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Case Report

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High dose glucocorticoids inducing hyperglycemia in patients with diabetes mellitus experiencingrecurent ischemic stroke attacks: A case report

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Abstract: Stroke is an acute and focal neurological syndrome characterized by clinical deficits resulting from vascular injuries such as infarction or hemorrhage in the central nervous system. Given the prevalence of multiple comorbidities among stroke patients, they often find themselves on more than five medications, falling into the category of polypharmacy. Beyond treatments aimed at improving stroke outcomes and managing comorbid conditions, the presence of additional diseases may necessitate new therapies, potentially leading to side effects that can intersect and exacerbate the existing disease. This case report aims to present instances of hyperglycemia in stroke patients undergoing high-dose glucocorticoid therapy and discuss potential strategies to address this issue. In this particular case, human insulin was selected to rapidly control the patient's hyperglycemic condition. Subsequently, adjustments to basal and bolus insulin doses were made based on the frequency of use and duration of action of the glucocorticoid, specifically methylprednisolone. In conclusion, the hyperglycemia induced by glucocorticoids was identified through postprandial sugar monitoring, necessitating treatment through modifications to basal and bolus insulin doses. Strategies for managing hyperglycemia should be tailored to the pharmacokinetics of glucocorticoids and insulin.

Keywords: Stroke, Polypharmacy, Comorbidities.

INTRODUCTION

Stroke is a sudden disturbance in brain function characterized by clinical signs and symptoms lasting more than 24 hours.[1] It results from either an ischemic or hemorrhagic process, often initiated by a lesion or injury to the arteries. Approximately two-thirds of strokes are ischemic, while one-third are hemorrhagic. Ischemic strokes are attributed to thromboembolic blockages in blood vessels, leading to an ischemic region beneath the obstruction. Conversely, hemorrhagic strokes result from the rupture of a microaneurysm.[2]

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In Indonesia, stroke accounts for 15.4% of deaths,[3] presenting the highest mortality incidence due to stroke in Southeast Asia—193.3/100,000 people per year—second only to Mongolia, with a mortality rate of 222.6/100,000 people per year.[4] The risk of recurrent ischemic stroke is notably elevated during the early post-acute phase, with at least 80% of ischemic events recurring in individuals with a history of ischemic stroke. A comprehensive preventive approach encompassing dietary modification, exercise, antiplatelet/anticoagulant therapy, antihypertensives, and statins is crucial.[5,6] However, this multifaceted treatment approach often leads to polypharmacy,[7]

defined as the prescription and use of more than five drugs. Analysis indicates that stroke patients with multimorbidity contribute to the escalating treatment burden.[8] The highest prescription rates are observed in patients with cardiovascular risk factors, particularly diabetes and coronary heart disease.[9] This comorbid therapy is essential for managing blood pressure, glucose levels, and lipid levels. Nevertheless, polypharmacy introduces the risk of drug interactions and side effects, potentially exacerbating the patient's condition.

Steroid therapy, particularly glucocorticoids, plays a pivotal role in treating and preventing acute and chronic inflammatory diseases, as well as disorders of the immune system.[10] The use of corticosteroids is intricately linked to various side effects, including fluid retention and edema, blurred vision, modulation of the immune response, and steroid-induced hyperglycemia. Other side effects encompass the development of avascular necrosis, cataracts, glaucoma, psychosis, impacts on the endocrine system, and the initiation of bone disease, dyslipidemia, obesity, and adrenal suppression.[11]

The prevalence of corticosteroid-induced hyperglycemia is contingent on the dose, indication, and context of use. Individual factors such as age, baseline body mass index (BMI), and a family history of diabetes are recognized as influencing the risk of developing steroid-induced hyperglycemia (SIHG).[12] Observational data indicates that approximately 2% of diabetes cases in the primary care population are attributed to corticosteroid therapy and contribute to the onset of new diabetes.[13] A meta-analysis revealed that in patients without a prior history of diabetes who received systemic glucocorticoids, the incidence rate of hyperglycemia was 32.3%, with 18.6% of this subgroup subsequently developing diabetes mellitus.[14] Conversely, in patients undergoing solid organ transplantation and glucocorticoid therapy, the prevalence of hyperglycemia ranged between 17% and 32%.[15,16] This case report aims to present instances of hyperglycemia in stroke patients undergoing high-dose glucocorticoid therapy and discuss potential strategies to address this issue.

