ORIGINAL ARTICLE

Frequency and Attributing Factors of Impaired Blood Glucose in Non-Diabetic Patients on Steroid Pulse Therapy

NAEEM AHMED[1], AQSA HAMEED[2], AMNA KIRAN SARWAR[3], SAQIB JAHANGIR[4]
[1]*FConsultant General and Laproscopic Surgeon District Headquarter Hospital, Jhelum*
[2]*MO, Incharge Health Officer BHU 105-RB, PHFMC, Faisalabad*
[3]*Senior Registrar Department of Medicine Shalamar Hospital, Lahore*
[4]*Working at Central Surgery Barton upon Humber DN 185ER, UK*
Correspondence to: Dr. Naeem Ahmed naeemkashmir@gmail.com; + 92 301 5617759

ABSTRACT

Objective: The objectives of this study were to determine the frequency of impaired blood glucose in non-diabetic patients on steroid pulse therapy and to compare the frequency of various attributing factors in patients with impaired blood glucose in non-diabetic patients on steroid pulse therapy.

Design: It was a cross-sectional study.

Study Settings: The study was at conducted at Department of Medicine Shalamar Hospital, Lahore over a period of 6 months from 09-01-2020 to 08-07-2020.

Material and Methods: Total 371 non-diabetic patients from both the genders were involved in this study, they had ages between 18-70 years, receiving steroid pulse therapy for rheumatoid arthritis or systemic lupus erythematosus. Blood glucose level was estimated after 2 hours of steroid pulse therapy and a rise of ≥20mg/dl blood sugar level from the baseline was labeled as impaired blood glucose. A written informed consent was obtained from every patient.

Results: The mean age of the patients was 43.75±14.33 years. There were 159 (42.9%) male and 212 (57.1%) female patients. Mean BMI of the patients was 27.34±3.72 Kg/m2. Number of hypertensive patients was 81 (21.8%) while 42 (11.3%) patients had positive family history of diabetes. Impaired blood glucose was observed in 204 (55.0%) patients after steroid pulse therapy. The frequency of female gender (69.1% vs. 42.5%; p-value<0.001), hypertension (26.5% vs. 16.2%; p-value=0.017) and positive family history (16.2% vs. 5.4%; p-value=0.001) was significantly higher in patients with impaired blood glucose after steroid pulse therapy.

Conclusion: A substantial proportion of non-diabetic patients receiving steroid pulse therapy had impaired blood glucose and female gender, hypertension and positive family history of diabetes were found attributable to this steroid induced hyperglycemic state which advocates routine monitoring of blood sugar level among patients receiving steroid pulse therapy, particularly females, hypertensive and patients with positive family history so that patient outcome may be improved by timely identification and management.

Keywords: Steroid Pulse Therapy, Impaired Blood Glucose, Attributing Factors

INTRODUCTION

The adrenal gland consists of cortex and medulla. The later secretes epinephrine and nor epinephrine while cortex synthesizes and secretes two major classes of steroid hormones adrenocorticoids (glucocorticoids and mineralocorticoids) and adrenal androgens[1,2]. Since the first isolation of cortisol in 1950 by Kendall and Hench[3] corticosteroids have proved to be extremely effective in treatment of various diseases like replacement therapies in primary (Addison's disease) and secondary and tertiary adrenocorticoid insufficiency, relief of acute inflammatory and chronic inflammatory diseases (rheumatoid, osteoarthritic inflammation) and treatment of allergies (bronchial asthma, allergic rhinitis and drug, serum and transfusion reaction)[4-6].

Adverse effects of ccorticosteroids include reduced growth in children, osteoporosis, peripheral edema, hypertension, hyperglycemia, menstrual irregularities, weight gain, peptic ulcer, glaucoma and increased risk of infections[7]. Corticosteroid use is associated with hyperglycemia in pre-existing diabetic and non-diabetic patients; it increases insulin resistance and gluconeogenesis through increased amino acid uptake by the liver. The effects of steroid administration on glucose levels are observed within hours of exposure[7,8].

