3-24-2019

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Risks Associated with Strict Glycemic Control of the 
Type 2 Diabetic Patient in the Intensive Care Unit

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RISKS ASSOCIATED WITH STRICT GLYCEMIC CONTROL OF THE TYPE 2 DIABETIC PATIENT IN THE INTENSIVE CARE UNIT

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Date: 3/22/2019
Risks Associated with Strict Glycemic Control of the Type 2 Diabetic Patient in the Intensive Care Unit

Abstract

Type 2 diabetes mellitus (T2DM) is a very prevalent chronic disease in the United States that costs Americans billions of dollars each year. According to the Center for Disease Control, more than 30 million people in the world are affected by diabetes and roughly 95% of those people have T2DM (2018). The prevalence of diabetes is even more predominant in the critical care setting, when compared to the general population. The case description in this report highlights a 65-year-old woman with T2DM and the management of the disease in the outpatient setting. Due to the progression of this disease, T2DM is frequently having to be managed on the inpatient setting in the critically ill with the use of insulin. There has been considerable debate over the last two decades as to the proper protocols when managing glycemic control in the critical care setting with the use of insulin. This literature review will focus on the current guidelines of glycemic control for T2DM in the intensive care unit (ICU) and why they are focused on a more lenient approach versus a stricter approach. The review will also look into hypoglycemia and glycemic variability as risks associated with strict glycemic control in the ICU. The clinical relevance of this topic is that up to 40% of the patients that are admitted to ICU are affected by type 2 diabetes, so the need for knowledge on appropriate guidelines and risks of strict control should be well understood (Palesh, Jones, Horowitz, & Deane, 2015).

Background

Type 2 diabetes can be managed in a variety of different ways. Often on the outpatient setting, patients are able to control their diabetes with oral and injectable medications until
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insulin may be warranted. More frequently in the inpatient setting, the use of insulin is the sole use for management of glycemic control. Outlined below is a case report of a type 2 diabetic patient in which a combination of injectable and oral medications is used to control her diabetes. The case report highlights the fact that management is often complicated and must be personalized to the patient. Glycemic control can be achieved in numerous different ways but patient compliance, as well as life style modifications, can be used to help to predict success.

The purpose of this report is to investigate conventional versus strict glycemic control of the type 2 diabetic patient in the ICU and the associated risks of hypoglycemia and glycemic variability when a strict approach is used. The rationale behind this topic is the fact that there has been much debate over the last 15 years in regard to the guidelines for optimal glycemic control in the ICU, with lesser focus being on the diabetic patient. Diabetes is a very common disease in this country as currently about 13% of the population of the United States is affected by diabetes, in which 40% of it is undiagnosed (Palesh et al., 2015). When looking at prevalence of diabetes specifically in the ICU, it is estimated that up to 40% of patients admitted have diabetes, with undiagnosed diabetes being about 6-14% (Palesh et al., 2015). This literature review will look into the current guidelines for glycemic control of the type 2 diabetic patient in the critical care setting and why they are focused on a more conventional approach versus a stricter approach. This review will also highlight the associated risks of strict glycemic control including hypoglycemia and glycemic variability and their associated implications for patients.

Case Report

A 65-year-old Caucasian female presents to a primary care clinic for a 6-month diabetes follow up. Patient has a history of T2DM in which she reports was diagnosed 10 years ago. Patient reports no concerns in regard to today’s visit and states she is compliant with her
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medications. She reports she currently takes Glipizide 10mg daily and Janumet 50-1000mg twice daily for her diabetic regimen. She reports checking her blood sugar 2-3 times a week and fasting values have ranged from 170-220s. When asked, she denies carbohydrate counting or regular exercise. She reports about a 5-10 pound weight gain this winter. Denies polydipsia, polyphagia, or polyuria. Denies any low blood sugars. She denies any open sores or non-healing wounds. Patient states that she does see the eye doctor on a yearly basis. Patient denies vision changes, headaches, chest pain, shortness of breath, abdominal pain, blood in stool/urine, fever/chills, body aches, or generalized malaise.

Patient’s pertinent medication history includes hypertension, obesity and hyperlipidemia. Her current prescription medication list includes Lisinopril 10mg daily, Toprol XL 50mg daily, Zocor 20mg daily, Aspirin 81mg daily, and a multivitamin. She has no allergies. Her pertinent surgical history is negative. Patient states only pertinent family history includes her father with noted “heart problems.” Patient currently lives with her husband in town and is a retired teacher. She has two grown children and no grandchildren. She denies tobacco use and reports occasional alcohol use on the weekends. She is up to date with her immunizations except her pneumococcal vaccine.

