IJBCP International Journal of Basic & Clinical Pharmacology

Original Research Article

Impact of metformin on the severity and outcomes of ischemic stroke

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ABSTRACT

Background: Stroke is the third most common cause of death in the United States and the most commonly diagnosed neurological disorder. About 750,000 strokes occur annually in the United States and about 150,000 people die as a result of stroke. The aim of this study was evaluation of the effect of Metformin on complication of ischemic strokes.

Methods: In this randomized, double-blind clinical trial study, 100 patients with ischemic stroke will be assigned randomly into two groups A and B. The National Institutes of Health Stroke Scale (NIHSS) will be used to evaluate the clinical manifestations of ischemic stroke. The two groups will be followed up for 3 months. Metformin 500mg twice in a day will be administered for seven days for group (A) and placebo will be administered for seven days for group (B). Blood glucose will be checked every 6 hours and will be recorded on the blood glucose (BS) chart. Before the intervention, the NIHSS questionnaire will be recorded in one day, three days, seven days and one month, two months, and three months after the intervention will be followed up respectively.

Results: In the present study, according to the neuro-protective effects of metformin, there is a significant difference in metformin taking in the reduction of NIHSS Score in non-diabetic stroke patients. There was a significant association in metformin taking and decrease in NIHSS scores in patients with cortical ischemic stroke.

Conclusions: According to the results, in patients with cortical stroke, there weren't a significant difference in NIHSS between the two groups in the first, third and seventh days but in the first, second and third months after intervention the difference was significant. Also, the results showed that metformin reduced the severity and stroke symptoms and accelerated recovery and functional output in patients with cortical stroke after the first, second and third months.

Keywords: Complications, Metformin, Recovery, Stroke

INTRODUCTION

Stroke is a non-communicable disease among the elderly population that is the third leading cause of death in developed countries after coronary artery diseases and cancers. According WHO report, 56.4 million deaths occurred worldwide in 2015 that 54% of them were among the top ten causes of death. Yearly about 750000 stroke have been occurred in USA and about 150000 of them have been died due to stroke. The incidence of stroke increases with age and about two third of stroke cases occur in upper 65 years old. In Iran the occurrence of stroke 10 year lower than world and several risk factors including age, sex, alcohol, smoking, high cholesterol, OCP, genetic and HTN are involved in the pathogenesis of stroke among people. Stroke is the main cause of physical disability among society's people which ws characterized

by the onset of acute neurological symptoms for 24 hours.[1-4]

Neurological symptoms are caused by the involvement of the central nervous system as a result of impaired cerebral blood flow which was determined by getting history. The location of the CNS is guessed according to the type of symptoms and diagnosed by neurologic examination and confirmed by uses CT-scan and MRI.[2,3,5,6]

The UKPDS study reported that treatment with Metformin decreases the risk of large vascular disease similar to small vascular disease. This is the opposite of other therapies that only reduce the deaths caused by sall vessels. The study showed that metformin protects cells from hypoxia and non-neuronal ischemia.

The protective effects of metformin may be due to AMPK activity. Research results indicated that metformin injection was performed 30 minutes after reperfusion injury in a complete brain ischemia in animal models involving 4 brain vessels and the deaths of the cells advance toward apoptosis.[7-9]

Also cerebrovascular disease is the most common neurological disease which can lead to complications or mortality. The incidence of ischemic stroke increases with age, and almost two thirds of cases occur in people over 65 years.[10]

Considering the protective effects of metformin in preventing secondary damage and due to lack of similar study in this area, the aim of this study was to investigate the impact of Metformin on the Severity and Outcomes of Ischemic Stroke.

METHODS

Study design and patients

This clinical trial study has been done on 100 patients with ischemia stroke which randomly assigned to two groups A and B. Inclusion criteria of the study is Ischemic stroke patients and focal neurological symptoms. Exclusion criteria of the study is intracerebral hemorrhage (ICH); Subarachnoid hemorrhage (SAH); subdural hematoma (SDH); hypoglycemia; contraindications for metformin use; diabetic patients; venous sinus thrombosis and drug side effects. The National Institutes of Health Stroke Scale (NIHSS) will be used to evaluate the clinical manifestations of ischemic stroke. Two groups were followed-up for three month and Metformin 500 mg was administrated for patients in group A and placebo for patients in group B twice a day for seven days. If any complications are detected, the patient will be excluded from the study.

