Original Article

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Radiology Section

Effect of Dipyridamole Injected for Myocardial Perfusion Imaging on Blood Glucose Concentration; A Preliminary Study

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ABSTRACT

Introduction: Dipyridamole inhibits adenosine reuptake and increases cyclic Adenosine Monophosphate (cAMP) levels in platelets, erythrocytes and endothelial cells, all of which influence blood glucose. Acute hyperglycaemia reduces endothelium-dependent vasodilation and suppresses coronary microcirculation; which, in theory, can alter the outcome of a radionuclide scan.

Aim: The present study was conducted with the aim to investigate the changes in blood glucose level of patients receiving dipyridamole for cardiac scan.

Materials and Methods: A total of 293 patients (85 men and 208 women, age: 60.59±10.43 years) were included in the study. Fasting Blood Glucose (FBG) was measured before and 8 min after dipyridamole (0.568 mg/kg) injection during myocardial perfusion imaging. The data in different groups were analysed by paired t-test.

Results: There was not a significant difference between first (106.89 ± 19.21mg/dL) and second (107.98 ± 17.57 mg/dL) FBG measurements (p= 0.293). However, when the patients were grouped based on the quartiles of first measurement, there was an increase in FBG following dipyridamole injection in the first quartile (mean difference: 7.15±21.27 mg/dL, p<0.01); in contrast, FBG levels showed a significant decrease after dipyridamole administration in the 4th quartile (mean difference: -9.53±18.20 mg/dL, p<0.001). The differences in 2nd and 3rd quartiles were negligible. The patients were divided into normal, ischemic and fixed lesions based on the outcome of scans, then the possible correlation of dipyridamole-induced FBG alteration and scan results were investigated. There were no significant difference between the FBG values before and after dipyridamole injection and the final outcome of scan.

Conclusion: The effects of dipyridamole on blood glucose highly depend on the initial blood glucose level.

Keywords: Blood glucose, Dipyridamole, Myocardial perfusion imaging

INTRODUCTION

Dipyridamole is a nucleoside transport inhibitor that augments endogenous adenosine [1]. Moreover, it inhibits phosphodiesterases and causes an increase in cellular content of cyclic Adenosine Monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [2]. Dipyridamole is indicated for the induction of stress in myocardial scintigraphy [3].

Adenosine plays an important role as a paracrine and/or an autocrine hormone in a variety of physiological or pathophysiological processes including cardiovascular diseases and diabetes [4,5]. It acts by binding to adenosine receptors and influences glucose disposal, carbohydrate metabolism, lipolysis and insulin sensitivity [6,7], local blood flow [8], mean arterial pressure and heart rate [9]. Four adenosine receptors (A1, A2a, A2b, and A3) have been cloned and characterized in mammalian species. While A1 and A3 receptors are preferentially coupled to inhibitory G-proteins (Gi/o), the A2 receptors interact with stimulatory G-protein (Gs) [10]. Adenosine A3 receptors were found to produce cardioprotective effects during myocardial ischemia/ischemic reperfusion [10]. On the other hand, blockade of adenosine A1 receptors improves glucose tolerance in obese Zucker rats; these rats show a better profile of peak serum insulin level and areas under glucose curves, compared to untreated rats [11]. Yet, adenosine is not the sole mediator of dipyridamole pharmacological effects [12].

It is noteworthy that the concentration of dipyridamole required to produce a significant effect on glycolytic rate (2μM) is much less than that required to exert a significant rise in intracellular and interstitial adenosine concentration in muscles (50μM) [12]. Dipyridamole reduces glucose-induced osteopontin expression in arterial vasculature, thereby decreasing the medial artery calcification and stiffness. This effect is mediated through inhibition of phosphodiesterase, and Reactive Oxygen Species (ROS) [2]. However, a net effect of dipyridamole in blood sugar during cardiac scintigraphy has been not investigated.

Cardiovascular stress test using exercise or pharmacological agents has long been established as a diagnostic procedure in cardiovascular scintigraphy. In this regard, pharmacological stress is produced by dobutamine, dipyridamole, adenosine or regadenoson [13]. Dipyridamole inhibits intracellular reuptake and deamination of adenosine, thereby producing a vasodilatory effect on coronary arteries. Such an effect on coronary vasodilation is attenuated in diseased coronary arteries, showing a reduced coronary flow reserve and failure of dilation in response to the drug [14].