CASE REPORT

Patient Mrs S, aged 52, presented with complaints of weakness on the right side of the body and difficulty swallowing. The patient had a history of cerebrovascular events one year prior and a concurrent diagnosis of diabetes mellitus (DM). The patient was on medication, although the specific details of the medication history were not recalled. The diagnosis upon admission was a second stroke accompanied by double hemiparesis. Additionally, the patient was diagnosed with bronchial asthma, sputum retention, and type 2 diabetes mellitus (DM).

Upon arrival at the emergency room, the patient's Glasgow Coma Scale (GCS) was 445, with a blood pressure of 215/116 mmHg, a pulse rate of 103 times/minute, and normal body temperature, respiratory rate, and O2 saturation. Her laboratory examination revealed a Hb value of 16.0 g/dL, a leukocyte count of 11,100 cells/mm^3, and a platelet count of 384,000 platelets/mm^3. The patient's serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) values were 28 U/L and 53 U/L, respectively. Her electrolyte levels were as follows: sodium 132.3 mmol/L, potassium 4.11 mmol/L, chloride

107.3 mmol/L, and calcium 4.44 mmol/L. The total cholesterol level was 252 mg/dL, with LDL at 139 mg/dL and HDL at 35 mg/dL. Hypertriglyceridemia was also noted, with a value of 542 mg/dL. A random blood sugar check in the emergency room showed a level of 248 mg/dL.

The emergency room treatment included IV Ranitidine 50 mg every 24 hours, IV Citicoline 500 mg every 24 hours, IV Ondansetron, SC Novorapid 3x10 units, and Levemir 18 units at night. Oral medications included Clopidogrel 1x1, Atorvastatin 20 mg 1x1, MgSO4 40% 5cc administered in 1 hour, N-acetylcysteine 3x200 mg, Cetirizine 10 mg, a combination of Salmeterol and Fluticasone, Methylprednisolone 62.5 mg every 12 hours, Nebule Combivent Budesma, and Lactulose 3x1c. On the 6th day of hospitalization, the patient received Actrapid 100 IU/50 cc NS. Following the administration of Actrapid, the blood glucose levels began to decrease from 534 to 300 at 7 hours after IV insulin. After nine days of treatment, the patient exhibited clinical improvement, manifested by an increase in GCS to 456.

RESULTS AND DISCUSSION

The recurrence of ischemic stroke poses a significant challenge due to the potential for broader physical and cognitive damage, leading to disability. Undetected risk factors contribute to the likelihood of recurrent strokes, as evidenced by a systematic review and meta-analysis highlighting large-artery atherosclerotic (LAA) and cardioembolic (CE) stroke patterns as common etiologies leading to recurrent events. This case report identified modifiable risk factors such as hypertension, diabetes mellitus, and atrial fibrillation as independent contributors to recurrence, aligning with the patient's condition of hypertensive emergency and uncontrolled blood sugar. Urgent implementation of secondary preventive therapy, including interventions to manage hypertension and hyperglycemia, becomes crucial to prevent similar events.[17]

During hospitalization, the patient received high doses of methylprednisolone for managing bronchial asthma. On the second day of post-methylprednisolone administration, a notable increase in the patient's blood sugar levels within the range of 358-534 mg/dL was observed. Glucocorticoids exhibit diabetogenic effects, particularly in individuals with insulin resistance, leading to hyperglycemia. The rise in sugar levels is attributed to increased postprandial blood sugar resulting from the metabolic impact of glucocorticoids.[18] This occurrence may be associated with the duration of action of glucocorticoids, classifying methylprednisolone as a medium-acting glucocorticoid.[19] The use of medium-acting glucocorticoids at doses 2-3 times divided can induce and sustain hyperglycemia throughout the day.[20] To address the patient's hyperglycemia, a rapid insulin infusion of 3 IU/hour is administered.

The effects of glucocorticoids on glucose metabolism likely stem from the disruption of multiple pathways, including beta cell dysfunction (sensitivity to glucose and insulin release) and insulin resistance in various tissues. The impact on beta cell function and insulin sensitivity may differ depending on whether glucocorticoid effects are acute or chronic. A study comparing a single acute dose of prednisolone (75 mg) with a daily dose of 30 mg for 15 days revealed that acute treatment inhibits several parameters of beta cell function. In contrast, prolonged exposure to glucocorticoids demonstrated partial recovery of beta cell function, yet glucose tolerance was impaired, suggesting additional factors play a role in steroid-induced diabetes mellitus (SIDM) beyond beta cell dysfunction.[21]

Several mechanisms underlie the diabetogenic effects of glucocorticoids, contributing to hyperglycemia. These include the reduction of peripheral insulin sensitivity, elevation of hepatic gluconeogenesis, induction of insulin resistance in lipid metabolism and adipose tissue, and inhibition of pancreatic insulin production

and secretion. Glucocorticoids pose the highest risk for hyperglycemia and the development of overt diabetes mellitus.[22]

