Neuroprotective Effects of Erythropoietin in Acute Ischemic Stroke

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Original Article

ABSTRACT

Background: Ischemic brain strokes consisttwo-thirdsof strokesand their complications bear a lot of disability for patient and society. In this study, we seek for effect of Erythropoietin on ischemic brain stroke's outcomes according to National Institutes of Health Stroke Scale (NIHSS) changes.

Methods: This study is a RCT (randomized clinical trial). All patients with focal neurologic deficit with primary suspicion of brain stroke undergone neuroimaging evaluations.After confirmation of new ischemic brain stroke, the patients with inclusion criteria'srandomized into two groups of cases and controls.

NIHSS was defined for each patient and all patients received a routine treatment protocol. Erythropoietin 16,000 IU as a bolus intravenous dose was given to case patients as soon as neuroimaging study confirmed new ischemic stroke and continued as 8000 IU each 12 h up to total dose of 56,000 IU during 3 days. Patients re-evaluated at days 14 and 28 and NIHSS was assessed by another neurologist blinded to patient's group. Finally, NIHSS changes of both groups compared with each other's.

Results: Evaluations revealed that in days14 and 28 during follow-up, Erythropoietin was effective in NIHSS (P= 0.0001). This effect was of value in level of consciousness Commands (P= 0.024), facial palsy (P= 0.003), motor arm (P= 0.0001), motor leg (P= 0.0001), sensory (P= 0.009), and best language (P= 0.023).

Conclusions: Administration of high-dose erythropoietin in first 24 h can be effective on reduction of ischemic stroke complication. A larger scale clinical trial is warranted.

Keywords: Erythropoietin, national institutes of health stroke scale, neuroprotection, stroke

INTRODUCTION

Stroke is the third most common cause of death and the most leadingcauseofdisabilityintheUnitedStates.[1-5]Annually,750,000 new cases are recorded with 150,000-200,000 deaths.[2-4] 80% of all strokes are ischemic and the remindersare hemorrhagic including subarcnoide hemorrhage.[4]

Stroke is a syndrome with acute neurologic deficit, which lasts at least 24 h and is directly due to impairment of cerebral blood-flow and central nervous system involvement. If symptoms revealed before 24 h (usually during 30 min), the term TIA (Transient Ischemic Attack) applies.[6,7]

Stroke can lead to hemiplegia, numbness, paresthesia, confusion, mental deficit, speech and language disorder, diplopia, visual field defect, and coma. Multiple risk factors are recognized for stroke. Hypertension, Chronic Heart Failure, Arterial Fibrillation, Diabetes Mellitus, long-term smoking, hyperlipidemia, and increased low density lipoprotein are the most common. Hyper-coagulation states and oral contraceptives are less common.[8-13]

Stroke incidence is increased with age. About two thirds of all strokes happen after 65 years old. Men are slightly more affected than women and blacks are more involved.[14]

Erythropoietin is made in human body and has erythropoietic effects. In addition, new studies suggest increased and enhanced angiogenesis and neurogenesis by erythropoietin.[15] erythropoietin is a glycoprotein, which is produced in kidneys and stimulates red cells syntheses in bone marrow. PD poetin is a recombinant erythropoietin, which is produced with recombinant DNA technology and has 165 aminoacids and molecular weight of 34000 Dalton. This drug mainly used in treatment of anemia in patients with chronic renal failure.[16]

In this study, we wanted to know, if erythropoietin has any effect on acute ischemic stroke outcome and which disability of stroke shows more improvement in response to erythropoietin administration.

METHODS

All patients with focal neurologic deficit during first 24 h after attack, which were recognized as ischemic stroke were evaluated and those who reach inclusion criteria were entered this study.

Including criteria planned as the first ischemic stroke, which confirmed by neuroimaging during initial 24 h.

Exclusion criteria planned as: Existence of other intracranial pathology, Previous stroke, age over 80 years old, unstable systemic condition such as uncontrolled hypertension and Diabetes mellitus, polycythemia, and other myeloproliferative diseases, serum cratinine (Cr), history of deep vein thrombosis, and recent erythropoietin consumption.

