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Persistent Hyperglycemia in Brain Tumor Patients Treated with Dexamethasone Peri-Operatively and Post-Operatively

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1. Abstract

1.1. Objectives: Corticosteroid are commonly used for the management of vasogenic edema and increased intracranial pressure in patients with brain tumors. The purpose of this study was to investigate postoperative and persistent hyperglycemia in patients with brain tumors treated with corticosteroid.

1.2. Methods: A total of 32 brain tumor patients met the inclusion criteria: 1) dexamethasone was administered for at least 3 to 10 days after surgery 2) fasting plasma glucose(FPG) before surgery, during hospitalization and during follow-up period up to 6 months were obtained; 3) Patients with hyperglycemia were consulted with endocrinologists. Persistent hyperglycemia was defined as FPG ≥126 mg/dL without administration of corticosteroid at 3 or 6 months postoperatively.

1.3. Results: Twenty-five patients had no diabetes mellitus (DM) before operation and 7 were already diagnosed with DM. Peak value of FPG (170.4±46.9 mg/dL) was noted in day 1 postoperatively and gradually decreased in non-diabetes group. Persistent hyperglycemia occurred in 11 (44%) of 25 non-DM patients who were not given with any steroid at the outpatient clinic. Body mass index and the level of glutamic oxaloacetate transaminase(GOT) were higher in patients with persistent hyperglycemia. FPG (158.71±32.77 mg/dL) is higher on day 4 postoperatively in patients with persistent hyperglycemia than those (123.83±17.85 mg/dL) without persistent hyperglycemia even though operation time, total dosage of steroid and duration of steroid administration were not different.

1.4. Conclusions: Persistent hyperglycemia is not uncommon in non-DM patients with brain tumors treated with corticosteroid perioperatively. We suggest that patients with high FPG on operation day and day 4 postoperatively have a risk of persistent hyperglycemia.

2. Introduction

Vasogenic edema is one of the most common and critical complication in brain tumor patients [1]. Corticosteroids are commonly used to treat vasogenic edema despite they might cause complications [2]. Among many complications of corticosteroids, hyperglycemia is crucial in that it may cause multiple organ failures [3]. It's been already published that hyperglycemia may even serve as a poor prognostic marker for brain tumors like glioblastoma [4]. Steroid-induced hyperglycemia occurs easily and may develop late postoperatively [5-7].

The duration of steroid therapy increases the frequency of side effects, and prolonged treatment (>3 weeks) is associated with greater toxicity [8]. Hypergycemia has been reported in up to 72% of patients with primary brain tumors receiving dexamethasone [9]. The hyperglycemia from corticosteroid therapy usually occurs in the first 6 weeks of therapy and is believed to be secondary to insulin resistance and increased hepatic gluconeogenesis [10]. Delayed and persistent hyperglycemia may occur, and can lead to

poor outcomes [5,7].

Here, we analyzed the effect of steroid administration for brain tumor surgery on postoperative hyperglycemia and investigated factors related with persistent hyperglycemia.

3. Materials and Methods

3.1. Patient population

This study was approved by the Institutional Review Board of a participating center. We retrospectively reviewed 103 cases underwent the first craniotomy for the resection of brain tumors by a single surgeon (SHY) from 2006 to 2014. Of these patients, 32 met retrospective selection criteria: 1) brain tumor patients were administered with dexamethasone to relieve peritumoral edema; 2) dexamethasone was administered perioperatively for at least 3 days or longer; 3) the values of FPG before surgery, during hospitalization and during follow-up period up to 6 months were measured using a glucose oxidase method (Beckman instruments, Chaska, MN); 4) Patients with hyperglycemia were consulted with endocrinologists. The exclusion criteria included: 1) dexamethasone was administered for less than 3 days; 2) chronic renal failure, liver cirrhosis, pancreatitis, inflammatory disease and autoimmune disease; 3) other medical illness treated with corticosteroid; 4) lack of FPG data during hospitalization and during follow-up period up.

Our dexamethasone protocol is as follows. 5 or 10 mg dexamethasone per day was administered preoperatively. 10 or 20mg dexamethasone per day was administered on day 1 postoperatively and tapered. When the patients require dexamethasone, dexamethasone was continued during hospitalization. Steroids were used up to 10 days after surgery. Immediate hyperglycemia during corticosteroid use was controlled with regular insulin schedule which was modified according to capillary glucose level every 4 hours. Then patients were consulted with an endocrinology specialist (JSY). The diagnosis of steroid-induced hyperglycemia followed the current criteria established by the American Association of Diabetes: blood glucose level of ≥126 mg/dL. Persistent hyperglycemia was considered if patients had FPG of 126 mg/dL or higher at 3 to 6 months after surgery.

