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Soluset Insulin Solution Treatment Algorithm (SISTA) for Hyperglycaemic Emergencies among Adults in Low Income Countries

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Abstract

Prevalence of diabetes mellitus is rising dramatically in low income countries. Hyperglycaemic emergencies are among the commonest medical emergencies in these countries. Managing these emergencies is faced with multiple challenges. Intravenous insulin is the preferred modality of administering insulin in these patients. Insulin pumps are the ideal means of administering insulin but these are unaffordable and relatively unavailable in the low income countries.

Administering insulin via the intravenous giving set is a common modality of insulin therapy in the developing countries. This is associated with wastages, discomfort for the patient and the insufficient nursing staff. Wide fluctuations in glucose patter is a common finding in these settings because the intravenous fluid giving set cannot be finely regulated. Soluset is a volumetric cylinder used commonly in Paediatrics but rarely used in Adult Medicine. It gives advantages such as the ability to fine tune the rate of administering intravenous medications.

Soluset Insulin Solution Treatment Algorithm (SISTA) is a proposed modality to solve the problems of intravenous insulin administration in adults especially in low income countries. It is readily available in low income countries. It is also affordable. It gives the chance of fine tuning insulin administration to optimize glycaemic control. The nursing staff are already familiar with soluset and it does not require any special training to use. It combines some of the advantages of insulin pump with the advantages of insulin infusion with intravenous fluid giving set. It is more affordable in low income countries compared with insulin pumps. It also prevents wastages and wide glycaemic fluctuations associated with intravenous insulin administration via the intravenous fluid giving set, which is what is most commonly used in low resource settings.

Background

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycaemia which results from a deficiency in insulin secretion and/or action [1]. The majority of people living with diabetes in the world are living in low income countries and the prevalence of diabetes is increasing dramatically in these countries [2]. According to the world bank, in 2019, low income counties are those countries whose gross national income per capita is less than $1025 [3]. Due to inadequate resources, health care financing in low income countries is suboptimal and this impairs health care delivery in these countries [4]. The facilities and infrastructure for managing in-patients available in the developed countries are largely unaffordable in low income countries and there is a need for adapting available technology with the aim of getting the best care with minimal cost.

Insulin is a peptide hormone that can be used as a drug in the treatment of hyperglycaemia. Frederick G Banting, Charles H Best and JJR Macleod were credited with the discovery of insulin following their works at the University of Toronto [5]. In documented literature, the first patient to be treated with insulin was a 14 year old boy, Leonard Thompson, who was a diabetic patient at the Toronto General Hospital [5]. Eli Lilly and Company was the first pharmaceutical company to produce insulin in commercial quantities [5]. This changed the history of management of diabetes from being a death sentence to a disease that can be managed through adequate replacement of the deficient hormone.

The insulins that were first administered to diabetic patients were derived from animals. These insulins were extracted from the pancreas of animals such as pigs (porcine insulin) and cattle (bovine insulin) and are later purified through meticulous industrial processes to prevent reactions to the animal insulins by the patients on insulin therapy. This went on until the 1980s. Through genetic engineering and intensive researches, Eli Lilly Corporation mass-produced human insulin [5]. This was a paradigm shift in insulin pharmacotherapy. Organisms such as Escherichia coli and yeasts are being used to grow human insulin through the process of Deoxyribonucleic (DNA) technology [5]. The manufactured insulins are subjected to purification processes such as high performance liquid chromatography, gel filtration and x-ray crystallography to ensure quality control. By the mid 1990's, researchers started working on the modification of the amino acid sequencing coded by the insulin gene so as to produce insulin with better pharmacokinetic and pharmacodynamic properties. These insulins are called analogue insulins. Examples of the analogue insulins include rapid actin insulins such as (lispro, aspart and glulisine), long acting insulins (such as detemir and glargine) and ultra-long acting insulins (such as degludec).

Insulin can be administered subcutaneously, intramuscularly or intravenously. Oral insulins are still under intense research while inhaled insulins have not received clinical patronization compared

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with the initial enthusiasm that welcomed their discovery. This is due to issues of efficacy and safety. Nasal, buccal, transdermal, rectal and transperitoneal insulin administration have all been documented in the literature but they have no clinical relevance as far as guidelines on diabetes management are concerned [6]. The subcutaneous route is the commonest route of administration of insulin. The modalities of subcutaneous insulin injections include the use of insulin syringe, insulin pens and Continuous Subcutaneous Insulin Infusion (CSII) [6].