The aim of this study was to evaluate the acute effect of dipyridamole on blood glucose in patients undergoing myocardial rest/stress scintigraphy using 99mTc-sestamibi. In addition, a potential alteration of the outcome of a radionuclide scan was explored.

MATERIALS AND METHODS

This cross-sectional study was performed on 299 patients who were recruited from the Department of Nuclear Medicine of

Shahroud University of Medical Sciences for about two years, starting in early 2013. Six patients were excluded from the study because of severe hypoglycaemia. The patients (85 men and 208 women, age: 60.59±10.43 years) were instructed to discontinue all cardiovascular medications 48h before the scan, and to fast overnight. Fasting Blood Glucose (FBG) was measured before and 8min after dipyridamole (0.568mg/kg) injection [15]. The study was conducted under a protocol approved by ethics committee of the Shahroud University of Medical Sciences. Furthermore, either the patients or their parents signed a consent form.

Acquisition Protocol

Technetium-99m metaiodobenzylisonitril (^{99m}Tc-MIBI) in a dose of 740MBq was injected intravenously (i.v.) and was administered 4min after dipyridamole injection, and gated single photon emission computed tomography (SPECT) was conducted 90min later, the patient being in the supine position. All patients underwent a rest-stress scan using a dual-head -camera (GE Healthcare) in 90° setting, equipped with high-resolution, low-energy (HRLE) collimators. Sixty-four views (25sec per view) over 180° (from 45° right anterior oblique to 45° left posterior oblique) were obtained with a zoom factor of 1.45 and gated at 8 frames per cardiac cycle using an R-wave trigger and stored in a 64×64 matrix [16]. The patients were then grouped as normal perfusion scan, ischemic scans and fixed scans.

STATISTICAL ANALYSIS

The distribution of variables was checked using probability plots and the Shapiro-Wilk test and they were fit to a gaussian distribution. The data are represented as mean ± Standard Deviation (SD). The potential difference between FBG values before or after dipyridamole injection as well as their quartiles was analysed by paired t-test. Spearman test was used to explore the correlation between FBG values and the final outcome of the scan. The p-values of less than 0.05 were considered statistically significant.

	N	FBG (mg/dL)				
		Mean	SEM	SD	Minimum	Maximum
FBG1_Q1	71.00	89.35	0.77	6.48	61.00	96.00
FBG1_Q2	74.00	101.03	0.29	2.50	97.00	105.00
FBG1_Q3	74.00	110.62	0.31	2.70	106.00	115.00
FBG1_Q4	74.00	130.16	1.98	17.00	116.00	197.00
Total	293.00	107.98	1.03	17.57	61.00	197.00

[Table/Fig-1]: Division of the patients based on the quartiles of the 1st FBG values (mg/dl).
Fasting blood glucose (FBG), Q: quartiles

RESULTS

FBG was measured before and 8min after dipyridamole administration. There was not a significant difference in FBG values before (106.89 ± 19.21 mg/dL) and after (107.98 ± 17.57 mg/dL) dipyridamole administration (p= 0.293). The patients were then divided into four groups based on the values of first FBG measurement [Table/Fig-1], and the difference between FBG values before and after dipyridamole was analysed in quartiles. We observed an increase in FBG following dipyridamole injection in the first quartile (mean difference: 7.15±21.27 mg/dL, p<0.01); in contrast, FBG levels showed a significant decrease after dipyridamole administration in the 4th quartile (mean difference: -9.53±18.20 mg/dL, p<0.001). The difference in the 2nd(-1.47±11.67 mg/dL, p=0.28) and the 3rd (-0.18±12.70 mg/dL, p=0.91) quartiles were negligible [Table/Fig-2]. In addition, FBG levels before and after dipyridamole did not show a significant difference in non-diabetic patients (1st FBG<126), whereas there were a significant decrease in FBG levels (mean difference: -14.03± 23.73 mg/dL, p< 0.01) after dipyridamole administration in diabetic patients (1st FBG>126 mg/dL, [Table/Fig-3]).