3.2. Statistical Analysis

Subjects were divided into 2 groups according to FPG above or below 126 mg/dL at follow-up 6 months. Chi-square analysis was performed for categorical variables and Mann-Whitney analysis was performed for continuous variables. In addition, Kruskal-Wallis analysis was conducted for continuous variables with the above two groups and those diagnosed with diabetes before surgery.

4. Results

Characteristics of 32 patients are summarized in Table 1. Baseline variables were compared between patients diagnosed preoperatively with diabetes mellitus and non-diabetes mellitus. BMI was higher in diabetes group than in non-diabetes group. The mean duration of steroid administration was 7.2 days. Other characteristics were not different. We serially assessed FPG preoperatively, perioperatively and postoperatively. Preoperative FPG were 101.1±13.5 and 133.6±52.0 mg/dL in non-diabetes and diabetes patients, respectively. Peak value of FPG was noted in day 1 postoperatively and gradually decreased in non-diabetes group. FPG in diabetes group were higher in day 3, 8 and 10 postoperatively than those in non-diabetes group even though operation time, total dosage of steroid and duration of steroid administration were similar between groups.

Next, we assessed FPG at 3 through 6 months after surgery in non-diabetes patients. Persistent hyperglycemia (≥126 mg/dL) occurred after more than 3 months in 11 (44%) of 25 patients who were not given with any steroid (Table 2). BMI and the level of Glutmic oxalacetic transaminase (GOT) were higher in patients with persistent hyperglycemia, but it was not statistically different. Preoperative FPG were 102.36±12.56 and 100.14±14.54 mg/dL in patients with and without persistent hyperglycemia, respectively. FPG on operation day was 150.55±38.05 mg/dL in patients with persistent hyperglycemia, compared with 123.23±32.17 mg/dL in patients without persistent hyperglycemia (p-value, 0.082). FPG (158.71±32.77 mg/dL) is higher on day 4 postoperatively in patients with persistent hyperglycemia than those (123.83±17.85 mg/dL) in patients without persistent hyperglycemia (p-value, 0.038) even though operation time, total dosage of steroid and duration of steroid administration were not different (Figure 1). In the case of patients diagnosed with diabetes before surgery, FPG at 3 months after surgery found to be 126 mg/dL or more in all but one patient despite they were managed with anti-diabetic agents.

Table 1: Comparison of patient characteristics and fasting plasma glucose according to diabetes mellitus

		All (n=32)	Non-diabetes (n=25)	Diabetes (n=7)	p-value
Age		57.3±13.0	55.7±13.9	63.0±7.5	0.254
Sex(male:female)		16:16	13:12	3:04	
Pathology	Meningioma	16	11	5	
	Glioma	8	6	2	
	Metastasis	4	4	0	
	Schwannoma	2	2	0	
	PCNSL	2	2	0	
Hypertension		14(43.8%)	10(40.0%)	4(57.1%)	0.419
Family history of diabetes mellitus		1(3.1%)	1(4.0%)	0(0.0%)	0.591

