



Research Article

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Evaluation of the Oral Sildenafil Effect on the Recovery of Patients with Acute Ischemic Stroke

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ABSTRACT

This study aimed to evaluate the effects of the oral sildenafil on the recovery of patients with acute ischemic stroke. This was a clinical study conducted on 42 ischemic stroke patients (older than 18 years old) with National Institutes of Heart Stroke Scale (NIHSS) of more than 5. The patients in their 3 hrs to 7 days of the attack onset were selected and divided into two equal groups. The control group received the standard treatments for ischemic stroke, and the case group received 25 mg daily oral sildenafil for 14 days in addition to the standard treatments. After a 3 month period, the NIHSS values were compared between the two groups. The NIHSS decreased significantly in both case and control groups after 3 months, but the difference was not statistically significant ($P=0.067$). Then, the patients were divided into two groups diabetic and non-diabetic, before and after treatment with sildenafil that seem the NIHSS is decreased significantly in non-diabetic patients ($P=0.046$) but the difference between two diabetic groups was not statistically significant ($P=0.058$). Although the results of our study were initially contradictory with the most of recent studies, comparing the diabetic and non-diabetic groups showed sildenafil is more effective in decreasing the NIHSS scores in the non-diabetic patients than the standard treatment alone. Sildenafil was not statistically significant in diabetic patients; this contradictory in overall and diabetic group may be results from selection bias for diabetes mellitus between the case and control groups. We had significantly more diabetic patients in case group (3 to 9), and perhaps diabetes inhibits the beneficial effects of sildenafil on ischemic stroke.

Keywords: Acute ischemic stroke, Diabetes, Sildenafil

INTRODUCTION

Ischemic stroke which include thrombotic and embolic types, considers one of the major causes of morbidity and mortality worldwide (1). This type of stroke occurs when a blood clot or fat be caused obstruction of vessel and cut off blood flow in the brain. Artery occlusion can occur inside or around the brain also, blood clots can be brought by the bloodstream from other parts of the body to the brain (2). When the blood flow stops, the neuronal function stops and irreversible damage and ischemic in blood flow speed occur less than 18 ml in 100 ml per minute. Cut off blood flow to the brain excludes neurons and other cells from glucose and oxygen. The lack of glucose and oxygen vacate cellular energy reserves that is required to keep the potential of cell membranes and ion gradient between the two sides of the membrane, which its result is the exit of potassium from the cells to the outside the cell and subsequently entry of calcium into cells. Entrance of too much calcium causes to activate of protease enzymes and lipase, and nuclease which these enzymes and products of metabolism and free radicals cause to breaks down the plasma membrane and the components of cytoskeleton that lead to cell Death (3). Following the ischemic stroke, Patients are at risk of catching to multiple neurological complications including cerebral edema, seizures, intracerebral hemorrhage (transformation of hemorrhagic stroke to ischemic) and progress of most defects neurological cause. Among the neurological complications, cerebral edema is the important factor of death in these

patients (2). Sildenafil is an inhibitor of phosphodiesterase 5 which are commonly used for erectile dysfunction. It may also have a useful therapeutic effect in the treatment of stroke and subarachnoid hemorrhage and dementia and learning, and neurodegenerative disorder (4). Also, this drug is infiltrated to the cycle of nitric oxide and the guanidine menu phosphate path that interfere in pathological path of number of neurological diseases (5). The drug has been used in diabetes and medullar patients for years It is certain that as the desired effects of this drug, t also has side effects which need to be considered and in people with outbreak of these effects and avoided consuming it. The objective of this study is evaluation of sildenafil effect on the recovery process of patients who catch acute ischemic stroke.

