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Impact of glibenclamide versus Insulin on neurological and functional outcomes of hemorrhagic stroke in diabetic patients

[1]Keyvan Ghasami, [2]Mohammad Reza Rezvanfar, [1]Fardin Faraji, [3]Abolfazl Mohammadbeigi, [4]Mohammad Rafiee,

[1]Department of Neurology, [2]Thyroid Research Center, Valiasr Hospital, Arak University of Medical Science, Arak; [3]Clinical Research Development Center, School of Medicine, Qom University of Medical Sciences, Qom; [4]School of Medicine, Arak University of Medical Science, Arak, Iran

Abstract

Background & Objective: Stroke is one of the common leading causes of morbidity and mortality worldwide. Diabetes is one of the modifiable risk factors of stroke which is related to a higher mortality and a poorer outcome**.** We aimed to evaluate the protective effect of Insulin versus glibenclamide on the improvement of neurological and functional outcomes of hemorrhagic stroke. *Methods:* The present single blind clinical trial was conducted on 100 patients with stroke and diabetes who had referred to Neurology Emergency Department of Vali-e-Asr hospital, Arak, Iran. The patients were categorized into two groups according to the glucose control treatment before stroke. Without any randomization, glibenclamide was used in 45 patients, while others (55 ones) received insulin. National Institute of Health Stroke Scale (NIHSS) and modified Rankin scale (MRS) systems were used for evaluating the neurological and functional outcomes. *Results:* Hemiparesis was the most common sign of the patients. The mean of changes in NIHSS and MRS scores of the two groups were -29.69±21.4 and -17.24±21, respectively. Although Insulin group had a higher decrease in NIHSS and MRS scores, no significant difference was found between the two groups. Both treatment methods had a significant decreasing effect on NIHSS and MRS scores ($p<0.001$).
Conclusion: Patients treated with both glibenclamide and insulin had similar decrease in their one week NIHSS and MRS scores with no significant difference in the two treatment groups.

INTRODUCTION

Stroke is one of the common leading causes of morbidity and mortality worldwide[1] and has several modifiable risk factors.[1] Diabetes mellitus (DM) is well-established as one of the most important modifiable risk factors of stroke.[2-9] This increased risk is related to the pathophysiological changes occurring in the cerebral vessels of the patients with diabetes.[9] Moreover, diabetes is related with two to three- fold increases in the risk of developing "first ever" and recurrent stroke in future.[6] In addition, stroke accompanied by DM has a higher mortality rate and poorer outcomes compared to the patients without diabetes.[1,9]

Based on a recent study, there was a rapid increase in the prevalence of diabetes in Iran from 7.7% in 2005 to 8.7% in 2007. About half of the current cases of diabetes in Iran were attributed to incident cases.[10] Therefore, diabetes is one of the most serious health problems in Iran and its macro-vascular complications of stroke, is of utmost importance.[1]

Furthermore, animal and human studies have shown that hyperglycemia during focal brain ischemia worsened the stroke outcomes, particularly in transient occlusion with reperfusion models.[5,11-14] These studies done controlling the multiple confounding factors, suggested that hyperglycemia worsened the outcomes of acute stroke.[5] Ischemic stroke is more common in diabetic patients than hemorrhagic stroke[15], with sub-cortical infraction being more prevalent in diabetic patients.[15,16] However, our recent study showed that blood sugar is higher in hemorrhagic stroke than in ischemic ones.[17] Moreover, hypertension is also an important risk factor for hemorrhagic stroke which is often associated with diabetes.[17,18] Hemorrhagic stroke is also problematic in diabetes, being less preventable than ischemic stroke.[16] Recent studies have reported some controversies about the effect

Address correspondence to: Mohammad Reza Rezvanfar; Thyroid Research Center, Valiasr Hospital, Arak University of Medical Science, Arak, Iran. Email: dr.rezvanfar@arakmu.ac.ir

of glucose control as well as glucose lowering drugs on prognosis of the stroke patients.[5,19-20] We carried out the current clinical trial to compare the treatment effect of insulin and glibenclamide on improving the neurological and functional outcomes of hemorrhagic stroke patients.

METHODS

Patients and study setting

This single blind clinical trial was conducted on 100 diabetic patients who were referred to the Neurology Emergency Department of the Vali-e-Asr hospital, Arak, Iran due to hemorrhagic stroke since 2009 to 2011. We included the patients who presented to the Hospital less than 24 hours after the onset of stroke. The stroke types were based on clinical criteria, MR imaging, and, in some cases, through vascular imaging which was performed by a Neurologist. The patients with transient ischemic attack, lacunar infraction, deep coma, and cavernous sinus thrombosis; patients with tumors, subarachnoid hemorrhage, infective meningitis; underlying cardiac, renal, or liver failures and sepsis were excluded from the study. Diabetic patients who needed to change from insulin to glibenclamide or vice versa were also excluded from the study.