Blood glucose in patients each 6 hour was checked and registered in chart of BS and in case of see any complications, the patient extracted from the study. Before

start the intervention, the NIHSS questionnaire was completed in baseline and 1, 3, 7 days and 1, 2 and 3 month after intervention completed for follow-up.

NIHSS questionnaire

The questionnaire NIHSS formed of 11 questions and the total score is in range 0 to 42 and each question had score 0 to 4. The score 0 for normal performance and the high scores show the upper degree of neourologic disorders in patients. The necessary tests such as level of consciousness (LOC), Eye movements, Field of vision, Fractional paresis, Arm movements (paralysis), Foot movements, Ataxia and sensory impairment, Ability to speak and Dysarthria was performed according to standard criteria of patients.

Statistical methods

Collected data were analyzed by statistical methods in SPSS version 19.

RESULTS

There were Fifty sex present of all patients were male and rest of them were female. The mean age of patients in Metformin group (A) was 68.9±10.6 years (range 42-90) and placebo group (B) was 67±11.63 years (range 41-86). The prevalent stroke risk factor was HTN with 43%.

Cortical stroke

The difference in NIHSS scores between two groups in patients with cortical stroke wasn't significant in days 1 (p=0.5), 2 (p=0.66) and 7 (p=0.18) after treatment by Metformin but the difference was significant in end of first month (p=0.038), second month (p=0.001) and third month (p=0.001) (Figure 1).
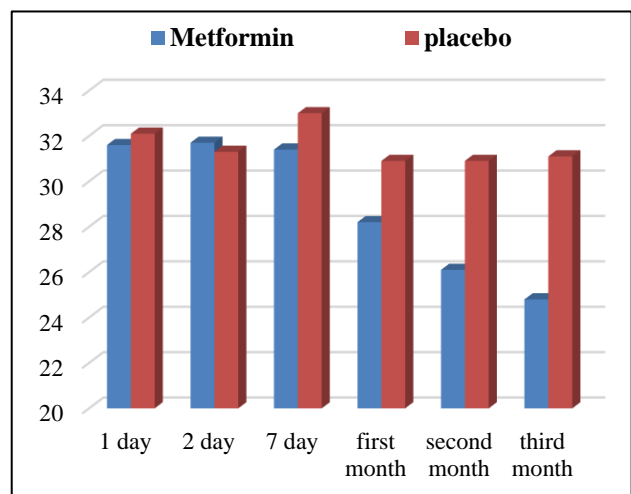

Figure 1: Compare the mean of NIHSS scores between two groups by times after intervention in cortical stroke.

Brain stem stroke

The difference in NIHSS scores between two groups in patients with brain stem stroke wasn't significant in days 1 (p=0.75), 2 (p=0.56) and 7 (p=0.48) after treatment by Metformin and in the end of first month (p=0.57), second month (p=0.51) and third month (p=0.33) (Figure 2).
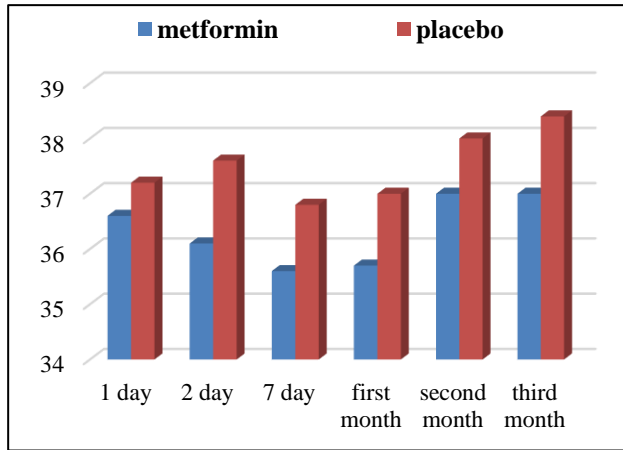

Figure 2: Compare the mean of NIHSS scores between two groups by times after intervention in brain stem stroke.