MATERIALS AND METHODS

During this study, 18 to 80-year-old patients with acute stroke syndrome who have hospitalized in Golestan hospital of Ahvaz (Iran) and based on imaging of the brain was proved being ischemic of stroke at the beginning of the hospitalization and lacking of exist criteria from study were studied including pregnant women or at the age of pregnancy with beta positive HCJ, patients who are used sildenafil or other drugs of this family from seven days before the stroke, existence of unstable thoracic angina, existence of myocardial infarction in 3 months ago, the use of nitrate compounds, use alpha channel antagonists, use of compounds with power of inhibition of cytochrome P450, existence of base systolic pressure less than 100 mmHg, penile deformity, existence of creatinine above 1.5, liver dysfunction, history of dementia, glucose more than 400 at the beginning the hospitalization, stroke or momentary ischemic attack within the last month, allergy to sildenafil, an evidence indicative the hemorrhagic stroke. Methods was to this case that, in this plan all patients with stroke on the territory of the middle cerebral artery at the beginning of hospitalization was studied in term of exclusion criteria and if there is, the patients were existed from the plan from the beginning. Otherwise, patients for Random Back were entered to one of the case or control groups. After completion of the initial studies and confidence the absence of contraindications for prescription of sildenafil to each of patients, sildenafil was daily prescribed during a two-week period. It is normal patients in terms of cardiovascular in this time were monitoring by doing a base echocardiogram before treatment and with fulfillment of specified intervals during treatment. Patients in term of biography and risk factors and the paraclinic results and neurological examinations at the beginning of hospitalization and during the registration were studied and divided into two treatment groups. Patients of control group were the patients who, were treated by common treatments of ischemic stroke (aspirin and placebo) and was not done any intervention in received drugs of the patients. The patients of case group were patients who, in addition to common therapies received oral sildenafil (Aspirin + sildenafil) and receipt of the first dose of sildenafil in these patients was recorded carefully to be carefully studied the delay in receipt of the first dose of sildenafil; receipt rate of daily Sildenafil 25 mg and its continuation was to 14 days. It should be noted, in case of occurrence of possible complications, sildenafil cut off and are done the treatment of pharmaceutical complications. Finally, obtained data were recorded in SPPSS software and with T-test independent test, were compared the NIHSS means before and after the treatment in two groups of control and case together. Before the disease be placed in group of case or control, for his entourage has been explained the beneficial effects of sildenafil in the treatment of patients with stroke and also harms and side complications of drug and from entourage was taken the written testimonial. Obviously, in case of rejection or dissuasion of patient or his escort in every moment of research, the patient was existed from study. On the implementation of the plan to follow up and examination of patients was not received any cost from the patients.

RESULTS

During this study, 44 patients were studied and divided into two groups (n=22). In the treated group with sildenafil, a patient due to lack of reference, a patient due to infarct hemorrhage of patients during hospitalization, and two patients due to reaction and sensitivity to sildenafil were existed from the study; in total 18 patients were placed in case group who 8 persons were female and 10 patients were male and their age mean was 69 ± 10.2 . 22 patients were studied in control group who 3 patients due to lack of reference and one patient also died, were existed from the study and among 9 patients male and 9 patients were female and the age mean of control group was also 68 ± 10.3 . The frequency distribution of smoking (Figure 1), Diabetes (Figure 2), blood pressure (Figure 3), hyperlipidemia (Figure 4), and patients gender (Figure 5) were shown in each of groups' charts.