The patients were divided into normal, ischemic and fixed lesions based on the outcome of scans. We then sought the possible correlation between the scan outcome and FBG values. There were not a significant correlation between the scan outcome and FBG values before (rho: 0.07, p=0.24) and after (rho: 0.037, p=0.53) dipyridamole administration, nor between the scan outcome and the dipyridamole-induced alteration of FBG value before and after dipyridamole (rho: -0.01, p=0.855).

DISCUSSION

Dipyridamole is a nucleoside transport inhibitor that augments endogenous adenosine and increases cellular content of cyclic neucleosides [1]. Dipyridamole produces a 44% increase in coronary blood flow as well as a 32% decrease in coronary vascular resistance. Moreover, dipyridamole increases glucose uptake by 5 times and ATP content by 11%. In contrast, it decreases lactate uptake by 97% and does not significantly alter ADP or AMP content of the myocardial tissue [17].

Paired Differences of FBG (mg/dL)										
group	FBG (mg/dl)		Mean Difference	SD	SEM	95%CI of the Difference		t	df	Sig. (2-tailed)
	Before dipyridamole	After dipyridamole				Lower	Upper			
FBG1_Q1	89.35	96.50	7.15	21.27	2.52	2.12	12.19	2.83	70.00	0.01*
FBG1_Q2	101.03	99.56	-1.47	11.67	1.36	-4.18	1.23	-1.09	73.00	0.28
FBG1_Q3	110.62	110.44	-0.18	12.70	1.48	-3.12	2.77	-0.12	73.00	0.91
FBG1_Q4	130.16	120.63	-9.53	18.20	2.12	-13.74	-5.31	-4.50	73.00	0.001*
Total	107.98	106.89	-1.09	17.33	1.01	-3.08	0.90	-1.08	292.00	0.28

[Table/Fig-2]: Difference between FBG values before and after dipyridamole administration when the patients were grouped based on the quartile of the first FBG measurement.
Fasting blood glucose (FBG) *statistically significant

Paired Differences of FBG (mg/dL)									
	FBG (mg/dL)		Mean Difference	SD	SEM	95% CI of the Difference		t	df	Sig. (2-tailed)
	Before dipyridamole	After dipyridamole				Lower	Upper			
FBG1<126	103.68	104.12	0.44	15.78	0.98	-1.48	2.36	0.45	261.00	0.65
FBG1>126	144.35	130.32	-14.03	23.73	4.26	-22.74	-5.33	-3.29	30.00	0.001*

[Table/Fig-3]: Difference between FBG values before and after dipyridamole administration when the patients were grouped into diabetic and non-diabetic according to first FBG.
Fasting blood glucose (FBG) *statistically significant

We observed a significant decrease in FBG levels after dipyridamole administration (0.568 mg/kg) in 4th quartile (mean difference: -9.53±18.20 mg/dL, p<0.001). Adenosine mediated increase of blood flow enhances glucose and insulin delivery to the active muscle fibers. In addition, activation of A1-adenosine receptors directly stimulates insulin-mediated glucose uptake in oxidative muscle cells [8]. However, hypoxia-induced muscle glucose uptake does not seem to be influenced by adenosine receptors [5,18]. Blockade of adenosine receptors by 8-phenyltheophylline (8-PTH) inhibits insulin-induced myocardial glucose uptake [19]. In this regard, an increase in plasma glucose in diabetic rats augments the expression of adenosine A1 receptor in the liver, highlighting the possible contribution of these receptors to glucose-lowering effects in diabetic rats lacking insulin [20]. Chronic administration of low dose dipyridamole (20mg/kg, 4 weeks) had no effect on the elevated glucose levels in streptozotocin-induced diabetic rats. However, it decreased structural and functional abnormalities in the kidney [21]. Dipyridamole (0.568mg/kg) consistently enhances myocardial glucose uptake in areas with diminished vasodilatory capacity of coronary arteries as demonstrated by fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG PET) [22]. Furthermore, intravenous injections of dipyridamole or N6-cyclopentyladenosine (CPA, Adenosine A1 receptor agonist) decrease plasma glucose in fasting streptozocine-diabetic rats in a dose-dependent manner [23]. Moreover, CPA augments glycogen synthesis in isolated soleus muscle [23]. Adenosine A2a receptor agonist, 5'-N-ethylcarboxamidoadenosine (NECA), is also shown to enhance beta cell regeneration and accelerate restoration of normoglycaemia in zebrafish [24]. It can also reduce serum glucose in diabetic mice [24]. Inhibition of phosphodiestrases by dipyridamole is also demonstrated to causes an increase in cAMP content of the cell; thereby activating the guanine nucleotide exchange factor activated by cAMP (Epac2) and protein kinase A (PKA). These intracellular molecules are reported to be involved in the stimulation of insulin exocytosis [25]. The above mentioned evidences indicate a possible role for adenosine and cyclic neucleosides in glucose-lowering effects of dipyridamole.