Patient’s vital signs during the visit are as follows: blood pressure - 138/80, heart rate – 72, respiration rate – 18, weight - 122kg, and BMI – 36.5 kg/m2. Upon physical exam, she is alert and orientated and in no acute distress. Red reflex is present in both eyes bilaterally and fundi are clear and with no arteriovenous nicking or retinopathy. Mucous membranes are pink, moist and intact. Upon auscultation, heart rate and rhythm are regular. No murmurs are heard. Lungs are clear to auscultation to bilateral lung fields. No enlarged lymph nodes are palpated. Her extremities are warm and well perfused. Her radial, pedal, and dorsalis pedis pulses are
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callable at a +2 grade. Her skin has no open areas and no obvious deformities are noted.
Diabetic foot exam was performed, and full sensation was noted with 10-gram monofilament and vibratory tool. No open areas or calluses noted. Feet appear well moisturized and toenails are intact and not thickened. There is no swelling, tenderness, or erythema noted.

Fasting labs were ordered including a microalbumin urine, lipid profile, comprehensive metabolic panel, and hemoglobin A1C. Lab values were as follows: fasting glucose 324 mg/dL, Hgb A1C 9.5%, triglycerides 167 mg/dL, HDL 39 mg/dL, and LDL 61 mg/dL. Her A1C six months ago was 8.1%. Her microalbumin and creatinine urine were within normal limits (WNL). All others laboratory values were WNL.

Diagnosis for today’s visit included Type 2 Diabetes Mellitus without complications, uncontrolled. Results were discussed with patient. Plan going forward includes discontinuing Janumet and Glipizide. Liraglutide (Victoza) subcutaneous injection ordered at a dose of 0.6mg daily for 1 week; then instructed to increase to 1.2 mg daily thereafter. Metformin 1000mg twice daily ordered as well. Patient educated on common gastro-intestinal side effects and black box warning of Victoza on thyroid tumors. Patient encouraged to check blood sugars two times daily, fasting and post-prandial, until next visit. Patient also to be scheduled to see diabetic educator. Patient encouraged to engage in thirty minutes of aerobic exercise five times a week. A nurse from the clinic will plan to reach out to patient in the next 1-2 weeks to review blood sugars and assess how the new medication regimen is going. The plan is to follow up in three months for a diabetic follow up with fasting labs. Pneumococcal vaccine (PSV-13) will be administered today in clinic.

Literature Review
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Glycemic control of the critically ill patient with T2DM has been a topic of attention for the last 15 years. There is debate whether strict glucose control serves better for this population versus conventional glycemic control. T2DM continues to remain very prevalent in our society in the United States. The case report described above shows the numerous ways that T2DM can be managed in an outpatient setting. T2DM is managed very differently in the inpatient setting. As stated above, compared to the general population, T2DM is more prevalent in hospitalized patients. The prevalence of T2DM in the intensive care unit (ICU) is estimated to be anywhere from 12-40% (Palesh et al., 2015). Hospital prevalence of undiagnosed T2DM is about 6-14% of patients. This is an important finding to keep in mind due to the fact that chronic glucose control may have implications on the optimal glycemic control during their stay in the ICU (Palash et al., 2015). It is recommended that a Hgb A1C be checked upon admission to the ICU if no prior records of one available within the last three months (ADA, 2016).

