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COMBINATION OF METFORMIN /SITAGLIPTIN ENHANCES CEREBRAL AUTOREGULATION IN PATIENTS WITH NEWLY DIAGNOSED TYPE2 DIABETES MELLITUS

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Abstract

Cerebral vasoreactivity may be impaired early in diabetic patients and it is associated with increased risk of stroke. Combination of metformin and sitagliptin can be used early in the disease. This combination has beneficial effects on glycemic control. Our study was conducted to find out beneficial cerebrovascular effect of this combination. Twenty patients with newly diagnosed type 2 DM were involved in the study and they were treated with metformin and sitagliptin for twelve weeks. All patients examined by transcranial Doppler of middle cerebral artery before and after treatment. Breath-holding index increased from 0.64±0.029 to 0.87±0.035 after treatment. We concluded that metformin /sitagliptin combination exerts advantageous effect on cerebral autoregulation in patients with newly diagnosed type 2 DM.

Keywords: metformin/sitagliptin combination, cerebral autoregulation, breath-holding index (BHI), type 2 DM.

Introduction

Cerebral autoregulation may be defined as the ability of cerebral arteries and arterioles to dilate and constrict in response to various stimuli thereby maintaining constant cerebral blood flow and cerebral perfusion pressure despite changes in arterial blood pressure[1]. Cerebral autoregulation can evaluated by the use of carbon dioxide inhalation or the use of breath-holding test. In 1992, Markus and Harrison first described breath-holding test. They found that breath-holding test was reliable and valid as CO2 inhalation. The time of breath-holding was about 30 seconds. It was 1.2±0.6 in normal individual[2]. For patients who cannot hold their breath for long time, a combination of breath holding with hyperventilation can be used[3]. It seems to be accurate, specific and sensitive method for evaluation of cerebral vasoreactivity in comparison with other methods like functional magnetic resonance imaging, positron emission tomography , single photon emission computed tomography which are complex, expensive and time consuming[1,2,3]. Breath-holding test would provide information about intracranial vessel function and compliance[4]. Therefore, this test provides useful information about vessel status and early subclinical atherosclerotic changes with loss of elasticity which can be utilized in early prevention of complications[5]. Breath-holding test is as valuable as CO2 inhalation and acetazolamide administration in assessment of cerebrovascular reactivity. This method is quick and does not require administration of CO2 or measurement of CO2 concentrations. It is more safe as it cause increase in endogenous CO2 rather than CO2 inhalation with its increase risk of tissue hypoxia. Therefore, it is more safe in patients with stroke and cerebrovascular disease[3,6,7]. It has been found that diabetic patients have deranged cerebrovascular reactivity. This derangement lead to loss of ability of the cerebral arteries to dilate which may be manifested early in the disease[8]. Impaired cerebrovascular reactivity is associated with increased risk of cerebrovascular accident[9]. Previous investigators found that cerebrovascular reactivity to carbon dioxide was impaired in diabetic patients with inability of the arteries to dilate or constrict in response to carbon dioxide[10]. Rapid progressive atherosclerosis with loss of elastic tissue and capability of cerebral arteries and arterioles may be feature of long standing diabetes[11]. Newly discovered diabetics without autonomic neuropathy, retinopathy, or other complications also had the abnormality[11,12]. Since this loss of reactivity was not observed in even the very elderly controls, it appears to be linked specifically to diabetes. Although the rate of overt cerebrovascular disease increases with age in both non-diabetic patients and diabetic patients, diabetic patients are at high risk because of their inability to tolerate with increased cerebral blood flow demands when metabolic requirements of the brain increase. In addition to that, the response to hypotension might be affected if vasodilatation were compromised[13]. Another study concluded that Type 2 diabetes is associated with diminished regional cerebral perfusion and vasoreactivity[11]. On the other hand diabetic patients exaggerated response of cerebral blood vessels to vasoconstrictors. This is associated with attenuated vasodilatory capacity and impaired compliance of cerebral arteries. Combination of metformin and sitagliptin are nowadays marketed under the name of (Janumet)®. Metformin has well recognized beneficial cardiovascular profile. It improve endothelial function and lower long term cardiovascular events [14,15]. In large clinical trial, metformin reduced stroke risk in diabetic patients [16]. Moreover, in another study metformin use could lower arterial stiffness [17]. On the other hand sitagliptin which is dipeptidyl peptidase-4 inhibitor may also improve cardiovascular risk in diabetic patients[18]. It was clear that DPP-4 is involved in variety of cardiovascular disease due to catalytic activity (enzymatic breakdown of GLP-1 and GIP) and non-catalytic activity (as mediator of T-lymphocyte activation)[19,20]. There is a sufficient evidence that inhibition of DPP-4 enzyme has protective effects on variety of cardiovascular diseases like myocardial infarction, hypertension and atherosclerosis[21]. Previous studies showed beneficial effects on endothelial function following inhibition of DPP-4 (an effect was beyond potentiation of GLP-1)[22]. Furthermore, DPP-4 enzyme plays a role in inflammatory response[23]. Recent studies showed that inhibition of DPP-4 with sitagliptin reduces the expression of adhesion molecules ICAM and VCAM as well as plasminogen activator inhibitor[24]. Previous studies showed that sitagliptin can reduce systolic and diastolic systemic arterial blood pressure. In a clinical trial conducted in 19 non-diabetic patients with mild and moderate hypertension , 100 mg of sitagliptin twice daily for 5 days reduce both systolic and diastolic blood pressure[25]. Incretins exert direct vasodilatory effect[19]. In animal studies, sitagliptin enhances acetylcholine induced vasodilatation in aortic ring of mice[26].