Insulin pumps joined the diabetes therapy armamentarium in the 1970s [6]. It comes in various sizes and models. In the developed countries, insulin therapy via insulin pumps is gradually becoming the standard of care, especially in type 1 diabetes [7]. While older generation insulin pumps are manually activated by the patient to deliver insulin, especially insulin boluses, the newer generation insulin pumps are mostly automated. With modern technology, data on glucose levels and insulin administered can be retrieved and reviewed by the patients and the physicians [7]. Randomized controlled trials and meta-analyses have reported the clinical advantages of insulin pumps compared with Multiple Daily Insulin Injections (MDII), in terms of glycaemic control [8]. Insulin pumps are however unaffordable and unavailable to diabetic patients in low income countries [8]. An average cost of insulin pump is about $10 000 and consumables such as reservoirs and infusion sets cost $25 - $30 per month. A systematic analysis reported the total cost of medications for the treatment of diabetes per year per capita in low income countries is about $15 - $500 [9]. Clearly, this shows that insulin pumps are not affordable in low income countries.

Overview of hyperglycemic emergency

In patients with diabetes mellitus, either previously or newly diagnosed, Hyperglycaemic Hyperosmolal State (HHS) and Diabetic Ketoacidosis (DKA) are forms of hyperglycaemic emergencies that have been documented in them. Both can occur in all forms of diabetes but DKA occurs mostly in type 1 diabetes while HHS occurs mostly in type 2 diabetes [10]. Also, while DKA tends to occur in younger adults, HHS is commoner in middle-aged and old people. Mortality rate in DKA was close to 100% before the discovery and clinical usage of insulin [10]. Following the use of insulins, mortality dropped rapidly to about 60% and this has progressively reduced over the century to about 2% in DKA and about 5-15% in HHS [11]. In low income countries, the mortality rates from hyperglycaemic emergencies is higher compared with the developed countries [11].

Common presenting symptoms in patients with hyperglycaemic emergency include polyuria, polydipsia, weight loss, weakness, nausea, vomiting, abdominal pain and altered sensorium [10]. The most documented signs in hyperglycaemic emergencies include altered consciousness, dehydration, hypothermia, tachycardia, hypotension and tachypnoea [10]. Kussmaul breathing and acetone breath are peculiar to DKA [10]. The triad of laboratory findings in DKA are hyperglycaemia, increased anion-gap metabolic acidosis and hyperketonemia (or ketonuria) [10]. In HHS, the common laboratory findings are severe hyperglycaemia (usually above 600mg/dl), hyperosmolality and the absence of severe ketoacidosis [12].

Intravenous insulin therapy

Hyperglycaemic crises are among the commonest reasons for admissions to the general medical wards, high-dependency units and the Intensive Care Units (ICU). Studies have shown that intravenous insulin therapy controls hyperglycaemia more efficiently than any other route of administering insulin and it is the recommended route in most guidelines [13]. Improved glycaemic control has been associated with improved clinical outcomes, in terms of morbidity and mortality [12].

In hyperglycaemic emergencies, critically ill patients, women in labour, diabetic patients on Nil Per Oral (NPO) and perioperative patients, intravenous insulin is the preferred route of administering insulin [14]. This is because the rapid onset (within seconds) and short duration (within 5-10 minutes) of soluble or rapidly acting insulin makes it easier to match insulin dose to the glucose level in order to achieve the glycaemic goals during the treatment of hyperglycaemic emergencies [13].

The necessary resources that must be available to attain the glycaemic targets when intravenous insulin therapy is used are insulins, trained nurses, glucometers and institutional protocols. Hypoglycaemia is the commonest drawback of intravenous insulin therapy and this is of great significance in critically ill patients who may not manifest the classical clinical features of hypoglycaemia. Intravenous insulin therapy and monitoring are supposed to be nurse-driven with valuable input from the physician. Intravenous insulin therapy is often implemented using either insulin pump (usually in developed countries) or intravenous fluid giving set in form of glucose-potassium-insulin infusion (usually in low resource settings) but both have significant demerits.