In contrast to the upper quartile (FBG: 116-197 mg/dL), we found an increase in FBG following dipyridamole injection in first quartile (FBG: 61-96 mg/dL; mean difference: 7.15±21.27 mg/dL, p<0.01). Dipyridamole (50mg/kg) mitigates endotoxin-mediated decrease in blood glucose and liver cAMP content in mice [26]. Translocation of Glucose Transporter GLUT4 from intracellular stores to the sarcolemma mediates the insulin or contraction-induced glucose uptake cardiac myocytes [27]. In adipocytes and L6 muscle cell lines, the glucose transport inhibitor, dipyridamole, binds with higher affinity to GLUT4 than to GLUT1 [24,25]. However, it does not seem to influence subcellular distribution of GLUT4 or glucose uptake in cardiac myocytes [27]. On the other hand, Shuralyova et al., demonstrated a dose-dependent inhibition of both basal and insulin-stimulated glucose transport by dipyridamole (basal, IC50 = 12.2μM, insulin stimulated, IC50 = 13.09μM) in HL-1 cardiomyocytes. This effect is more likely to be mediated through pathways other than the inhibition of adenosine reuptake [28]. These observations may explain the proischemic effects of dipyridamole at high doses [29] as well as a significant rise of FBG following dipyridamole administration in 1st quartile (FBG: 61-96 mg/dL) in this study.

Acute hyperglycaemia reduces endothelium-dependent vasodilation and suppresses coronary microcirculation. Williams et al., investigated the endothelium-dependent vasodilation through brachial artery infusion of methacholine before and during intra-arterial infusion Dextrose 50% for 6h they observed a significant reduction of forearm blood flow after local hyperglycaemia (300 mg/dL) in healthy subjects, indicating the impairment of endothelium-dependent vasodilation during acute hyperglycaemia in vivo [30]. Similarly, Fujimoto et al., reported a significant decline in coronary flow velocity reserve 1 hour after acute oral glucose loading (4.4±0.7 vs. 3.8±0.7 cm/sec, respectively) using transthoracic Doppler echocardiography in healthy men. This result suggests that acute hyperglycaemia may have adverse effects on coronary microcirculation [31]. There was not a significant correlation between the scan outcome and FBG values before (rho: 0.064, p=0.273) and after (rho: 0.04, p=0.486) dipyridamole administration, nor between the scan outcome and dipyridamole-induced changes in blood glucose (rho: -0.001, p=0.982). In this regard, Capaldo et al., investigated the effects of acute hyperglycaemia on coronary flow reserve (the ratio of dipyridamole/resting coronary peak diastolic flow velocity) in healthy volunteers using transthoracic colour Doppler echocardiography. They found a substantial increase in coronary flow velocity after dipyridamole infusion. However, acute hyperglycaemia (glucose and octreotide (0.4mg/h) infusion for 3h to reach an approximate glucose concentration of 252 mg/dL and stable plasma insulin) did not seem to influence the vasodilatory response of coronary microcirculation [32].

LIMITATION

In this study, the effects of dipyridamole on blood glucose was investigated, yet it lacks a control group with exercise stress. It is reported that moderate or high –intensity exercise can influence blood glucose in healthy or diabetic patients. This study showed significant alteration of blood glucose by dipyridamole in patients with FBG less than 96 or above 116 mg/dL. Future studies with both pharmacological and exercise stress are required for accurate conclusion.

CONCLUSION

Dipyridamole may increase, decrease, or not influence blood glucose depending on its initial level. However, these changes in blood glucose do not seem to be correlated with final outcome of the scan.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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