INTRAVENOUS INSULIN INFUSION THERAPY

Indications of intravenous insulin infusion

The medical literature supports the use of intravenous (IV) insulin infusion in several clinical indications, including
**Diabetic ketoacidosis and nonketotic hyperosmolar state
**myocardial infarction
**cardiogenic shock,
**the postoperative period after cardiac surgical procedures
. Although the level of evidence is weaker with respect to outcome data, other indications for IV insulin infusion therapy include patients with type ١ diabetes who are being given nothing by mouth general preoperative care, including organ transplantation total parenteral nutrition (TPN) hyperglycemia during high-dose corticosteroid therapy stroke use as dose-finding strategy, anticipatory to initiation of SC insulin therapy in patients with type ١ or type ٢ diabetes labor and delivery; and other acute illnesses for which prompt glycemic control is judged important for recovery, such as prevention or treatment of infection .Some patients can be managed safely with SC administration of insulin. During many medical illnesses such as acute gastroenteritis or gastroparesis with vomiting, or during prolonged “nothing by mouth” status, the use of IV insulin infusion is often necessary to control blood glucose (BG). For patients on general hospital wards, a decision to abandon SC insulin therapy depends on the response to current therapy and whether the patient is at the target BG level. Repeated doses of SC rapid-acting insulin analogue can be administered at ٢-hour intervals to attempt to achieve BG control for appropriately selected but not critically ill patients. A reasonable guideline for conversion to IV insulin infusion therapy is failure to maintain the target BG level with correction-dosed SC insulin therapy after ٦ hours. The threshold for initiation of an IV insulin infusion is defined by failure to maintain target BG values. Preoperative insulin infusion may be

initiated for any surgical procedure in patients with type ١ or ٢ diabetes as the preferred method to prevent glucose excursions from exceeding target range or for preoperative correction of hyperglycemia. For the patient with diabetes undergoing an elective surgical procedure who previously received basal insulin by injection, an appropriate approach is to perform frequent glucose monitoring preoperatively and intra-operatively and to begin an insulin infusion when the glucose level is ١٤٠ mg/dL or more. Because of concern about perfusion of SC sites, the reliability of the delivery of basal insulin by continuous SC insulin infusion is questionable. Therefore, pump therapy should be replaced with IV insulin infusion from the start in critical care patients. Some medical centers continue SC insulin pump therapy for minor surgical procedures.

During TPN, enteral nutrition, or corticosteroid therapy, any BG measurement above ١٤٠ mg/dL should trigger initiation of IV insulin therapy. For any patient in the surgical intensive-care unit (ICU) who does not have known diabetes, a BG level exceeding ١٤٠ mg/dL predicts persistent above-target values and the need for IV insulin therapy. For patients in the surgical ICU just returning from the operating room, an initial BG value of more than ١٤٠ mg/dL can be treated with an IV bolus of insulin or a single SC injection of rapid-acting insulin, calculated by using the following formula: (BG - ١٠٠)/٣٠ = units of rapid-acting insulin. This correction dose should be repeated every ٢ hours. If hyperglycemia (BG levels exceeding ١٤٠ mg/dL) persists at ٦ hours, the patient should then be given IV insulin infusion therapy **(Murphy MB, et al. . ٢٠٠٣.)**

Thresholds for Initiation of intravenous Insulin Infusion Therapy **(Van den Berghe et al ٢٠٠٢)**

Situation (mg/dL)	Glucose threshold
Preoperative care	>١٤٠
Surgical ICU care	>١١٠-١٤٠†
No surgical illness	>١٤٠-١٨٠‡
Pregnancy	>١٠٠

Table ١

†The study by Van den Berghe et al supports ١١٠ mg/dL; the study by Finney et al supports ١٤٥ mg/dL.
‡The patient who will start IV insulin infusion therapy because of failure of subcutaneous management might have a higher threshold for initiation of the infusion than the patient who requires IV insulin infusion
because of medical conditions, such as myocardial infarction or type ١ diabetes with "nothing by mouth" status.

METHODS FOR IV INSULIN INFUSION

Numerous methods for IV insulin infusion therapy have been published The ideal IV insulin infusion method should be effective with minimal risk of hypoglycemia, easily used in all hospital units including any outpatient unit, easily prescribed, easily implemented, and cost-effective. Few methods meet all these criteria. It is beyond the scope of this report to discuss all the major protocols published. Instead, basic componentsof the IV insulin infusion therapy will be discussed, and sample algorithms are presented ***(Trence DL, Kelly JL, et al*** ٢٠٠٣***)***