Smoking		5(15.6%)	3(12.0%)	2(28.6%)	0.286
Alcohol		1(3.1%)	1(4.0%)	0(0.0%)	0.591
BMI (kg/m^2)		24.3±3.1	23.5±2.9	27.1±1.6	0.002
Cholesterol (mg/dL)		186.7±47.9	186.2±48.9	188.7±48.1	0.979
Triglyceride (mg/dL)		123.4±85.8	120.5±95.0	135.2±31.6	0.161
LDL (mg/dL)		119.1±41.4	119.0±43.8	119.4±33.2	0.795
HDL (mg/dL)		38.7±11.3	38.7±11.5	38.8±11.3	0.959
Total Bilirubin (mg/dL)		0.7±0.3	0.7±0.3	0.5±0.2	0.096
GOT (IU/L)		22.5±13.1	24.0±14.3	17.3±5.9	0.226
GPT (IU/L)		28.3±20.0	28.9±21.5	25.9±14.2	0.855
ESR (mm/h)		15.1±15.9	14.6±17.1	16.6±11.8	0.423
CRP (mg/dL)		0.4±0.7	0.4±0.6	0.6±0.7	0.283
Creatinine (mg/dL)		0.8±0.2	0.7±0.2	0.9±0.4	0.398
Operation time (min)		347.7±187.1	321.5±152.1	437.9±272.1	0.267
Total dosage of steroid (mg)		84.6±44.2	87.3±39.9	74.7±59.8	0.178
Duration of steroid administration (day)		7.2±3.1	7.6±3.1	5.7±2.8	0.121
FPG (mg/dL)					
Pre-op		108.2±29.2	101.1±13.5	133.6±52.0	0.151
Op day		141.8±41.3	135.8±36.9	165.8±52.7	0.195
POD#1		183.0±59.7	170.4±46.9	217.0±80.1	0.133
POD#2		153.6±36.7	146.1±29.4	179.2±50.5	0.147
POD#3		155.6±44.8	144.7±38.2	197.0±47.5	0.021
POD#4		147.4±35.3	142.6±31.6	178.5±57.3	0.234
POD#5		145.0±45.4	135.1±42.5	194.5±23.3	0.086
POD#6		128.3±44.7	125.1±44.8	170.0±0.0	0.263
POD#7		133.4±36.5	133.3±37.9	134.0±41.0	0.844
POD#8		116.6±27.0	110.4±23.7	151.0±17.0	0.048
POD#9		110.0±27.0	110.0±27.0		
POD#10		125.2±26.0	115.5±19.8	157.7±15.2	0.028

PCNSL, Primary Central nervous system Lymphoma; BMI; Body mass index; LDL, Low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol; GOT, Glutmic oxalacetic transaminase; GPT, Glumic pyruvate transaminase; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; FPG, fasting plasma glucose; Op, operation; POD, Post-operative day. Mean±SD.

Table 2: Difference of variables between groups with/without persistent hyperglycemia

	≥126 mg/dL (n=11)	<126 mg/dL (n=14)	p-value
Sex			
Male	7	6	0.302
Female	4	8	
Hypertention	4	6	0.742
Diabetes	0	0	1
Family history of diabetes	0	1	0.366
Smoking	1	2	0.692
Alcohol	1	0	0.25
BMI (kg/m^2)	24.73±3.20	22.54±2.38	0.079
Cholesterol (mg/dL)	185.80±31.30	186.43±59.56	0.77
Triglyceride (mg/dL)	112.20±48.08	126.36±119.49	0.66
LDL (mg/dL)	121.20±30.24	117.36±52.46	0.838
HDL (mg/dL)	34.20±9.85	41.86±11.92	0.151
Total Bilirubin (mg/dL)	0.71±0.29	0.68±0.28	0.901
GOT (IU/L)	25.82±9.24	22.57±17.51	0.075
GPT (IU/L)	31.09±15.00	27.21±25.97	0.261
ESR (mm/h)	13.36±11.75	15.64±20.79	0.762
CRP (mg/dL)	0.21±0.20	0.53±0.84	0.763
Creatinine (mg/dL)	0.75±0.15	0.71±0.21	0.473
Op time (min)	259.50±147.17	365.71±144.47	0.143
Total dosage (mg)	101.59±51.84	76.14±23.92	0.218
Duration of steroid administration day)	8.09±3.75	7.21±2.64	0.431
FDG (mg/dL)			
Pre-op	102.36±12.56	100.14±14.54	0.51
Op day	150.55±38.05	123.23±32.17	0.082

POD#1	171.25±55.56	169.82±42.30	0.934
POD#2	156.86±33.44	138.60±25.22	0.172
POD#3	149.38±48.72	141.36±30.63	0.901
POD#4	158.71±32.77	123.83±17.85	0.038
POD#5	164.00±62.79	122.71±28.21	0.425
POD#6	136.00±58.63	120.22±40.46	0.698
POD#7	129.86±34.06	139.25±48.82	1
POD#8	122.75±13.18	103.29±26.30	0.186
POD#9	112.00±0.00	109.67±29.56	1
POD#10	116.80±28.26	114.20±8.87	0.53

BMI; Body mass index; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; GOT, Glutmic oxalacetic transaminase; GPT, Glumic pyruvate transaminase; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; FPG, fasting plasma glucose; Op, operation; POD, Post-operative day. Mean±SD.