Insulin therapy using intravenous pumps

Insulin pump is a medical device that is programmed to deliver insulin at a controlled rate. The various intravenous pumps that are available include gravity-infusion device, volumetric pumps and syringe pumps. Syringe pumps are the most commonly used type [13]. The intravenous pump is relatively accurate in the delivery of the required insulin doses. Some pumps have in-built batteries so that they can function during power outage. While insulin is being administered via the pump, glucose infusion is given via the fluid giving set to prevent hypoglycaemia.

The pumps are built with safety measures such as the ability to detect air in the tubing. Insulin pumps have some disadvantages. In low resource settings, cost and availability are the main issues. Also, there is a need for special training in the usage of the pumps. Repair and replacement of malfunctioning parts may be difficult in low resource settings. Additionally, in low resource settings where power supply is erratic, use of intravenous pumps may be a challenge. Also, an abnormality with either the pump tubing or the fluid giving set tubing results in hyperglycemia or hypoglycemia respectively.

Intravenous insulin therapy using the Glucose-Potassium-Insulin (GKI) infusion

GKI infusion is a solution of a dextrose fluid (5% dextrose water for example), intravenous potassium and insulin (usually soluble insulin but rapid acting insulins may also be used). It is also known as the Alberti regimen [15]. The amount of each constituent depends

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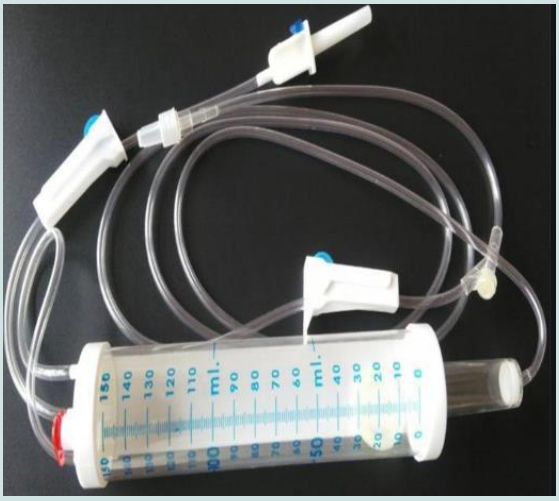

Figure 1: Soluset

on the glucose level, glycaemic target and potassium level. This allows insulin, electrolyte and fluid to be given together. Blood glucose level is checked hourly. Some of the challenges with the use of GKI infusion include the fact that it is difficult to regulate and it exposes the patient to wide fluctuation of glucose levels. It is also wasteful because whenever the checked blood glucose is not up to the expected level, the on-going fluid has to be discarded and a new solution reconstituted. For patients who pay out of pocket, which is a common thing in low resource settings, this is of enormous financial impact. GKI involves administering insulin mixed with fluids and this may become a significant clinical challenge in people with fluid retaining co-morbidities such as heart failure o renal failure. Hypokalemia is also a common finding with the use of GKI.

Soluset

Solusets are special volumetric cylinders often used for intravenous administration of medications, especially in Paediatrics [16]. A soluset is shown in Figure 1 below.

Principles of intravenous insulin therapy using soluset

With soluset intravenous infusion, 60 drops = 1 ml.

The formula that underlies intravenous drug infusions is given below.

Amount of insulin given (Units) = Concentration (Units/ml) X volume of the solution given (ml)

In a hyperglycaemic emergency, the patient typically needs two Intravenous (IV) accesses. One access is connected to the GKI infusion for intravenous insulin therapy and the other access is connected to IV fluid (usually 0.9 or 0.45 saline) for rehydration of the patient. With soluset, only one IV access is needed because the second IV giving set for rehydration is connected to the 'Y' junction of the soluset tubing. This translates to better comfort for the patient and lower risk of thrombophlebitis.

During resuscitation of a patient with hyperglycaemic emergency, capillary glucose is monitored regularly, usually hourly. If there is a need to increase or reduce the rate of insulin infusion, the GKI infusion has to be discarded and a new one reconstituted at every instance, causing a lot of wastages. With soluset insulin infusion however, the rate of infusion, in terms of number of drops per minute, is the only thing that is changed while the ongoing infusion continues.