Glucose Target Ranges for IV

Insulin Infusion Therapy

The glucose target ranges for IV insulin therapy depend on the goals of treatment in specific situations. In the surgical setting
Suggested that those patients randomized for maintenance of the BG level at a value between ٨٠ and ١١٠ mg/dL had a better prognosis than did those randomized to a BG target of ١٨٠ to ٢٠٠ mg/dL. A retrospective analysis of the data suggested there was no threshold at which benefit occurred above the upper limit of the normal fasting glycemic range, ١١٠ mg/dL. In contrast**,**
Finney et al in a retrospective study of ٥٢٣ surgical ICU patients suggested a speculative upper limit of ١٤٥ mg/dL for the target BG level. In the nonsurgical setting, data in the areas of cardiac disease, infection control, and metabolic control support assignment of target BG levels to a range below١٨٠ mg/dL, but little evidence supports the necessity of

maintaining BG levels in the normal fasting range. In fact, in the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study and subsequent work with glucose-insulin-potassium therapy for cardiac disease, glycemic control was not the direct goal of IV insulin therapy; rather, an infusion of glucose, insulin, and potassium in a fixed ratio was used .Adjustments of the infusion were made if the BG concentration declined outside a target range of ١٢٦ to ٢٠٠ mg/dL Because patients are asked to obtain near-normal BG levels at home, a similar goal in the hospital setting is reasonable.
During labor and delivery, control of BG should be the same as during pregnancy. Of note, one of the principal barriers to widespread implementation of IV insulin infusion therapy is the fear that therapy targeted at a lower glycemic range might increase the risk of hypoglycemia, as it does during intensification of SC insulin therapy in the ambulatory setting. In fact, in comparison with SC insulin therapy, the frequent monitoring and brief duration of action f IV insulin therapy probably reduce the risk of hypoglycemia. Suggested BG target ranges during IV insulin infusion therapy ***(Van den Berghe et al ٢٠٠١)***

Specific IV Insulin Infusion Algorithms.

Numerous algorithms for IV insulin infusion are in clinical use; however, few have been subjected to analysis. Studied algorithms that work seem to have certain characteristics in common.
First, algorithms must be designed to reach the target BG range by adapting to the individual's response to insulin. Algorithms that rely on a fixed relationship between infusion rate and BG cannot seek and maintain target BG levels.
Second, algorithms must deal with the limited availability of glucose data in the clinical setting. There are practical limits to how often point-of-care BG can be monitored. For safety and the practical consideration of workload, algorithms should be able to vary the interval between glucose measurements on the basis of BG trending.

Finally, algorithms must balance stability and responsiveness.
An aggressive algorithm may overshoot the BG target and result in oscillation between hyperglycemia and hypoglycemia. In contrast, an algorithm that is slow to reach a target BG level may subject a patient to unnecessarily prolonged periods of hyperglycemia or hypoglycemia and fail to respond to changing clinical situations. Ultimately, the implementation of any algorithm is dependent on orders that can communicate effectively.
Orders must be unambiguous and understandable. Unfortunately, many orders in clinical use require the nursing staff to remember or review the sequence of previous actions and then to perform detailed calculations.
Three examples of orders of IV insulin infusion therapy are presented in the appendices of this report; the first is a protocol from Van den Berghe et al and the other two are used clinically by the authors of this report.
The algorithm of Van den Berghe et al , which was used in the Leuven postsurgical ICU , adjusts the insulin infusion to obtain BG levels in the range of ٨٠ to ١١٠ mg/dL.
Hypoglycemia, defined as a BG level of less than ٤٠ mg/dL, occurred in ٥,٢٪ of patients. No patients had seizures or convulsions. With use of this algorithm, the nurses are required to make many decisions. The ambiguity and complexity of the algorithm and the imposed decision making limit its use to an ICU setting.
The algorithm of Braithwaite et al, shown in was first published in Endocrine Practice by ***Markovitz et al*** then revised by ***Trence, Hirsch et al*** and subsequently modified to achieve a target range BG of ١٠٠ to ١٥٠ mg/dL. It is currently used at the University of North Carolina-Chapel Hill. In this protocol, the columns are selected to maintain the BG level within
the target range. The corrective insulin infusion rates were calculated by the rule of ١٥٠٠. This method has the feature of seeking a target. The initial order is to begin at column
٢ and to switch columns on the basis of the patient's response. The BG is measured at hourly intervals and if results are stable,

the intervals can be increased to ٢ hours, with reversion to more frequent measurements in periods of instability. Multiple complicated decision points are avoided.

The algorithm of (***Davidson et al***) is widely used in numerous hospitals both as a manual drip and later as a computerized version This algorithm was based on a prior study by (***White etal)*** who showed that IV insulin infusion in a pediatric clinical research center resulted in the equivalent of any BG level above ٦٠ mg/dL times a sliding scale factor which in the pediatric center was approximately ٠,٠٢. The formula was then adapted to vary this insulin sensitivity factor, known as the multiplier, to seek the appropriate glycemic target in all individual patients. The following formula was developed:

Insulin (units per hour) = multiplier (BG - ٦٠) with use of this algorithm manually, the initial multiplier is set at ٠,٠٢, and a BG value is determined every hour in conjunction with calculation of the units of IV insulin therapy per hour. The multiplier is adjusted every hour by ٠,٠١ to obtain the target BG level—if the result is less than the target, decrease by ٠,٠١; if within target range, no change is needed; if more than the target and the BG level has not decreased by ٢٥٪, increase by ٠,٠١. The BG is always determined hourly until stable results are achieved; then it is measured every ٢ hours. In ١٩٨٤, Steed and Davidson computerized this algorithm and developed the Glucommander, which automatically calculates the units per hour of insulin based on the BG level and the insulin sensitivity of the specific patient.***(Kitabchi AE, etal*** ٢٠٠٢***)***