

ARTIGO ORIGINAL

Glucose disturbances in non-diabetic patients receiving acute treatment with methylprednisolone pulses

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SUMMARY

Objective: Methylprednisolone pulses are used in a variety of disease conditions, both for acute and chronic therapy. Although well tolerated, they increase glucose levels in both non-diabetic and diabetic patients. They may also be considered a significant risk for acute metabolic alterations. The purpose of this report is to determine the metabolic changes in blood glucose levels in non-diabetic patients receiving methylprednisolone pulses and identify the presence of predictive factors for its development. **Methods:** Observational, prospective study in 50 non-diabetic patients receiving 1 g intravenous methylprednisolone pulses for three consecutive days as an indication for diverse autoimmune disorders. Demographic, anthropometric, and metabolic variables were analyzed, and glucose, insulin and C-peptide levels after each steroid pulse were identified. Different variables and the magnitude of hyperglycemia were analyzed using Pearson's correlation. **Results:** 50 patients were included, predominantly women (66%, n = 33). The average age was 41 ± 14 years with a BMI of 26 ± 3 kg/m². Baseline glucose was 83 ± 10 mg/dL. After each steroid pulse, glucose increased to 140 ± 28 , 160 ± 38 and 183 ± 44 , respectively ($p < 0.001$). C-peptide and insulin concentrations increased significantly ($p < 0.001$). The prevalence of fasting hyperglycemia after each pulse was 68%, 94% and 98%, respectively. We found no correlation between the magnitude of hyperglycemia and the studied variables. **Conclusion:** Methylprednisolone pulses produced significant increases in fasting glucose in most patients without diabetes. Further studies are needed to define its role in long-term consequences.

Keywords: Methylprednisolone; *diabetes mellitus*; hyperglycemia.

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RESUMO

Distúrbios de glicose em pacientes não diabéticos que recebem tratamento agudo com pulsos de metilprednisolona

Objetivo: Pulsos de metilprednisolona são usados em diversas doenças, tanto para tratamento agudo quanto crônico. Embora bem tolerados, eles aumentam os níveis de glicose em ambos os pacientes, não diabéticos e diabéticos. Eles também podem ser considerados um risco significativo para alterações metabólicas agudas. O propósito deste estudo é determinar as alterações metabólicas nos níveis de glicose no sangue de pacientes não diabéticos que recebem pulsos de metilprednisolona e identificar a presença de fatores preditivos para seu desenvolvimento. **Métodos:** Estudo observacional prospectivo em 50 pacientes não diabéticos que recebem pulsoterapia com 1 g de metilprednisolona intravenosa por três dias consecutivos como tratamento para diversas doenças autoimunes. Variáveis demográficas, antropométricas e metabólicas foram analisadas, e glicose, insulina e níveis de peptídeo C foram identificados após cada pulso de esteroide. Diferentes variáveis e a magnitude da hiperglicemia foram analisadas utilizando a correlação de Pearson. **Resultados:** 50 pacientes foram incluídos, predominantemente mulheres (66%, n = 33). A idade média foi de 41 ± 14 anos com um IMC de 26 ± 3 kg/m². A glicose de base foi de 83 ± 10 mg/dL. Após cada pulso de esteroide, a glicose aumentou para 140 ± 28 , 160 ± 38 e 183 ± 44 , respectivamente ($p < 0,001$). Peptídeo C e concentrações de insulina aumentaram significativamente ($p < 0,001$). A prevalência de hiperglicemia em jejum após cada pulso foi de 68%, 94% e 98%, respectivamente. Não encontramos nenhuma correlação entre a magnitude da hiperglicemia e as variáveis estudadas. **Conclusão:** Os pulsos de metilprednisolona produziram aumentos significativos na glicemia de jejum na maioria dos pacientes sem diabetes. Mais estudos são necessários para definir o seu papel nas consequências em longo prazo.

Unitermos: Metilprednisolona; *diabetes mellitus*; hiperglicemia.

