Management of Severe/Acute Hyperglycemia in Hospitalised Type 2 Diabetes Mellitus Patients

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Abstract: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder comprising 90% of all diabetes worldwide. T2DM is characterized by hyperglycemia resulting from insufficient secretion of insulin by beta cells of pancreas, peripheral insulin resistance and accompanied by impaired regulation of hepatic gluconeogenesis. T2DM can be classified into acute complication and chronic complication. Severe/acute hyperglycemia is an acute complication of T2DM, which commonly seen in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS). DKA and HHS are acute metabolic complications caused by absolute or relative deficiency in endogenous insulin level. The presence of severe/acute hyperglycemia is often associated with increasing hospital stays, worsening of infection, post-discharge disability and death. Hence, insulin therapy is the method that most preferred to treat severe/acute hyperglycemia and controlling glycemic level in hospital setting. The subcutaneous insulin administration is the most frequently used in non-critically ill patients admitted to hospital. Management of severe/acute hyperglycemia involves basal-bolus insulin versus sliding-scale insulin and continuous insulin infusion versus subcutaneous insulin infusion. This review focuses on treatment options available in hospitalised T2DM patients with acute hyperglycemia.

Keywords: Acute hyperglycemia, type 2 diabetes mellitus, insulin, sliding scale, basal-bolus.

INTRODUCTION

Diabetes mellitus is a significant global health disorder. According to International Diabetes Federation (IDF) report, the number of individuals with diabetes is predicted to rise steeply from 366 million in 2011 to 552 million by 2030, corresponding to a prevalence of 7.7% [1,2]. Malaysia was listed among the top ten countries in the world for diabetes prevalence, which increased dramatically from 8.3% in 1996 to 14.9% by 2006 and eventually reached 20.8% in 2011 [3]. Type 2 diabetes mellitus (T2DM) is becoming more common in almost every population, whereby accounting approximately 90% of all cases in adults as reported by DiabCare Malaysia 2008 [4].

Severe/acute hyperglycemia is an acute complication of diabetes mellitus that commonly occurs in T2DM patients requiring intensive treatment and hospitalisation [5]. Importantly, severe/acute hyperglycemia is associated with poor patient outcomes with increased mortality rates by 1.35% [6], lengthened duration of hospital stay with a mean of 9.1 days [7] and high risk of infectious complications. According to a prospective cohort study, patients with T2DM frequently admitted to hospital due to severe or acute hyperglycemia secondary to acute diseases including diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS) and serious infections [8]. The concurrent use of glycemic altering medications such as corticosteroids, antipsychotics and diuretics tend to worsen the severe or acute hyperglycemia by increasing hepatic gluconeogenesis besides impairing peripheral glucose uptake [5].

The effective management of severe/acute hyperglycemia in T2DM patients requires the administration of insulin [5]. The use of scheduled subcutaneous insulin consisting of basal insulin, nutritional bolus insulin and correction insulin is recommended in non-critically ill patients with severe/acute hyperglycemia [9]. The available insulin regimens for severe or acute hyperglycemia management include the use of sliding scale regular insulin as a sole therapy, scheduled subcutaneous with basal-bolus insulin and intravenous insulin infusion. Nevertheless, despite all the available treatment options for severe or acute hyperglycemia in T2DM patients, the glycemic control in this group of population remains suboptimal [10]. This is partly due to the continued use of sliding scale insulin regimen in managing severe or acute hyperglycemia even though many treatment guidelines recommend the discontinuation of its use.

The achievement of euglycemic state in T2DM patients with severe or acute hyperglycemia is crucial in reducing patients’ hospital stay, risk of infections and multi-organ failure [11]. In addition, there are limited
local and global data on the glycemic control achieved in T2DM patients with severe/acute hyperglycemia based on the types of insulin regimens.

COMPLICATION OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder comprising 90% of all diabetes worldwide [1]. In Malaysia, T2DM commonly affects older adults whereby 1 in 4 adults aged between 60 to 70 years claimed to have T2DM in 2006 [12]. Currently, a rising trend of T2DM has been observed among children, adolescents and younger adults.

The complications of T2DM are the major causes resulting in hospital admissions and can be classified into acute or chronic associated complications as shown as in Figure. Acute complications of T2DM include severe/acute hyperglycemia due to serious infection, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) [13]. Severe/acute hyperglycemia which caused by infection, composed of 44.9% of the admissions and this was followed by diabetic ketoacidosis (13.4%), uncontrolled diabetes secondary to non-compliance (13.4%) and cardiovascular diseases (13%). Similarly, of 156 patients enrolled in another study, 77.6% had acute infection on admission contributing to the development of severe/acute hyperglycemia [14]. Also, cardiovascular diseases and non-compliance to diabetes medications were found to be common among the 156 patients, which made up of 7.1% and 8.3% respectively. According to National Diabetes Surveillance Program of the Centers for Disease Control, the hospital discharges with DKA in United State shows an increasing trend from approximately 80,000 in 1998 to 140,000 in 2009 [15]. Apart from that, the mortality rates of DKA had remained in the range of 3.4% to 4.6% for the past 20 years. As compared to DKA, the HHS associated mortality rates remained higher to about 15% [16].