How to adjust soluset insulin infusion

The first thing is to determine the amount of insulin to be given per time. For example, if 0.1 Unit/kg/hr of insulin is to be administered via soluset, how that can be achieved.

A pint of IV Normal saline (500 ml) is used to prepare the insulin solution. 50 units of soluble insulin is injected into the 500 ml of normal saline.

The concentration of insulin in the normal saline is calculated as follows:

$$C = \frac{n}{V}$$

C- Concentration of insulin in the normal saline (U/ml)

n- Amount of insulin added into the insulin = 50 units (as given above)

V- Volume of the normal saline=500ml

Kg- weight in kilogram

hr- time in hours

Therefore

$$C = \frac{50}{500}$$

C = 0.1 U/ml

The concentration of insulin in a 500ml of normal saline when 50 units of soluble insulin is added into it is 0.1 U/ml.

The normal saline is then connected via a port to the cylinder of the soluset and some insulin solution is allowed to flow into the cylinder (usually 150 ml at a time, as that is the maximum capacity of the soluset cylinder).

So, in order to administer 0.1 U/Kg/hr of insulin to the patient using the solution constituted above, the next thing is to determine the weight of the patient. 70 kg is adopted for this illustration.

The amount (A) of insulin to be administered per hour to this patient is calculated below:

A = 0.1 X 70 X 1

A= 7 U/hr

So, it has been determined the 7 Units of insulin will be given per hour, so the next thing is to determine the volume of the insulin solution (constituted above) that will be administered via the soluset.

$$A = C \times V$$

Therefore

$$V = \frac{A}{C}$$

Where V-volume of insulin solution to be administered per hour

A - Amount of insulin to be administered per hour = 7 U/hr (as determined above)

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Table 1:

Advantages
1. Cost effectiveness
2. Minimal monitoring
3. Less prone to error
4. Avoids wastages
5. Dual pathways for fluid and insulin infusion
6. It does not require power supply
Limitations
1. It is not automated
2. It requires minimal calculations to ensure accurate dosing.

C - Concentration of insulin in the insulin solution = 0.1 U/hr

V = 7/0.1

V = 70 ml/hr

So, in order to give 0.1 U/kg/hr of soluble insulin to a 70 kg man, using insulin solution containing 50 Units of soluble insulin inside 500 ml of normal saline, the patient will need 70ml/hr of the solution.

In order to give 70ml/hr of the insulin solution administered via soluset, the number of drops per minute has to be determined.

Using a soluset, 6 drops = 1 ml (rule of thumb)

Therefore, 70 ml= (70 x 60) drops = 4200 drops

So, 4200 drops are to be given per hour

Which means 4200 drops are to be given per 60 minutes

There 70 drops are to be given per minute.

In summary, in order to give 0.1 U/kg/hr of soluble insulin to a 70 kg man, using insulin solution containing 50 Units of soluble insulin inside 500 ml of normal saline, the patient will need 70 ml/hr of the solution which translates to 70 drops per minute when given via soluset. So, adjusting the dose of insulin given is simply by changing the number of drops per minute without discarding the on-going infusion.

Soluset Insulin Solution Treatment Algorithm (SISTA) for hyperglycaemic emergencies using the American Diabetes Association (ADA) guidelines

According to ADA, there are four main goals of therapy in the management of hyperglycaemic emergency. These include circulatory volume restoration, gradual reduction of osmolality and glucose, addressing electrolyte derangement and treating co-morbidities [17].

Fluid therapy with SISTA

Fluid resuscitation is central to the management of hyperglycaemic crisis [17]. The fluid deficit in DKA is about 6-8 L while for HHS, it is about 8-10 L. With SISTA, an IV normal saline is connected via the IV fluid giving set to the 'Y' junction of the soluset tubings. About 1- 1.5 L of normal saline is given in the first hour, then another 1-1.5L in the next 2 hours. Thereafter, 1-1.5 L is given over the next 4 hours. If the patient is making adequate urine and he/she is not hypotensive and not hyponatraemic, the fluid may be changed to 0.45% saline to prevent hypernatremia. If 0.45% saline is not available, as it is the case in many low resource settings, 5% Dextrose in 0.45% saline is constituted, under sterile technique, by mixing 250 ml of 10% Dextrose water with 250 ml of normal saline. 5% Dextrose in 0.45% saline can be used but insulin flow rate has to be adjusted. The target rate of drop of osmolality is about 3mosm/kg/hr while the target rate of drop of sodium is 0.5 mmol/L.