The body's level of cortisol in the bloodstream displays a diurnal variation, that is, normal concentrations of cortisol vary throughout a 24-hour period. Cortisol levels in normal individuals are highest in the early morning at around 8 AM and are lowest just after midnight. This early morning dip in cortisol level often corresponds to increased symptoms of inflammatory diseases [9]. Overlaid upon this diurnal variation is the pulsatile nature of cortisol release under the control of local and central 'clocks'. By mimicking this pulsatile cortisol release it is hoped to reduce the detrimental side effects of exogenous steroids while enhancing their anti-inflammatory properties[9].

The results of this study are worrisome; proving that substantial proportion of non-diabetic patients receiving steroid pulse therapy had impaired blood glucose and female gender, hypertension and positive family history of diabetes were found attributable to this steroid induced hyperglycemic state which advocates routine monitoring of blood sugar level among patients receiving steroid pulse therapy, particularly females, hypertensive and patients with positive family history. However, this study is first of its kind and no other local or international arch study was available. Therefore, the purpose of the current study was to conduct this trial and confirm the role of steroid pulse therapy in impaired blood glucose in various subjects in local population.

MATERIAL AND METHODS

It was a cross sectional study conducted at Department of Medicine Shalamar Hospital, Lahore over a period of 6 months from 09-01-2020 to 08-07-2020. Sample size of 370 cases was calculated with 95% power of test, 5% level of significance and expected frequency of steroid induced impaired blood glucose to be 40.6%.[7] Patients of both genders aged in the range of 18-70 years receiving steroid therapy (at least 1 pulse) suffering from Rheumatoid Arthritis as per history and lab findings and systemic lupus erythematosus were included from outpatient department. Patients who were already diagnosed diabetes mellitus, had taken anti-diabetic medicines before or who had taken steroids one year during last one year (as per clinical record and history) were excluded from the study. Informed written consent and detailed history of each patient was obtained. A bolus of l gm. of methylprednisolone was given and blood was drawn after 2 hours to measure blood glucose level. Impaired blood glucose was labeled as per operational definition (Estimation of blood glucose level after 2 hours of steroid pulse with no dietary intake. A raise of ≥20mg/dl blood sugar level from the baseline was treated as impaired blood glucose in non-diabetic on steroid pulse). Number of previous steroid pulses received were also noted and documented into the same proforma along with demographic details of the patient. All the labs tests were acquired from same lab (Hospital Lab) and glucometer for eliminating biasness and exclusion criteria was sued to control confounding variables. Numerical variable; age has been presented by mean ±SD. Categorical variable i-e gender, impaired blood glucose and attributing factors (female gender, BMI, hypertension and positive family history of diabetes) have been presented by frequency and percentage. To address effect modifiers, data has been stratified for age, gender, BMI, impaired blood glucose and attributing factors. Post-stratification independent sample t-test has been applied taking p-value ≤0.05 as significant.

RESULTS

The mean age of patients was 43.75±14.33 year ranging between 18-70 years. Majority of the patients were aged 45 years (n=177, 47.7%) and above followed by 30-44 years (33.2%) and under 30 years of age (19.1%). There were 159 (42.9%) male and 212 (57.1%) female patients with a male to female ratio of 1:1.3. The BMI of these patients ranged from 20.6 Kg/m^2 to 33.9 Kg/m^2 with a mean of 27.34±3.72 Kg/m^2. 81 (21.8%) patients were hypertensive while 42 (11.3%) patients had positive family history of diabetes as shown in Table 1. Impaired blood glucose was observed in 204 (55.0%) patients after steroid pulse therapy.

The frequency of female gender Yes versus No (69.1% vs. 42.5%; p-value<0.001), hypertension (26.5% vs. 16.2%; p-value=0.017) and positive family history (16.2% vs. 5.4%; p-value=0.001) was significantly higher in patients with impaired blood glucose after steroid pulse therapy. For various age groups i.e <30 years (54.9%), 30-44(55.3%) years and ≥45(54.8), p-value=0.977 of impaired blood glucose after steroid pulse therapy was statistically insignificant with p-value=0.977. Similarly for BMI 20-25 Kg/m^2(54.5%), 25-30 Kg/m^2(55.6%) and 25-30 Kg/m^2 (54.5%, p-value=0.977 was statistically insignificant. Likewise differences were observed across various groups on the basis of age and BMI as shown in Tables 2 and 3 respectively.