Randomization was not done due to the ethical considerations. Nevertheless, we tried to assign the patients to the two study groups by matching them regarding age, sex, and the initial neurological and functional scores. Informed consent was obtained from all the eligible patients who were willing to participate in the study. The study protocol was approved by the ethical committee of Arak University of Medical Sciences, Arak, Iran.

Two treatments regimes were used for the patients based on the diabetes treatment before stroke. Glibenclamide was used for the patients who were on diet regime or were using glibenclamide (45 patients). Insulin was used for the patients who used insulin for treatment of diabetes before stroke (55 patients). The two groups were matched according to age, sex, and other neurological treatments. We aimed to decrease the blood sugar to the normal range and avoid hypoglycemia.

Measurements

Among the baseline investigations were blood sugar, urea, creatinine and full blood count. The neurological status and outcomes were measured by a trained Physician using National Institute of Health Stroke Scale (NIHSS) and modified Rankin scale (MRS), which were widely used in clinical trials[21-22] and previously validated.[21-26] The Physician who measured the neurological scores was blinded to the type of treatment given. These measurements were taken by the same physician at the time of discharge.

Statistical analysis

The patients' data, including their demographic characteristics and NIHSS and MRS scores, were recorded in a checklist and entered into the Statistical package for Social Sciences (SPSS) software. Descriptive statistical methods, such as mean, percent, and bar chart, were used for presentation of the results. Independent sample t-test, paired t-test, and chi-square test were applied for statistical analysis. $P<0.05$ was taken as statistically significant.

RESULTS

Among all the stroke patients with diabetes who were referred to Vali-e-Asr hospital, 60% were female, only 5% of the subjects were smokers. The most prevalent signs of the patients were hemiparesis (54%), coma (26%), paraparesis (13%), and others (7%). Among the patients under study, 55% were treated with oral drug regime, including gelimanglamide, while 45% were treated by Insulin.

The baseline characteristics of the study patients are shown in Table 1. As shown, there was no difference between the patients in the Insulin and Glibenclamide Groups regarding age, sex, duration of diabetes, first blood sugar, and MRS. However, the Glibenclamide Group had a higher NIHSS score as compared to the Insulin Group ($p=0.025$).

The treatment effect of each drug regime (glibenclamide and insulin) is shown in Table 2. As shown, based on the paired t-test, both groups had a significant decrease in the NIHSS and MRS scores ($p<0.001$).

The mean change for the two groups of patients in NIHSS and MRS scores were -29.69±21.4 and -17.24±21, respectively. A higher decrease was seen in the Insulin Group, but the difference was not statistically significant (Table 3). Independent sample t-test was used to compare the decreasing effect of the two treatment methods and the results did not show any significant difference between the two groups regarding the rate of changes in these scores. Figure 1 shows that the mean changes in NIHSS score in Glibenclamide and

Table 1: Baseline characteristics of the study groups

	Glibenclamide mean±SD	Insulin mean±SD	P value
Age, mean±SD	69.18±10.13	68.84±10.44	0.871§
Female sex, n (%)	31(56.4)	29(64.4)	0.270‡
Diabetes duration, mean±SD in years	2.95±2.99	3.33±0.883	0.452§
First blood sugar, mean±SD	215.95±77.38	234±72.27	0.234§
NIHSS	13.29±6.27	10.64±5.12	0.025§
MRS	3.49±1.05	3.29±1.08	0.347§

§ Independent sample t-test
‡ Chi square test
NIHSS, National Institute of Health Stroke Scale; MRS, modified Rankin scale

Table 2: Treatment effect of glibenclamide and insulin on improving the neurological and functional scores in diabetic hemorrhagic stroke patients

Treatment group	Neurological score	Before Mean±SD	After Mean±SD	P value
Glibenclamide	NIHSS	13.29±6.27	9.73±5.95	<0.001†
	MRS	3.49±1.05	2.87±1.09	<0.001†
Insulin	NIHSS	10.64±5.12	7.09±4.09	<0.001†
	MRS	3.29±1.08	2.67±1.11	<0.001†

† Paired t-test

Table 3: The mean change in percent of the NIHSS and MRS scores between the two groups of diabetic hemorrhagic stroke patients

Neurological score	Mean change for two groups	Glibenclamide mean±SD	Insulin mean±SD	P value
NIHSS	-29.69±21.4	-27±21.8	-32.9±20.8	0.175
MRS	-17.24±21	-17.06±19.7	-17.5±22.7	0.925

NIHSS, National Institute of Health Stroke Scale; MRS, modified Rankin scale

Insulin Groups was 3.49±3.01 and 3.44±2.98, respectively. The difference was not statistically significant (p=0.939). Also, the mean changes in MRS score was 0.618±0.65 and 0.62±0.834 for Glibenclamide and Insulin Groups, and the difference was also not statistically significant (p>0.05)

DISCUSSION

Our results showed that the use of sulphonylurea has the same outcome as insulin in hemorrhagic stroke in diabetic patients. We did not find similar previous study in the published literature. We belief that this is the first study to compare the effect of sulfonylurea and insulin on diabetic patients with hemorrhagic stroke.