Glycemic Control

A literature review conducted on optimal glucose control for the critically ill type 2 diabetic patient found that the risks of strict glycemic control in the ICU outweighs the benefits. A landmark study titled The NICE-SUGAR Study (2009) found that that intensive glucose control versus conventional glucose control increased the absolute risk of death in the patients by 2.6%. Intensive glucose control was defined as target ranges of 80-110 mg/dL for blood sugars and conventional was defined as 140-180 mg/dL. This study still remains the most comprehensive study of glycemic control strategies performed to date in the critical care setting. There was also shown to be a significant increase in severe hypoglycemia in the group being treated with strict glucose control. Severe hypoglycemia was found to occur in 6.8% of patients who were part of the intensive insulin therapy, versus 0.5% in the conventional insulin therapy group. In the
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subgroup analysis there was no statistical difference in treatment effects when comparing patients with or without type 2 diabetes (Van den Berghe). This study, along with Clain, Ramar, & Surani (2015), Luethi et al., (2018), Palesh et al., (2015), and the American Diabetes Association (2016), recommend a starting threshold for treatment of insulin therapy at >180 mg/dL. Once insulin therapy is initiated, target goal of blood sugars should range from 140-180 mg/dL (versus 80-110 mg/dL). The American Diabetes Association (2016) does point out that more stringent goals of glucose control, such as 110-140 mg/dL, may be appropriate in some critically ill patients if able to avoid significant hypoglycemia. These studies had a common theme of increased mortality of patients being treated with strict glycemic parameters during their stay in the ICU. Not only did the literature support increased mortality with strict glycemic control, but also showed an increase in hypoglycemia and glycemic variability, which can also have adverse effects on patients. Although uncontrolled hyperglycemia is clearly harmful to patients with T2DM in the ICU, there has been inconsistent data as to its effects on mortality and morbidity on patients (Palesh, et al., 2015). Any state of health where the body is stressed, including a period of disease, some degree of hyperglycemia is to be expected and can be seen as protective. Severe hyperglycemia is thought to be a marker of illness severity and often subsides after the illness has resolved (Silva-Perez, Benitez-Lopez, Varon & Surani, 2017).

As outlined above, it is clear that the current literature does not support strict glycemic control of the critically ill with T2DM. Evidence supports that the risks outweigh the benefits in this population. Hypoglycemia and glycemic variability are two major risks that have been shown to occur with strict glycemic control and are discussed below.

Hypoglycemia
Numerous articles reviewed on the topic of hypoglycemia in the critically ill with T2DM demonstrated the harmful effects it can have on this population. Hulkower, Pollack, & Zonszein, (2014), Braithwaite et al., (2017), Claine et al., (2015), Silva-Perez et al., (2017), and Martin-Timon & Canizo-Gomez (2015) report that hypoglycemia is associated with increased morbidity and mortality in the type 2 diabetic patient in the ICU. Hypoglycemia can be defined as a blood sugar <70 mg/dL. It is more common in those with T1DM, but due to the overwhelming presence of T2DM in the inpatient setting, it is seen more frequently in the patient with T2DM in the hospital setting (Hulkower et al., 2014). The literature also supports that there are numerous harmful effects that hypoglycemia can have in the critically ill diabetic patient. For example, Hulkower et al., (2014) and Silva-Perez (2017) agree that hypoglycemia can affect cognitive function in adults and cause brain injuries. Hypoglycemia can lead to neuronal death that may damage areas of the brain that oversea memory. Behavioral changes, cognitive impairment, and seizures are all neurological complications that can occur due to hypoglycemia in the diabetic patient.

Hulkower et al., (2014), along with Silva-Perez (2017), Martin-Timon (2015), and Suh & Kim (2015) particularly point out the cardiovascular implications that can occur when hypoglycemia is present. Hypoglycemia triggers the sympathetic nervous system causing adrenaline secretion. This may induce arrhythmias, as well as increase cardiac workload, which may be fatal to diabetic patients, especially those with underlying endothelial dysfunction. In patients with T2DM and coronary artery disease, hypoglycemia was shown to be associated with electrocardiogram changes along with chest pain, that could account for sudden mortality. ECG changes include increased QT intervals and changes in cell repolarization, which can lead to life threatening ventricular arrhythmias. Patients who experienced severe hypoglycemia showed to
have an increased likelihood of experiencing acute cardiovascular events when compared to patients without severe hypoglycemia. Palesh et al., (2015) specifically points out that hypoglycemia can increase the inflammatory response, impair sympathetic nervous system, inhibit the stress response, induce cerebral vasodilation, and increase neural defects. Due to the rising increase of diabetic patients in the critical care setting, the risk of severe hyperglycemia is quite high. The consequence though of treating severe hyperglycemia is hypoglycemia. This puts diabetic patients even more at risk for hypoglycemia, as patients with persistent states of hyperglycemia due to insulin resistance are more likely to require control with insulin (Silva-Perez et al., 2017). Proper use of current evidence based literature on glycemic control protocols for this population is critical to avoid the harmful effects that can occur from hypoglycemia.