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ASSOCIATION OF SEVERE/ACUTE HYPERGLYCEMIA AND CLINICAL OUTCOMES

The presence of severe/acute hyperglycemia is often associated with increasing hospital stays, worsening on infection, post-discharge disability and death [20]. In a prospective cohort study consisting 2471 patients, risk of death in patients with admission blood glucose of greater than 11 mmol/L is higher than those with less or equal to 11 mmol/L (13% vs 9%, P=0.03) [21]. When compared to those with admission blood glucose of less than or equal to 6.1 mmol/L, the mortality risk and in-hospitals complications was higher among those greater than 11 mmol/L by 73% and 52% respectively. In general, the risk of in hospital complications increased by 3% for every 1 mmol/L increase in admission blood glucose level [21].

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12 days respectively. Every 1 mmol/L rise in blood glucose level was linked to 15% higher risk of adverse clinical effect such as death and more than 9 days of hospital stay.

MANAGEMENT OF SEVERE/ACUTE HYPERGLYCEMIA IN HOSPITALISED TYPE 2 DIABETES MELLITUS PATIENTS

Insulin therapy is the most preferred method of controlling glycemic level in the hospital setting. The basal bolus subcutaneous insulin therapy is the most frequently used in non-critically ill patients admitted to hospital. On the other hand, the oral hypoglycemic agents are recommended to be discontinued in the inpatient setting [9]. In addition, the administration of repeated doses of short-acting insulin per sliding scale alone should be discouraged as it tend to predispose patients to persistent hyperglycemia and fluctuation of glucose levels.

An optimal management of severe/acute hyperglycemia among non-critical hospitalised T2DM patients involves the administration of scheduled subcutaneous insulin incorporating basal, nutritional, and correction insulin [9]. A basal-bolus insulin regimen is a more physiologic approach in managing severe/acute hyperglycemia as it closely mimics the insulin secretion endogenously.

Basal insulin such as long-acting insulin glargine or intermediate-acting Neutral Protamine Hagedorn insulin given once and twice daily respectively to inhibit hepatic gluconeogenesis and hence decreases the glucose production during the night time [11]. The basal component is supplemented with prandial bolus insulin consisting of short-acting or rapid-acting insulin to prevent or control excessive postprandial rise of blood glucose levels [22]. In addition, correction doses using short-acting or rapid-acting insulin along with bolus doses are used to treat unexpected rise in blood glucose levels, which more likely to occur before or between meals and in patients who are unable to consume food orally [22].

INSULIN TREATMENT REGIMENS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH SEVERE/ACUTE HYPERGLYCEMIA

There are two options for managing severe or acute hyperglycemia in non-critical setting which includes short-acting insulin on a sliding scale and subcutaneous basal-bolus therapy. However, the use of sliding-scale insulin is discouraged due to the fluctuation in blood glucose levels and it acts as a reaction approach to hyperglycemia rather than preventing its occurrence. On the other hand, infusion of intravenous insulin is only appropriate therapy in certain situations including diabetic hyperglycemic emergencies [9]. In general, insulin is an effective means of managing glycemic level and targeted glucose range is achievable with adequate doses of insulin [23].

Basal-Bolus Insulin Versus Sliding-Scale Insulin

A recent cross-sectional study revealed that basal-bolus insulin regimen is superior to sliding-scale insulin regimen in managing glucose levels [2]. The findings of this study showed that mean ± standard deviation of daily blood glucose level in patients treated with basal-bolus insulin was 1.6 ± 3.7 mmol/L lower than baseline glucose level after day 1 of therapy and remained 1.6 ± 2.4 mmol/L lower than the corresponding baseline levels throughout the study (p<0.001). Unlike that of basal-bolus insulin regimen, patients on sliding-scale insulin failed to show significant differences in mean daily glycemic level from the baseline throughout the insulin therapy [2].

In addition, a prospective randomised trial had studied the efficacy and safety of basal-bolus regimen compared with sliding-scale regular insulin in 130 patients of T2DM [25]. The study demonstrated that basal-bolus therapy resulted in significant glycemic control improvement than that of sliding-scale regular insulin. The mean glucose levels was significantly lower in basal-bolus group as compared to sliding-scale group (9.2 ± 1.8 mmol/L versus 10.7 ± 3 mmol/L, p<0.001). Moreover, approximately two-thirds of patients treated with insulin glargine and glulisine presented within the mean glucose target of less than 7.8 mmol/L, but only one-third reached the targeted range with sliding scale insulin therapy. Apart from that, the use of sliding scale regular insulin alone resulted in 14% of the patients remained with blood glucose level of greater than 13.3 mmol/L even after sliding-scale insulin doses has been raised [25].