Table 1 Baseline Characteristics of Study Sample

Characteristics	Participants N=371
Age (years)	43.75±14.33
• <30 years	71 (19.1%)
• 30-44 years	123 (33.2%)
• ≥45	177 (47.7%)
Gender	
• Male	159 (42.9%)
• Female	212 (57.1%)
BMI (Kg/m2)	27.34±3.72
• 20-25 Kg/m2	112 (30.2%)
• 25-30 Kg/m2	160 (43.1%)
• 30-35 Kg/m2	99 (26.7%)
Hypertensive	
• Yes	81 (21.8%)
• No	290 (78.2%)
Family History of Diabetes	
• Positive	42 (11.3%)
• Negative	329 (88.7%)

Table 2 Comparison of various Attributing Factors in patients with and without Impaired Blood Glucose after Steroid Pulse Therapy across Age Groups

Age	n=371	Attributing Factors	Impaired Blood Glucose		P value
			Yes (n=204)	No (n=167)	
<30 years	71	Female Gender	27 (69.2%)	14 (43.8%)	0.031*
		Hypertension	10 (25.6%)	5 (15.6%)	0.304
		Positive Family History	6 (15.4%)	2 (6.3%)	0.226
30-44 years	123	Female Gender	47 (69.1%)	25 (45.5%)	0.008*
		Hypertension	18 (26.5%)	9 (16.4%)	0.178
		Positive Family History	11 (16.2%)	3 (5.5%)	0.063
≥45 years	177	Female Gender	67 (69.1%)	32 (40.0%)	<0.001*
		Hypertension	26 (26.8%)	13 (16.3%)	0.092
		Positive Family History	16 (16.5%)	4 (5.0%)	0.016*

*Difference was found statistically significant through Chi-square test

Table 3 Comparison of various Attributing Factors in patients with and without Impaired Blood Glucose after Steroid Pulse Therapy across BMI Groups

BMI	n=371	Attributing Factors	Impaired Blood Glucose		P value
			Yes (n=204)	No(n=167)	
20-25 Kg/m^2	112	Female Gender	42 (68.9%)	20 (39.2%)	0.002*
		Hypertension	8 (13.1%)	7 (13.7%)	0.925
		Positive Family History	11 (18.0%)	3 (5.9%)	0.053
25-30 Kg/m^2	160	Female Gender	65 (73.0%)	35 (49.3%)	0.002*
		Hypertension	27 (30.3%)	12 (16.9%)	0.049*
		Positive Family History	11 (12.4%)	3 (4.2%)	0.070
30-35 Kg/m^2	99	Female Gender	34 (63.0%)	16 (35.6%)	0.007*
		Hypertension	19 (35.2%)	8 (17.8%)	0.053
		Positive Family History	11 (20.4%)	3 (6.7%)	0.051

*Difference was found statistically significant through Chi-square test

DISCUSSION

Since first isolation of cortisol, corticosteroids have proved to be extremely effective in the treatment of acute and chronic inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus[1]. Corticosteroid use is associated with hyperglycemia in pre-existing diabetic and non-diabetic patients[5-8]. Female gender, hypertension and positive family history of diabetes have been reported as attributing factors of impaired blood glucose with steroid pulse therapy among non-diabetic patients.[8] However, the available evidence was limited while scarcity of locally published material necessitated this study.

The objectives of this study were to determine the frequency of impaired blood glucose in non-diabetic patients on steroid pulse therapy and to compare the frequency of various attributing factors in patients with impaired blood glucose in non-diabetic patients on steroid pulse therapy.