In addition to the duration of exposure, the potency-related duration of action of glucocorticoids is a crucial factor influencing the severity of post-glucocorticoid hyperglycemia. Research by Yasuda et al. in 1982 demonstrated that hydrocortisone, dexamethasone, and prednisone induced varying degrees of insulin resistance, primarily through a decrease in insulin binding affinity rather than a reduction in the number of receptors.[23]

Glucocorticoids directly impact glycogen synthesis pathways, insulin-mediated degradation, and protein synthesis. The primary site for insulin-mediated glucose uptake is skeletal muscle. Insulin facilitates the recruitment of the glucose transporter (GLUT-4) to the cell surface, enabling the uptake of glucose into the cell. Glucocorticoids disrupt insulin-mediated glucose uptake by directly interfering with key components of the insulin signaling cascade, including glycogen synthase kinase-3, glycogen synthase, and GLUT-4 translocation.[24]

The management of corticosteroid-induced hyperglycemia differs from that of non-steroid-related diabetes. Insulin sensitizers such as metformin, commonly used as a first-line treatment for type 2 diabetes mellitus, are not recommended for steroid-induced diabetes mellitus (SIDM). This is attributed to relative or absolute contraindications to metformin use, including nausea/vomiting, hypoxia, liver disorders, and kidney disorders.[12]

In outpatient management, certain oral hypoglycemic drugs (OHO) show the potential to improve glycemic control and prevent or delay the onset of corticosteroid-induced hyperglycemia.[25] However, there is limited evidence demonstrating the clinical effectiveness of OHO use for in-hospital hyperglycemia caused by glucocorticoids.[26]

Management strategies for controlling hyperglycemia induced by glucocorticoids have been investigated in various studies. The hyperglycemic effects of different glucocorticoids influence the pharmacokinetic profile of the glucocorticoid. Therefore, the choice of insulin therapy in SIDM must take into account the specific glucocorticoid therapy, its current dose, and the timing and intervals of administration.[12] NPH insulin, based on body weight, was selected due to its duration of action being similar to that of medium-acting glucocorticoids, thereby mitigating the risk of hypoglycemia once the steroid effect diminishes.

For corticosteroids administered twice daily, long-acting insulin such as glargine or detemir may be preferable during periods of hyperglycemia.[19] The 2012 Endocrine Society guideline recommends initiating insulin at 0.3-0.5 units/kg/day when using glucocorticoids, with no specific recommendations regarding the proportion of basal and bolus insulin.[27] Suh's research in 2017 suggested an NPH insulin dose of 10% of the corticosteroid prednisone dose.[18] Thus, adjustments to basal and bolus insulin doses are necessary to manage hyperglycemia. The target for monitoring pre-prandial blood sugar is < 140 mg/dL, and < 180 mg/dL for post-prandial sugar.

When hyperglycemia due to steroids is not controlled with oral hypoglycemic drugs, insulin may be administered once a day or through a more complex insulin regimen 2-3 times a day, such as premixed insulin or basal-bolus insulin. Insulin dose titration is crucial for maintaining glycemic control by adjusting the insulin dose as needed. In critically ill patients with severe hyperglycemia, intravenous insulin infusion (drip insulin) may be required.[28]

The initiation of glucocorticoids may induce postprandial hyperglycemia, while the reduction of glucocorticoids may result in the normalization of glycemic control. Combination basal-bolus insulin therapy, incorporating basal insulin, prandial insulin, and an additional correction factor insulin, remains the most flexible option for patients.[29] However, conventional use of high doses of long-acting basal insulin can lead to nocturnal hypoglycemia.[30]

CONCLUSION

In conclusion, the hyperglycemia induced by glucocorticoids was identified through postprandial sugar monitoring, necessitating treatment through modifications to basal and bolus insulin doses. Strategies for managing hyperglycemia should be tailored to the pharmacokinetics of glucocorticoids and insulin.

AUTHORS' CONTRIBUTIONS

Fatimatuz Zahro and Tita Sugesti took research data and wrote this journal. Siska Hermawati, M. Hari Pristantiningtyas, Herya Putra Dharma and Muhammad Muchlis chose cases in the hospital that could be used as case reports, as well as guiding the writing of this journal. Jainuri Erik Pratama, Fauna Herawati, Adji Prayitno Setiadi and Marisca Evalina Gondokesumo reviewed and supervised the journal. All authors have read and approved the final journal.

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