Lacunar stroke

The difference in NIHSS scores between two groups in patients with Lacunar stroke wasn't significant in days 1 (p=0.69), 2 (p=0.58) and 7 (p=0.51) after treatment by Metformin and in the end of first month (p=0.46), second month (p=0.55) and third month (p=0.21) (Figure 3).
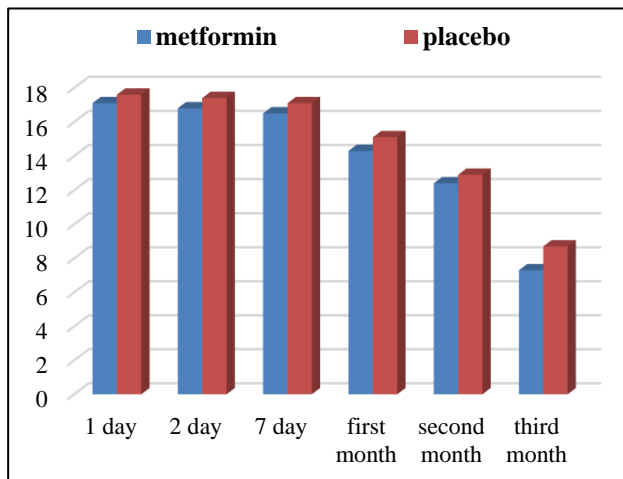

Figure 3: Compare the mean of NIHSS scores between two groups by times after intervention in lacunar stroke.

DISCUSSION

In line with our study, Mima and et al in a study in 2016, showed that treatment with Metformin in patients with stroke was associated with mild brain symptoms (p=0.026). But neural function didn't show significant relation. Also patients with history of stroke, gain taking Metformin on improving symptoms (p=0.046).[5]

According to the Wu and et al study in 2016 which has been done on ICH diabetic patients, results showed that Metformin was related with death below 90 days (p=0.014) which was in line with our study results.[11]

Venna and et al in study 2014, showed that there was inconsistent evidence on effect of metformin on RSN as a marker for mortality in repeated CV and Atrothrombotic ischemia stroke.[12]

According to the study of Kuwashiro and et al in 2012, using metformin in patients with stroke to prevent, had about 9% positive and 6% negative results that there wasn't significant relation between taking metformin and occurrence stroke. The severity of stroke defined by NIHSS and the mild neurologic defined as a score low than 3 for NIHSS. According to the function results, postoperative dysfunction after discharge assesed by MRS and the desirable performance defined as MRS score 2 or below.[7,13]

There was significant difference between patients which used metformin before stroke and in diabetic patints that not had proper treatment. On the other hand, given the effects of the previous use of anti-diabetic drugs, currently there was no evidence indicating the improvement in the severity or outcome of stroke.[8,9,12-15]

In contrast, use metformin was considered as a proper factor in reducing the severity of stroke in the study population of Mima and et al, study that in non-diabetic patients with stroke (64% of all patients), about 75% had NIHSS below 3 and the effects of metformin was observed on functional outcomes only in the mild to severe stroke. In addition to the initial score of NIHSS, occurrence of stroke relapse was related with increasing stroke severity and mild prognosis of stroke.[5,16,17]

Jiang and et al in a study showed that the drugs such as metformin, pioglitazone and semaglutin were effective in the decreasing the risk of stroke.[18]

In a sample of 14856 diabetic patients from Taiwan after 4 years follow-up, the relation between metformin uses and stroke reducing wasn't significant. A multi-center study conducted in 1998 by UKPDS, presented evidence that treatment with metformin in comparison with insolin and SU deal to reducing the coronery side effects related to the T2D that's it deals to accelerate the use of metformin in diabetic treatment.[13,19]

In this study in line with other studies, results showed that taking metformin in non-diabetic patients with stroke could cause to decreasing the stroke intensity and its

effects such as functional effects which was assessed in this study by NIHSS.

CONCLUSION

In cortical stroke, the difference in NIHSS between two groups wasn't significant in first, third and seventh day after intervention but it was significant in one, two and three months after intervention. The results of this study showed that taking metformin was reduced the intensity and symptoms of stroke and also deal to accelerated recovery and functional output in patients with cortical stroke one, two and three months after intervention.

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