In the present study, the mean age of the patients was 43.75±14.33 years. A similar mean age of 43.8±10.6 years has been reported by Zafar et al. (2016) among patients presenting with rheumatoid arthritis at Shaikh Zayed Hospital, Lahore[10]. Rais et al. (2014) also reported similar mean age of 43.7±18 years among such patients presenting at Liaquat National Hospital, Karachi[11] while Shamim et al. (2015) reported it to be 47.3±2.9 years at Jinnah Postgraduate Medical Centre, Karachi[12]. A similar mean age of 41±14 years has been reported by Perez et al. (2011) among such patients in Mexico[5] while Bedi et al. (2005) reported it to be 42±13 years in India[13].

We observed that majority (47.7%) of the patients were aged 45 years and above followed by 30-44 years (33.2%) and under 30 years of age (19.1%). Our observation matches with that of Shamim et al. who reported similar distribution of <30 years (20.0%), 30-44 years (36.0%) and ≥45 years (44.0%) age groups among such patients at Jinnah Postgraduate Medical Centre, Karachi[12]. Similar results have also been reported by Zafar et al. <30 years (14.6%), 30-44 years (40.4%) and ≥45 years (45.0%) among such patients at Shaikh Zayed Hospital, Lahore[10].

In the presents study, there were 159 (42.9%) male and 212 (57.1%) female patients with a male to female ratio of 1:1.3. Shamim et al. (1:2.4), Rais et al. (1:2.8) and Zafar et al. (1:3) reported similar female predominance among RA patients in local population [10-12]. den Uyl et al. (1:1.5), Miyawaki et al. (1:1.1), Perez et al. (1:1.9) and Bedi et al. (1:2.1) also observed similar female predominance[6,13-15].

BMI of these patients was observed in the range from 20.6 Kg/m^2 to 33.9 Kg/m^2 with a mean of 27.34±3.72 Kg/m^2. Similar mean BMI of 26±3 kg/m^2 has been reported by Perez et al. among such patients in Mexico while den Uyl et al. reported it to be 25.4±4.2 Kg/m^2 in Netherlands[14]. In the present study, impaired blood glucose was observed in 204 (55.0%) patients after steroid pulse therapy. Our observation is in line with that of den Uyl et al. who observed similar frequency of impaired blood glucose after steroid pulse therapy and reported it to be 57.0% [14]. Karthik et al. (2016) reported similar frequency of 59% in Indian such patients[8].

The female gender (69.1% vs. 42.5%; p-value<0.001), hypertension (26.5% vs. 16.2%; p-value=0.017) and positive family history (16.2% vs. 5.4%; p-value=0.001) was significantly higher in patients with impaired blood glucose after steroid pulse therapy. A similar difference in the frequency of female gender (68.8% vs. 41.7%; p-value<0.008), hypertension (28.8% vs. 16.4%; p-value=0.018) and positive family history (16.8% vs. 3.1%; p-value<0.001) between patients with and without steroid pulse induced impaired blood glucose has been reported by Yang et al[5]. Miyawaki et al. reported similar difference in the frequency of hypertension (63.2% vs. 28.9%; p=0.0077) and positive family history (47.4% vs. 14.5%; p=0.0037)[15].

In local population this study is first of its kind and has found that a substantial proportion of non-diabetic patients receiving steroid pulse therapy had impaired blood glucose and female gender, hypertension and positive family history of diabetes were attributable to this steroid induced hyperglycemic state which advocates routine monitoring of blood sugar level among patients receiving steroid pulse therapy particularly females and hypertensive patients with positive family history so that patient outcome may be improved by timely identification and management.

A very strong limitation to the present study was that the results for the underlying medical condition requiring steroid pulse therapy nor the dose of steroid pulse given which may be attributable to impaired blood glucose could

not be stratified. Relationship of these factors is necessary to be investigated to give further insight into this phenomenon and management planning of such patients. That is why, in future, such study is highly recommended.

CONCLUSION

A substantial proportion of non-diabetic patients receiving steroid pulse therapy had impaired blood glucose and female gender, hypertension and positive family history of diabetes were found attributable to this steroid induced hyperglycemic state which advocates routine monitoring of blood sugar level among patients receiving steroid pulse therapy particularly females and hypertensive patients with positive family history so that timely identification and management can improve the patient outcome.

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