Furthermore, the results of another recent trial performed among the general surgery patients also showed improvement in glycemic control with basal-bolus insulin regimen than sliding-scale regular insulin [26]. The mean daily glucose during hospital stay was significantly lower with basal-bolus insulin treatment as compared to sliding-scale insulin regimen (8.7 ± 1.8 mmol/L versus 9.8 ± 2.4 mmol/L, p<0.001). The
percentage of glucose readings lower than 7.8 mmol/L was achieved in 55% and 31% of the patients treated with basal-bolus insulin and sliding-scale insulin respectively (p<0.001). There were also reductions observed with the administration of basal-bolus insulin, compared to sliding-scale insulin in wound infections (2.9% versus 10.3%, p=0.05), pneumonia (0% versus 2.8%, p=0.247), and acute renal failure (3.8% versus 10.3%, p=0.106). Results of this study revealed that basal-bolus therapy of glargine and glulisine regimen led to better glycemic control and reduction in hospital related complications among the general surgery patients [26].

When compared with sliding-scale insulin, basal-bolus insulin regimen is a preferred and safer treatment approach in managing severe or acute hyperglycemia. The use of sliding scale insulin alone is discouraged in inpatient setting [22]. Sliding-scale insulin does not prevent the occurrence of hyperglycemia episodes in hospitalised patients since it attempts to decrease the blood glucose level after it was elevated. Overall, sliding-scale regimen is an ineffective approach as it may predispose patients to the risk of hypoglycemia and hyperglycemia episodes.

**Continuous Intravenous Insulin Infusion Versus Subcutaneous Insulin Infusion**

Continuous intravenous insulin infusion is mainly reserved for inpatient use and during DKA, HHS, critical illnesses, and uncontrolled hyperglycemia following corticosteroid therapy, stroke and post-organ transplant. This treatment approach was demonstrated to be effective in maintaining targeted glycemic control in non-critically ill patients outside a critical care area [27]. A retrospective study involving 200 patients admitted to general medicine or surgical service received continuous intravenous insulin infusion to achieve a target of 8.3 mmol/L [27]. It was reported that 85% of the patients achieved the targeted blood glucose within 48 hours of the initiation of insulin. However, hypoglycemia (blood glucose less than 3.3 mmol/L) and severe hypoglycemia (blood glucose less than 2.2 mmol/L) occurred in 22% and 5% of the patients respectively. From the retrospective study, the use of continuous insulin infusion was found to be beneficial for patients on nothing per oral as the hyperglycemic and hypoglycemic events was significantly higher in patients who are able to eat, compare to intravenous insulin infusion as it give less beneficial because of continuous intravenous infusion it is a mainly of targeting glycemic control.

Conversely, a recent prospective controlled trial which involving 58 non-diabetic trauma patients were randomised to receive either intravenous or subcutaneous insulin therapy [28]. The findings of this trial reported that mean number of hypoglycemic episodes was higher in the intravenous group as compared to subcutaneous group (0.9 versus 0.1, p=0.002). However, the intravenous group resulted in significantly lower mean blood glucose levels for the first 3 days than the subcutaneous group (6.7 mmol/L versus 7.4 mmol/L, p=0.043).

In addition, from the prospective study on the efficacy and safety of subcutaneous insulin lispro against low-dose intravenous infusion of regular insulin for the DKA treatment discovered that the duration of treatment until correction of hyperglycaemia (7 ± 3 hours versus 7 ± 2 hours) and resolution of ketoacidosis (10 ± 3 hours versus 11 ± 4 hours) was not different between the treatment groups. Also, there were no differences in terms of length of hospitalisation, amount of insulin until resolution of diabetic ketoacidosis and hypoglycemia rates between the treatment groups. However, intravenous infusion protocol was associated with 39% higher hospitalization charges. Hence, subcutaneous administration of rapid acting insulin for the treatment of mild to moderate DKA was reported to be cost-effective and safe [29].

Apart from that, there were several prospective randomized open trials have reported on the efficacy and safety of subcutaneous rapid acting insulin compared with standard intravenous infusion of regular insulin in DKA. In a trial involving insulin lispro, the treated patients received subcutaneous lispro of 0.3 unit/kg as initial dose and followed by 0.1 unit/kg body weight per hour until correction of hyperglycaemia is achieved. The respective insulin doses then reduced to 0.05-0.1 unit/kg per hour until DKA resolves [29]. The study findings revealed that there were no statistical differences in terms of length of hospital stay, amount of insulin used until DKA is resolved, number of hypoglycemic episodes among patients treated with subcutaneous insulin lispro versus those on continuous intravenous regular insulin [29].

In general, it has been recommended to start subcutaneous insulin therapy once the hyperglycemic crisis is resolved by intravenous insulin administered continuously [16]. Intravenous insulin infusion continuation for 1 to 2 hours after administration of subcutaneous insulin is recommended to avoid...
recurrence of ketoacidosis and hyperglycemia. Figure 1 summarizes the management of acute hyperglycemia in T2DM patients.

CONCLUSION

Optimisation of treatment during severe/acute hyperglycemia is necessary to achieve the desired clinical outcome. The use of subcutaneous insulin consisting of basalin insulin is recommended in treatment for severe/acute hyperglycemia. Therefore, effective management of severe/acute hyperglycemia is essential in managing T2DM, which may substantially reduce the risk of developing hyperglycemic crises and the associated serious complications.

REFERENCES