There has however been some previous clinical and animal studies on the effect of sulphonylurea and insulin on ischemic stroke. Kunte *et al* reviewed the medical records of 33 patients taking sulphonylrea with 28 controls, and showed a significantly larger proportion of those taking

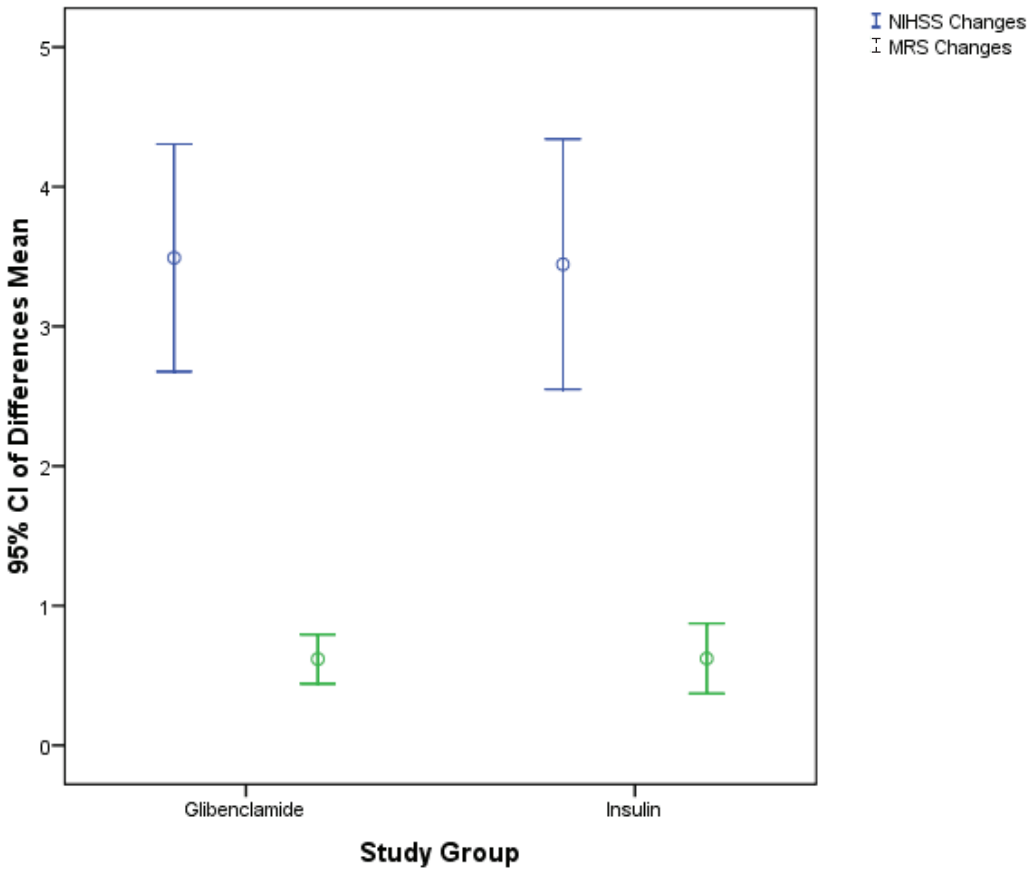

Figure 1. The mean differences in neurological and functional scores in diabetic hemorrhagic stroke patients using glibenclamide and insulin (NIHSS, National Institute of Health Stroke Scale; MRS, modified Rankin scale)

sulphonylurea to be able to achieve a decrease in NIHSS score of 4 or more points, suggesting that it may have beneficial effect.[27] Simard *et al*. showed that glibenclamide was able to eliminate the occurrence of progressive secondary hemorrhage, and reduce the size of necrotic tissue in a rat brain contusion model.[28] On the other hand, Weih *et al*. showed that sulphonylurea drugs did not influence the initial stroke severity.[29] Favilla *et al*. analysed 298 patients with stroke, who had sulphonylurea prior to onset of stroke, and showed that it has no effect on stroke severity and long-term functional outcomes compared to other diabetic treatment[30], casting doubts on sulphonylurea for prophylactic neuroprotection.

As for insulin, Bruno *et al*. showed that intravenous insulin protocol corrected hyperglycemia during acute brain infarction was significantly better than the usual care.[5] This has been confirmed by animal studies using insulin in ischemic infarct rat.[19,20]

In conclusion, we compared the functional outcome and neurological effects of using glibenclamide or insulin on glucose control in diabetic patients with hemorrhagic stroke. We showed that there was no significant difference in the two modalities of treatment, both groups of patients showed improvement in their one week NIHSSS and MRS scores.

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DISCLOSURE

Conflict of interest: none

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