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INTRODUCTION

Glucocorticoids are compounds that have long been used for a variety of diseases, both as chronic therapy and in acute cases. Methylprednisolone pulses are recommended for critical events that require urgent treatment for an exacerbation of a known disease or when vital organs are compromised¹.

Although generally well tolerated, they are not free of complications such as glucose intolerance, urinary tract infections, gastritis, fluid retention, nausea, vomiting, insomnia, altered consciousness, joint effusion, abnormal taste, hypertension and electrolyte disturbances such as hypokalemia².

Glucocorticoids can worsen known diabetes and precipitate previously unidentified diabetes³. In all cases, it transiently increases up to 50% baseline glucose levels⁴. An OR of 1.36 to 2.31 of de novo diabetes has been reported in patients treated with steroids with an incidence of 12%⁵. Steroids can also trigger a severe hyperosmolar hyperglycemic decompensation and, in rare cases, death, especially in patients with preexisting diabetes⁶.

The aim of this paper is to present the changes in blood glucose levels in non-diabetic Mexican patients undergoing methylprednisolone pulses, and identify factors that correlate with the development post-bolus hyperglycemia.

METHODS

We performed an observational, longitudinal, prospective study in the Medical Specialties "Hospital No. 25 IMSS" in Monterrey, Nuevo Leon, from September to November 2010. We included 50 patients referred by specialists from the neurology, rheumatology and hematology services and hospitalized in the internal medicine department with the therapeutic indication of 1 g pulses of methylprednisolone for 3 consecutive days. Inclusion criteria were: individuals of both sexes, Mexican, aged 18 years or more and with no previous history of DM. The study was approved by the institutional ethics committee.

Demographic, anthropometric and metabolic variables were analyzed. Glucose measurements were performed at baseline and after each 1 g pulse of intravenous methylprednisolone. We also determined insulin and C-peptide levels after each pulse. All examinations were performed after 8 hours of fasting. Glucose levels were determined by the glucose oxidase method, insulin by electrochemiluminescence, and C-peptide levels by chemiluminescence.

The statistical analysis of all data was performed using SPSS version 19. The prevalence of post-bolus hyperglycemia was calculated. Continuous variables are expressed as measures of central tendency and dispersion, and comparisons were made using Student's *t*-test. Correlations between quantitative variables (age, BMI, fasting glucose and post-bolus glucose levels) were made with Pearson's correlation coefficient. A $p \leq 0.05$ was considered significant.

RESULTS

We included 50 patients with no previous diagnosis of *diabetes mellitus* (DM)⁵. Gender distribution was 33 women (66%) and 17 men (34%). Average age was 41 ± 14 years with a BMI of 26 ± 3 kg/m². Overweight was found in 22 patients (44%) and obesity in 11 (22%). A family history of DM was present in 42%.

The main diagnoses for patients referred by the attending physician (blinded to the objectives of the study), were: systemic lupus erythematosus (22%), idiopathic thrombocytopenic purpura (24%), multiple sclerosis (22%), autoimmune hemolytic anemia (8%) and others (18%).

The baseline glucose level was 83 ± 10 mg/dL. After each pulse of methylprednisolone, glucose levels increased to 140 ± 28 mg/dL, 160 ± 38 mg/dL and 183 ± 44 mg/dL, respectively ($p < 0.001$). C-peptide and insulin concentrations also showed statistically significant increases ($p < 0.001$) (Table 1).

The prevalence of post-bolus hyperglycemia (glucose ≥ 126 mg/dL) was: 68% after the first pulse, 94% after the second, and 98% after the third pulse. When performing Pearson's correlation we found no predictive factor with statistical significance for the development of post-bolus hyperglycemia (Table 2).