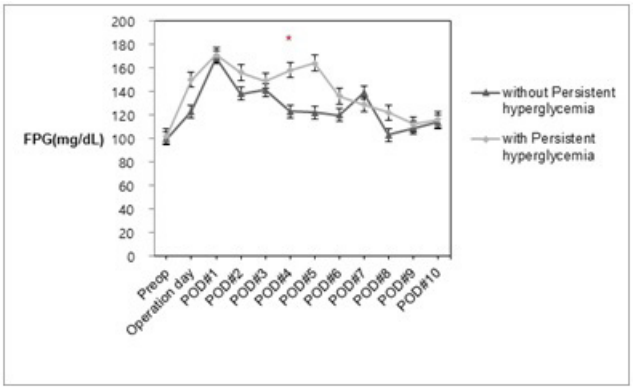

Figure 1: Serial assessment of fasting plasma glucose (FPG) in patients with/without persistent hyperglycemia. * p-value <0.05.

5. Discussion

This study investigated the association between steroid administration for brain tumor surgery and postoperative hyperglycemia. It was found that the diagnosis of diabetes mellitus was associated with high FPG postoperatively. We found that 44% nondiabetic patients treated with brain tumor surgery and steroid therapy had FPG ≥126 mg/dL after three months of surgery. FPG on day 4 postoperatively could predict the occurrence of persistent hyperglycemia (3 through 6 months postoperatively) in non-diabetic patients who were administered with dexamethasone for mean 7.6 days. On day 4 postoperatively, FPG was 158.0±32.77 mg/dL in nondiabetic patients with persistent hyperglycemia, which was significantly higher than 123.83±17.85 mg/dL in nondiabetic patients without persistent hyperglycemia.

Steroid administration increases insulin resistance with the subsequent state of hyperinsulinism. In healthy subjects, this mechanism is compensated by an increase in pancreatic insulin secretion, causing serum glucose levels to remain within normal range [11]. However, in susceptible populations, such as normoglycemic individuals with reduced insulin sensitivity and a low rate of production of the same prior to steroid use, this offsetting effect is lost, resulting in hyperglycemia [12]. Treatment of brain tumor (surgery, chemotherapy, or radiotherapy) is most frequently associated with disorders of the endocrine system [13]. Patients treated for brain tumor experience a lack of physical activities over the entire course of their treatment, which leads to physical deconditioning [14, 15]. Our data suggest that BMI could be associated with persistent hyperglycemia. The risk factors of developing diabetes following steroid administration are the dose of steroid, [16] duration of treatment, [17] a continuous steroid scheme, [18] older age, [19] and body mass index [11]. In our series, operation time, total dosage and duration of steroid administration were not associated with persistent hyperglycemia.

Most patients with brain tumors begin to improve symptomatically within hours of dexamethasone administration, achieving maximum benefit within 24-73 hours [20]. A high rate of side effects is associated with prolonged dexamethasone use, as is a risk of suppression of the hypothalamic-pituitary-adrenocortical axis. All patients who are started on steroid treatment should have a baseline glucose, as well as education on daily self-monitoring of glucose. In hospitalized patients, monitoring should start with capillary glucose determination from the start of steroid treatment. Since almost 94% of cases of hyperglycemia develop within 1 to 2 days of initiation of steroid therapy in the hospital setting, other authors reported that in nondiabetic patients who maintain glucose levels < 140 mg/dL without insulin requirements of 24-48 hours, glycemic monitoring can be discontinued [6].

However, we found that obese patients with high FPG on operation day and day 4 postoperatively have a risk of persistent hyperglycemia. We recommend that clinicians pay attention to steroid-induced and persistent hyperglycemia even in nondiabetic patients with brain tumors. The proper management is needed because hyperglycemia caused by steroid has a significant effect on prognosis [21].

This study includes several limitations; the first is the small size of our groups. A larger-scale study is now needed to validate the association of steroid administration and persistent hyperglycemia in brain tumor patients; the second is the diagnosis of diabetes. Only one FPG results is not sufficient for the diagnosis. We depend on self-reporting by the patients: the third is the lack of hemoglobin A1C data. In this study, HbA1c could not be screened for all patients due to domestic insurance standards.

To predict and prevent hyperglycemia event can lead to a better outcome treating brain tumor patients. FPG during the first week after surgery can be used as a predictor for persistent hyperglycemia in brain tumor patients treated with corticosteroid. Close monitoring of FPG is mandatory to prevent steroid-induced morbidities.

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