Potassium therapy with SISTA

After the first hour of IV fluid, IV Potassium Chloride (KCl) may be added into the fluid, depending on the serum potassium. If serum potassium is above 5mmol/L, potassium should not be added. If potassium is 3.5-5 mmol/L, add 20 mmol of IV KCl into 1L of fluid. If serum potassium is less than 3.5 mmol/l, add 40 mmol of IV KCl into IL of fluid and wait for the potassium to rise to at least 3.3 L/min before commencing insulin therapy.

Insulin therapy with SISTA

Continuous infusion of insulin via the soluset at 0.1 U/kg / hr is commenced. How to give this via soluset has been illustrated above. Random Blood Glucose (RBG) is monitored hourly and the target rate of drop of glucose is 50-70 mg/dl/hr. Too rapid drop may precipitate cerebral oedema (especially in children and adolescent) and hypoglycaemia. If the rate of drop of blood glucose is less than desired, the insulin rate may be doubled to 0.2 U/Kg/hr. Similarly, if the rate of drop of the blood glucose is higher than desired, the rate of drop may be halved to 0.05 U/kg/hr.

When RBG is less than 250 mg/dl, the rate of insulin therapy is halved into 0.05 U/Kg/hr. Also, the fluid that is connected to the 'Y' junction of the soluset is changed into 5% Dextrose water in 0.45% normal saline. How to constitute 5%Dextrose water in 0.45% normal saline is explained above.

Advantages of SISTA and the relevance in low resource settings

Intravenous drug treatment with soluset is not new. It is a common practice in Paediatrics, especially in Neonatology. However, there is no documentation of its usage in hyperglycaemic emergencies among adults. In a hyperglycaemic emergency, intravenous insulin is the preferred route of administering insulin. The two commonly documented avenues of doing this is through insulin pumps and insulin infusion using IV fluid giving set.

Insulin pump is expensive and it is not readily available in low-resource settings. Intravenous insulin infusion via the IV fluid giving set is prone to wide fluctuations in glycaemic control. The monitoring may be suboptimal in low income countries where the nurses: patients ratio is very low. Poor monitoring is associated with suboptimal glycaemic control. It is also prone to wastages.

The Soluset Insulin Solution Treatment Algorithm (SISTA) is being proposed as an effective alternative for intravenous insulin therapy, especially in low income countries. It mitigates against wastages because adjusting insulin dose does not require discarding the on-going fluid and reconstituting another one. Rather, adjusting the number of drops per minute is sufficient to bring about the desired change in the insulin dose. The soluset is readily available in low resource settings. It is relatively cheap and it is easy to use by the nursing staff. It is relatively easy to calculate the number of drops per minute, and it is less prone to wide fluctuations in glycemic control. It has a 'Y' junction where the giving set for the rehydrating

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fluid is connected. This is more comfortable for the patient and the risk of thrombophlebitis is reduced. A clinical trial is being proposed to document the efficacy of SISTA. Ethical approval and feasibility studies are presently ongoing to facilitate the trial. The summarizes the advantages and the limitations of adopting SISTA (Table 1).

Conclusion

Diabetes mellitus is most prevalent in the low income countries. Similarly, episodes of hyperglycaemic emergencies are high in these counties. Intravenous insulin therapy is the preferred route of administration. Insulin pumps are largely not affordable and available in low resource settings. Intravenous therapy using GKI is also faced with its own challenges such as wastages and wide fluctuations in glycaemic pattern. Soluset Insulin Solution Treatment Algorithm (SISTA) is hereby being proposed as an effective alternative for intravenous insulin therapy during hyperglycaemic emergencies in low income countries. The advantages include the affordability, the widespread availability, the comfort for the patient and the ease of monitoring the treatment. It is an outcome of adapting available technology to solve clinical problems in resource deficient areas. There are however needs for clinical trials to validate the effectiveness of this novel approach of administering insulin, especially in low income countries.

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