Vildagliptin improved acetylcholine induced vasodilatation in forearm by increase forearm blood flow velocity following administration of acetylcholine. Like cerebral CO2 vasoreactivity, Acetylcholine induced vasodilation is endothelium dependent[27]. In another clinical trial ,GLP-1 infusion enhanced acetylcholine mediated vasodilatation in brachial artery of non-diabetic normotensive individuals[28]. Furthermore, GLP-1 infusion increased flow-mediated vasodilatation in brachial artery in diabetic patients with stable coronary artery disease[29]. In a clinical trial, GLP-1 infusion increased flow-mediated dilatation in both diabetic and control groups[30]. The relationship between DPP-4 inhibitors and cardiovascular morbidity and mortality has to be proven and major multicenter clinical trial launched out to discover this relationship[19,31]. Our study was conducted to confirm beneficial cerebrovascular effect of combination of sitagliptin and metformin in patients with type 2 DM.

Methods

A total number of 20 patients with newly diagnosed DM were included in the study. They are randomly selected from center of diabetes and endocrinology in Al Sadr medical City in Najaf City / Iraq. They were diagnosed with diabetes mellitus type 2 according to World Health Organisation definition of diabetes as fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) , 2-hour post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dL) or HbA1C ≥6.5% [32]. The study started from November 2014 and end in October 2016. A verbal consent were taken from each participant. The study was approved by Kufa Medical College Ethical Committee for clinical trials. Six patients were excluded from the study due to insufficient trans-temporal window. Fasting biochemical laboratory tests, blood specimen was obtained from each one enrolled in this study after an overnight fasting in the laboratory of Al-Sadr Hospital in the morning for analysis of fasting blood sugar, glycosylated hemoglobin (HbA1c), and serum lipid profile. Inclusion and exclusion criteria of the patients are illustrated in table1 and 2. Transcranial Doppler examination with its measurements were under taken at TCD department/ Middle Euphrates Neuroscience center/ Al Sadr Medical city/Najaf. Studies were conducted in the morning (9:00 am) after overnight fasting and subjects refrained from products containing caffeine 24 hours before study sessions. The time required for every subject to complete study sessions was approximately 30 minutes. Digital transcranial Doppler with M-mode WAKIe with continuous monitoring and physiological test software (Atys medical, France) and EZ-Dop DWL , COMPUMEDICS, GmbH, Germany. These instruments are provided with head-band as probe holder for pulse-wave 2 MHz phase array transducer for continuous monitoring and achievement of physiological tests. This pulse wave phase array 2MHz transducer was used for examination of middle cerebral artery on both sides. All subjects were allowed to rest quietly and examined in supine position . Before proceeding to the definitive recording, subjects were trained to perform the procedure of breath hold and hyperventilation correctly. Blood pressure , using mercurial sphygmomanometer ALPK2, was recorded and