**Glycemic Variability**

Glycemic variability is another risk that can occur with strict glycemic control in the ICU and can be potentially harmful to diabetic patients. Glycemic variability is the fluctuation in blood glucose concentrations and there is currently no established gold standard guideline for measuring this (Palesh et al, 2015) & (Caine et al. 2015). When patients are treated with stricter insulin parameters, the likelihood of variable highs and lows in blood glucose ranges is increased. Palesh et al. (2015), Baptista et al., (2018), Suh & Kim (2015), and Caine et al., (2015) all had the common theme that glycemic variability in the critically ill type 2 diabetic is likely to increase mortality and cause other complications. This was found to be an independent predictor of mortality. The use of strict glycemic control protocols in the ICU was shown to increase glycemic variability, thus potentially causing adverse effects to those patients affected. Patients with T2DM are more at risk for glycemic variability due to increased chance of needing insulin treatment for blood glucose management.
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The literature review on this topic supports that glycemic variability has been shown to increase cell death, increase cytokine production, impair endothelial function, and increase oxidative stress (Palesh et al., 2015), (Baptista et al., 2018), (Suh & Kim, 2015), and (Caine et al., 2015). This can lead to further vascular complications, both microvascular and macrovascular effects. Suh & Kim reported that even short-term glucose variability can play a substantial role in the development of microvascular complications, specifically retinopathy (2015). When blood sugar drops from a high value to a low value, an inflammatory response is initiated which induces the release of inflammatory cytokines. This also leads to an increase in both platelet and neutrophil activation. This can cause adverse effects to the type 2 diabetic patient as it often increases cardiovascular risk due to endothelial dysfunction (Suh & Kim, 2015). Baptista et al. (2018) pointed out that glycemic variability not only lead to an increase risk of mortality, but also was shown to increase length of hospital stay and mechanical ventilation days. One important takeaway from this particular study was the importance of sufficient nursing participation in controlling glucose levels in order to increase survival rates and ensure effective care. Palesh et al., does point out that data is somewhat inconsistent as to whether or not patients with diabetes who experience glucose variability are in fact at an increased risk for mortality. The article mentions this may be due to the fact that only a small number of studies have been conducted on this topic specifically related to patients with diabetes and that chronic hyperglycemia can be seen as somewhat protective in acute illness. Further research on this topic for this specific population is recommended (2015).

In conclusion, glycemic control of patients with T2DM in the critical care setting is not always an easy thing to achieve. Currently, guidelines recommend approaching these patients with a more lenient approach, versus a stricter approach. Insulin therapy is recommended to start
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when blood sugars reach 180 mg/dL, with a target range of 140-180 mg/dL. Hypoglycemia and glycemic variability are two main adverse effects that are more likely to occur when a stricter protocol is in place for glycemic control. These have both been shown to have many associated undesirable effects, as well as increasing mortality in this patient population.

Literature Search

A thorough literature search was conducted to yield adequate articles appropriate for this research topic. A literature search of the key words “type 2 diabetes” in the major database of CINAHL (Cumulative Index to Nursing & Allied Health) revealed over 20,000 articles. CINAHL is a very widely used and respected database that covers numerous areas in the profession of nursing. To narrow the search, search terms “type 2 diabetes” along with subject major heading “critical care” was used. Limiters placed included English language, published in the years 2014-2019, and peer reviewed articles. This search narrowed down the number of appropriate articles greatly and one article was selected. A search of the key works “hypoglycemia” and “ICU” yielded 22 articles in which two were chosen. An additional search on CINAHL with key works “glucose control” and “critical care” yielded one article that was chosen.

Another search was conducted in the major database of PubMed. This database focuses on more biomedical and clinical literature. A search of “World Journal of Diabetes” with the same limiters as listed above, yielded three appropriate articles. The World Journal of Diabetes articles were used throughout an UpToDate review of this topic, in which PubMed was used to find the primary source. An additional search of “glycemic variability” was used in PubMed in which two articles where chosen. PubMed was also used to find the landmark study from the New England Journal of Medicine on the NICE-SUGAR study. The American Diabetes
Association provided statistics along with current guideline recommendations and was a helpful tool in this literature search.

**Learning Points**

- Currently, guidelines of glycemic control in the intensive care unit are focused on a conventional approach versus a strict approach, as risks have been shown to outweigh the benefits. Guidelines state that insulin therapy should be initiated when blood sugar has reached 180 mg/dL, with a target range of 140-180 mg/dL while receiving insulin therapy.

- The risk of hypoglycemia that can occur with strict glycemic control in the type 2 diabetic patient has been shown to increase mortality in the ICU. Hypoglycemia has also been shown to have detrimental cardiovascular and neurological implications in critically ill patients with T2DM.

- The risk of glycemic variability has also been shown to increase mortality in the type 2 diabetic patient in the ICU. This can contribute to microvascular and macrovascular complications and is a greater risk when strict glycemic parameters are in place. More research is recommended for diabetics specifically and the implications of glycemic variability.
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