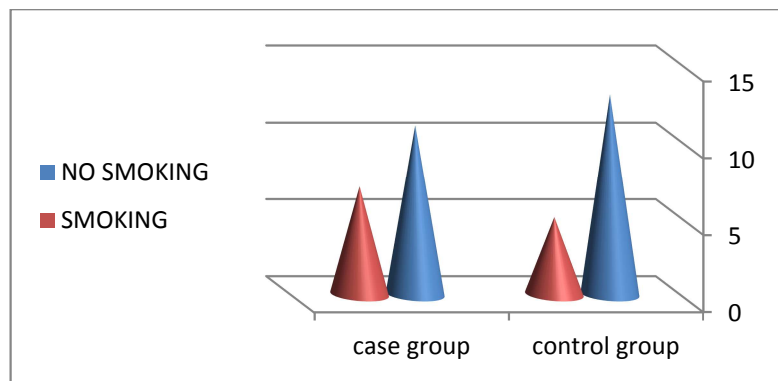


Figure 1. Frequency distribution of smokers in two groups of case and control

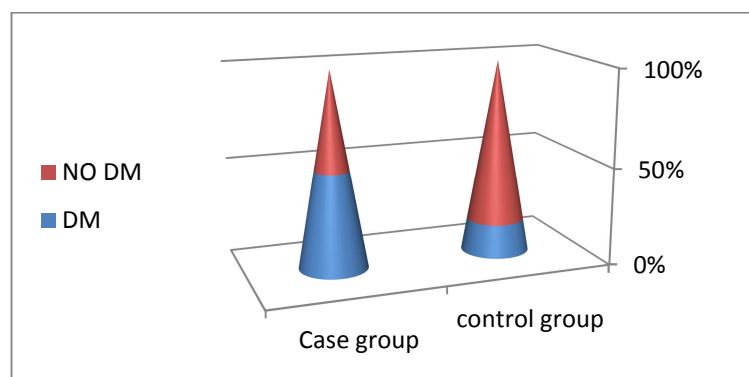


Figure 2. Frequency distribution of diabetic patients in the two groups of case and control

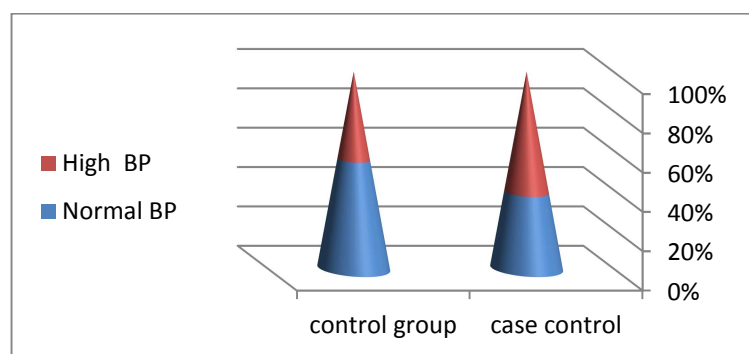


Figure 3. Comparison of frequency distribution of blood pressure in the two groups of case and control