heart rate and oxygen saturation using digital infra-red pulse-oximeter was also recorded. To study the MCA blood flow velocities, the subject was asked to tilt his head to a side and to breath normal quiet breathing , the MCA was first identified by Doppler probe through trans-temporal window. For identification of middle cerebral artery, spectral wave form window was started at 20mm and then decreased gradually to 12mm to get rid of ultrasound noise and obtain accurate measure.The depth of Doppler beam that was adjusted at 45-55 mm, utilizing a trans-temporal window above zygomatic arch. To obtain MCA spectral wave form, probe is directed backward and slightly upward. To recognize the waveform of middle cerebral artery, the waves are above zero line in spectral wave display screen. After localization of middle cerebral artery waveform and getting the optimal signal of middle cerebral artery, we fix the TCD transducer to the head band (probe holder) by special screw provided with the device. We started with the option of diagnostic in the device for examination of artery of interest and monitoring of the arterial wave to detect any abnormality regarding stenosis or turbulent flow or signals of micro-emboli The means of peak systolic velocity, diastolic velocity, resistive index and pulsatility index of 10 cardiac cycles were automatically recorded by specific TCD software of the device as following:

1. Hemodynamic parameters of MCA on both sides : maximum systolic velocity (PSV), diastolic velocity (DV), mean flow velocity (MFV), pulsatility index (PI) , and resistive index (RI) were recorded.
2. To demonstrate the response of middle cerebral artery flow to breath-hold, the subject was asked to hold his/her breath, as long as possible, after normal quite breathing referred as normal ventilation by the display screen of transcranial Doppler device. The changes of blood flow hemodynamics of MCA is in

the means of the above mentioned parameters during the last 5 sec were measured in the screen displayed by the TCD device. The mean flow velocity of MCA to breath hold was calculated as following[6,7]:
The breath hold index (BHI) is calculated as:

BHI=[(MFVBH – MFVbaseline)/MFVbaseline] X100 / seconds of breath hold.

Then patients were treated by one tablet of metformin (Glucophage, Merk company)® 1000mg/day with 100mg/day of sitagliptin (Januvia, MSD company) ® for 12 weeks and then they were re-examined for biochemical and transcranial Doppler including breath-holding test. Statistical analysis were obtained by using SPSS version 20 and the use of paired t-test to compare between means of before and after treatment of the same group. Data are expressed as mean±SEM.

Results

Mean age of patients was 45.95±1.22 years with 40% female (n=8) and 60 % male (n=12). Fasting blood sugar (FBS) significantly reduced after treatment from 167.5±5.19 mg/dL to 114.2±2.41 mg/dL ($p<0.000$). Glycosylated hemoglobin significantly reduced from 7.99±0.17 to 6.47±0.08 ($p<0.000$) as shown in the table (2); while PI and RI significantly reduced with significant increase in diastolic and mean flow velocity. Breath holding index after treatment from 0.64±0.029 to 0.87±0.035 ($p<0.000$) as shown in the table(2), figures (1) and (2).