DISCUSSION

Pulsed methylprednisolone is highly effective in autoimmune diseases due to its anti-inflammatory and immunosuppressive effect. It reduces pain and active disease and provides acute symptomatic relief, while the beneficial effect of other drugs occurs¹. The symptomatic benefit offered by steroid pulses causes them to be frequently used despite their adverse effects. Our group recently published the changes in serum electrolytes in a cohort of patients. Without being the objective of that study, we identified a change in glucose levels⁷, which had already been observed in specific groups of patients in the absence of

Table 1 – Metabolic changes after methylprednisolone pulses

Variable	First pulse	Second pulse	Third pulse	p
Glucose (mg/dL)	140 ± 28	160 ± 38	183 ± 44	< 0.001
C-peptide (ng/mL)	9 ± 2	10 ± 2	11 ± 2	< 0.001
Insulin (μ U/mL)	32 ± 10	38 ± 9	43 ± 10	< 0.001

Data are presented as mean and SD.

Table 2 – Pearson's correlation analysis between post-pulse hyperglycemia and age, BMI and baseline glucose

Variable	Methylprednisolone pulses		
	First pulse	Second pulse	Third pulse
Age	0.023 (p = 0.88)	0.264 (p = 0.06)	0.269 (p = 0.06)
BMI	0.086 (p = 0.55)	0.153 (p = 0.29)	0.057 (p = 0.06)
Baseline glucose	0.199 (p = 0.17)	0.084 (p = 0.56)	0.052 (p = 0.72)

BMI, body mass index.

diabetes^{8,9}. Mignogna et al. reported that this represents the most common complication¹⁰, and Feldman-Billard et al. identified increases of up to 50% compared to baseline levels prior to treatment⁴.

In our study, we found a significant increase in post-bolus glucose levels, similar to what has previously been reported for non-diabetic patients. This increase was more evident after the first pulse with an elevation of about 40 mg/dL, an increment up to 68% with respect to the basal level. At the end of the third pulse, 98% of the patients developed diagnostic criteria for *diabetes mellitus*, which could be explained by a loss of pancreatic islet adaptive phenomenon due to an acute and supra-physiological steroid load. In this phenomenon secretion disorders, insulin resistance and counterregulatory hormones are involved, together with alterations in the secretion and action of incretins¹¹. The only patient that did not develop *diabetes mellitus* criteria presented baseline glucose level below 54 mg/dL, however the metabolic changes were similar in proportion to the total group.

Although the increase is transitory and some authors feel that it does not have clinical relevance, there is evidence that identifies acute hyperglycemia as a cardiovascular risk factor, independently of the presence of previous diabetes. It has been associated with an increase in LDL cholesterol oxidation, impaired endothelial function, activation of the coagulation cascade, increased production of pro-inflammatory cytokines and oxidative stress^{3,5,12-14}.

The magnitude of the hyperglycemic response has been previously associated with age, time and steroid dose, obesity, and in patients with type 2 *diabetes mellitus*, to poor glycemic control^{5,15}. In contrast with previous reports, our work shows no link between the different variables studied. This difference could be explained by genetic and environmental factors related to the high prevalence of diabetes and insulin resistance in our country, confirmed in our work by the significant increases in insulin levels.

As an observational non randomized study, we cannot exclude factors that could influence our results such as stress hyperglycemia as well as the inpatient condition. However, considering the fact that glycemic levels increased progressively after each pulse, we highly suggest that these modifications were due to a cause-effect phenomenon.

Some authors consider it unnecessary to monitor glucose levels in non-diabetic patients because these changes are transient and well tolerated⁴. We do not know the long-term evolution of this expression in our population. We suggest monitoring blood glucose levels in all non-diabetic patients scheduled for methylprednisolone pulse therapy, because it is a simple, safe, and inexpensive procedure. Additionally, we do not know whether these increments in glucose levels, although transient, could predict future diabetes as well as cardiovascular co-morbidities. It is important to recall that our results need to be confirmed in further observational and randomized studies.

CONCLUSION

In conclusion, we found that the glucose profile changes significantly after the administration of high doses of methylprednisolone. BMI, age and baseline glucose levels in non-diabetic patients do not correlate with the magnitude of hyperglycemia. This alteration requires long-term studies to identify the clinical significance of these findings in our population.

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