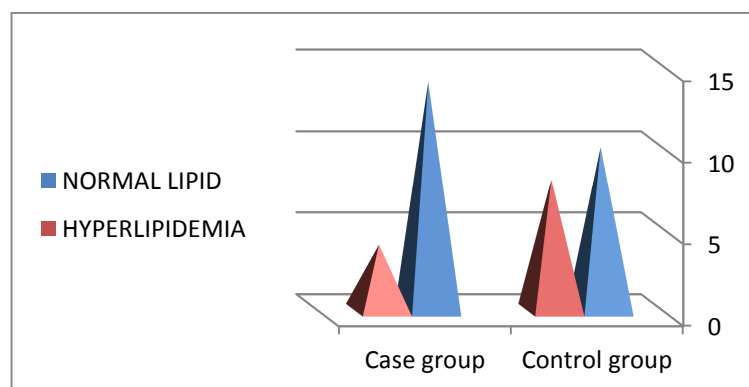


Figure 4. The comparison of blood pressure in the two groups of case and control

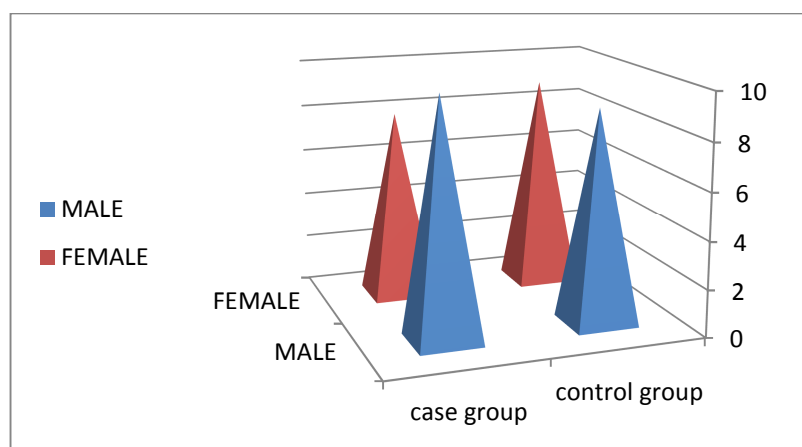


Figure 5. The distribution of gender in the two groups of case and control

In treated group with NIHSS sildenafil before treatment 9.55 was with standard deviation of 2.2 which after treatment reached to mean of 6.11 with standard deviation 2.05. The study of the results showed that, there is a significant difference in case group before and after the treatment ($P < 0.05$). Also, in control group, NIHSS before the treatment 10 was with standard deviation of 2.1 that after treatment reached to mean of 7.33 with standard deviation of 1.8 that showed there is a significant difference in control group before and after the treatment ($P < 0.05$). For comparison of sildenafil impact between the case and control groups T-test independent was used to compare the NIHSS of two control and case groups. It showed no significant difference between the two groups in the sildenafil effects on NIHSS after 90 days ($P = 0.061$) (Figure 6).

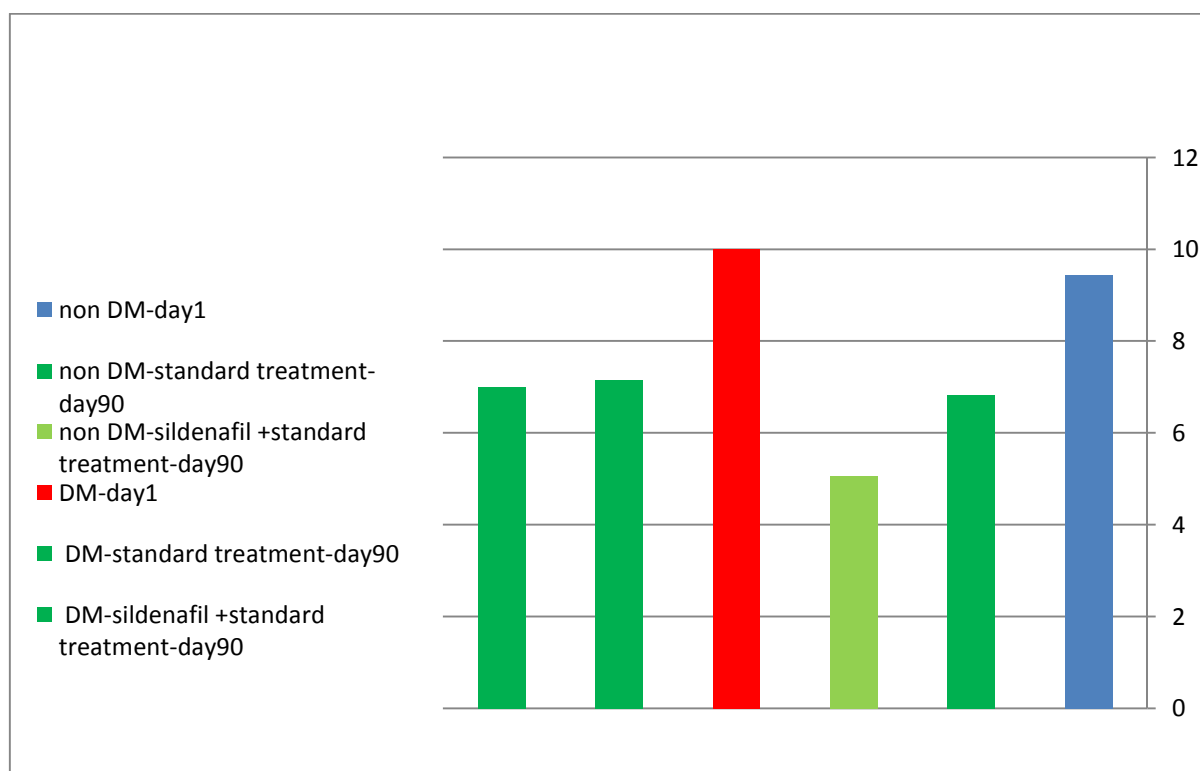


Figure 6. The mean of NIHSS criterion in the two groups of case and control in the first days and day of 90 after stroke