Discussion

Some patients with new-onset type 2 diabetes mellitus have both high FBS and high HbA1c. Scientific references recommend the use of combination in these patients. Many previous studies and endocrinology societies guidelines recommend the combination of DPP-4 inhibitor with metformin for patients with HbA1c higher than 7%[33]. This combination is more safe and with low risk of hypoglycemia[34]. Furthermore, no weight gain occurs so it is more suitable for obese patients[35]. In our study, we found that combination of metformin and sitagliptin have the most significant effect on reduction of blood glucose and HbA1c toward favorable glycemic control. It has been found that synergistic effect between DPP-4 inhibitor and metformin exists[36]. The use of both agents together will increase β-cell mass by decreasing apoptosis and increase cellular proliferation[37]. In addition to that, there may be reduction in the adverse effects of both drugs by decreasing the maximum dose[38]. Metformin also decrease the risk of pancreatitis that associated with the use of sitagliptin by decreasing pancreatic duct hyperplasia. This is may be part of anti-proliferative effects of metformin that is mediated by AMP-kinase pathway[39]. From our result, we see the pronounced effect of combination treatment on diastolic velocity , resistive index and pulsatility index. This study is unique about effect of combination (sitagliptin+metformin) on cerebral hemodynamics in diabetic patients by using transcranial Doppler. As mentioned above the combination of sitagliptin and metformin has complementary effect. In addition to the effect of sitagliptin as inhibitor of DPP-4 , metformin also decreases plasma concentration of DPP-4 with increase in GLP-1. Both drugs have beneficial antihyperlipidemic, anti-oxidant and antiatherosclerotic effect. It is obvious nowadays that both drugs delays the onset of vascular complication especially if started early [40]. there was no previous study dealing with the effect of combination of sitagliptin and metformin on cerebral vasoreactivity in diabetic patients. However, many studies showed synergistic effect between sitagliptin and metformin when used together in diabetic patients[35-38]. Great evidence is available about this synergism. Glucagon like polypeptide-1 was also found in tissues other than the intestine like liver , pancreas and vascular endothelium[18,19,41-46]. It was concluded that GLP-1 has favorable effect on endothelial function and nitric oxide synthesis(20). Metformin can increase the level of GLP-1[47,35-38] by unknown mechanism and DPP-4 inhibitors also increase GLP-1 level by inhibiting its catabolism[51,52]. Therefore, some sort of potentiation of effect will occur and definitely the response will be greater than either alone. Little data are available about the effect of combination of metformin and sitagliptin on vasculature but this combination was well studied regarding its effect on level of blood glucose and HbA1c[35-38]. In addition to what we mentioned above, metformin can inhibit DPP-4 so there will be significant sparing of incretin axis which is disrupted in diabetic patients[50,51]. From the explanation above, it is clear that the effect of combination therapy may be complementary rather than additive. Studies are deficient regarding the long term effects of DPP-4 inhibition and our study may be genuine in this field. It is important to mention that combination therapy with lower doses may reduce unwanted effects and improve patient

compliance[34-39]. It has been found that combination of metformin and sitagliptin was also associated with gastrointestinal upset and diarrhea but to a lesser degree than when metformin used in high doses alone[52]. Many clinical trials and medical associations suggest to start with combination of metformin and sitagliptin because of their positive impact on cardiovascular outcome and other long term complication[53]. Furthermore, better glycemic control can be achieved with this combination. During our study, hypoglycemia did not recorded in our patients. It is well known that combination of sitagliptin and metformin carries the lowest risk of hypoglycemia, therefore, there will be lower risk of blood glucose fluctuation[52,53]. It is worth mentioning that fluctuation of blood glucose with frequent hypoglycemic attacks is associated with further increase in the risk of oxidative stress, atherosclerosis and microvascular complications with subsequent increase in the risk of heart attacks and stroke[54,55]. We concluded that use of combination of metformin and sitagliptin together will achieve good glycemic control with favorable effect of cerebral autoregulation and improve cerebral hemodynamic toward reduction of risk of cerebral ischemia. Further studies are recommended to confirm beneficial effects of insulin and other antidiabetic agents on cerebrovascular reserve capacity.

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