Comparison of NIHSS of two groups of case and control did not statistically show a significant difference at the beginning of first day ($P = 0.548$). Based on other studies and with possibility of diabetes interference as a confounding factor and according to remarkable number of diabetics in case group than control (9 versus 3 persons), in next stage two groups of control and case each of them has divided into two categories of diabetic and non-diabetic and the comparison between NIHSS of them were separately done and finally, using T-test independent. Accordingly, in control group were studied 15 non-diabetic and 3 diabetic patients that age mean of non-diabetic

control group, 66 ± 11.5 and diabetic control group was 68 ± 10.5 . In case group were studied 9 non-diabetic and 9 diabetic patients that age mean of non-diabetic group, 67 ± 10.5 and diabetic group was 67 ± 9.5 . In comparison of NIHSS treated non-diabetic control group with routine medicines, NIHSS before treatment was 9.43 with standard deviation of 2.11 that after treatment reached to mean of 6.82 with standard deviation 2.00 and treated non-diabetic case group with sildenafil along with routine medicines, NIHSS before treatment was 9.35 with standard deviation of 2.1 that after treatment reached to mean of 5.07 with standard deviation of 1.98 that showed there is a significant difference between two groups ($P= 0.046$). In other side, the comparison of NIHSS of treated diabetic control group with routine drugs before treatment was seen 10.01 with standard deviation of 2.37 that after treatment reached to mean of 7.16 with standard deviation of 2.53 and also in treated diabetic case group with sildenafil along with routine drugs, NIHSS before treatment was 10.1 with standard deviation of 2.04 that after treatment reached to mean of 7.00 with standard deviation of 2.13. Statistical surveys showed that, there is not a significant difference between two groups ($P= 0.058$). The comparison of NIHSS of two case and control groups, there was not statistically a significant difference at the beginning of the first day ($P= 0.548$).

DISCUSSION AND CONCLUSION

The results of our study showed that the mean baseline NIHSS and post treatment at day 90 follow up in the control group (receiving aspirin) significantly reduced. Similarly, this value in the case group (sildenafil + aspirin) showed significant reduction. However, the two groups showed no significant difference. Based on the study, we can conclude that 25 mg daily consumption of sildenafil for 14 days in the acute phase was effective in improvement of in non-diabetic patients with acute ischemic stroke through enhancing the rehabilitation of the patients over a period of 3 months. The findings of this study were consistent with most of the results obtained from sildenafil effect on the recovery process of patients in acute ischemic stroke (3, 6).

In a study by Silver *et al.* (2009) meta analysis of six studies with reliable values concluded that, although, the effect of sildenafil in ischemic stroke has shown some degree of success in rehabilitation, despite broad criteria of exit from study and also elimination of risk factors with practical effect, cannot definitely attribute the result to real community of stroke with a variety of risk factors therefore, it is better in selection of case and control populations, act in a way that create less bias (7). In addition, in a study by Bednar *et al.* sildenafil impact in ischemic stroke in 50 patients in two groups of 25 persons with daily prescription of 25 mg sildenafil to 7 days after stroke and comparison of recovery with control group that only had been received placebo; the result of the study has been the significant reduction of NIHSS in case group. However, they recommended the broader period than 3 weeks for better result (8). In a human study on 120 patients, sildenafil administered within the first 24 hours after stroke and for the first 7 days and its effect was studied on the patients showed promising results was obtained in the study that is justified the use of it (9). Another important point of the study is the effects of diabetes as confounding factor of sildenafil impact which is necessary the more studies be studied in this field.

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