NIHSS was defined for each patient and all patients received a routine treatment protocol. Only patients with arterial fibrillation, coronary heart failure and vertebrobasilar stroke received Low molecular weight heparin. Patients randomized into two groups of cases and controls. Erythropoietin16,000 IU as a bolus intravenous dose was given to case patients as soon as neuroimaging study confirmed new ischemic stroke and continued as 8,000 IU each 12 h up to total dose of 56,000 IU during 3 days. Blood pressure assessed each 15 min at the first 2 h of each injection and serum level of blood urine nitrogen (BUN), Creatinine, uric acid, Na, K, complete blood count (CBC), and Reticulocyte count checked for patients.

Patients re-evaluated at days 14 and 28 and NIHSS was assessed by another neurologist blinded to patient's group.

Finally, NIHSS changes of both groups analyzed by SPSS software [Table 1].

RESULTS

This study was carried out between April 2009 and June 2010 in three university hospitals in Tehran and Isfahan, Iran. On a total of 67 patients treated with erythropoietin but 30 of them were excluded. The most common cause was deterioration of patient's general condition due to systemic infections particularly pneumonia, bedsore, and second stroke, which significantly damaged patient's condition and responses.

Table1: Patients distribution based on EPO in men and women

Patient distribution	Sex		Total
	Male	Female	
EPO			
Count	21	16	37
% within group	56.8	43.2	100
NO EPO			
Count	27	16	43
% within group	62.8	37.2	100
Total			
Count	48	32	80
%	60.0	40.0	100

EPO=Erythropoietin

Thirty seven patients of erythropoietin group and 43 of control group completed study. Mean of age was 64.19 and 67.56 in case and control groups respectively [Table 2].

Initial total score of NIHSS was 9.03 ± 4.83 in erythropoietin group and 9.70 ± 5.82 in control group, which had not statistically significant difference.

After 2 weeks, total NIHSS decreased to 3.35 ± 2.17 in case group and 7.95 ± 5.65 in control group, which were significantly different ($P = 0.0001$).

After 4 weeks, total NIHSS reached to 2.11 ± 1.61 in case group and 6.05 ± 4.87 in control group, which are significantly different ($P = 0.0001$) [Table 3].

Level of consciousness (LOC) commands score was 0.35 ± 0.716 in erythropoietin and 0.51 ± 0.827 in control group as the first assessment. After 2 weeks, they decreased to 0.03 ± 0.164 and 0.33 ± 0.680 respectively ($P = 0.008$). After 4 weeks, they reached to 0.00 ± 0.000 in erythropoietin and 0.12 ± 0.324 in control groups, which had significant difference ($P = 0.024$).

Initially, facial palsy score in erythropoietin group was 1.16 ± 0.958 and in control group was 1.16 ± 0.814. After 2 week, they decreased to 0.59 ± 0.599 and 1.09 ± 0.781 in two groups respectively ($P = 0.002$).

Table2: Mean and standard deviation of age and scores of NIHSS of the participants

Group	*N*	Mean	Standard deviation
Age			
EPO	37	64.19	9.988
NO EPO	43	67.56	8.921
Initial total score			
EPO	37	9.03	4.833
NO EPO	43	9.70	5.821
Second total score			
EPO	37	3.35	2.176
NO EPO	43	7.95	5.652
Third total score			
EPO	37	2.11	1.612
NO EPO	43	6.05	4.874

NIHSS differences	*P*	Mean difference	Standard error difference
Initial total score	0.580	−0.67	1.208
Second total score	0.0001	−4.60	0.933
Third total score	0.0001	−3.94	0.789

EPO=Erythropoietin

Table 3: Mean difference and standard error difference of the NIHSS scores

Group	*N*	Mean	Standard deviation
Level of consciousness (1)			
EPO	37	0.41	0.725
NO EPO	43	0.65	0.752
LOC questions (1)			
EPO	37	0.35	0.716
NO EPO	43	0.65	0.813
LOC commands (1)			
EPO	37	0.35	0.716
NO EPO	43	0.51	0.827
Best gaze (1)			
EPO	37	0.05	0.229
NO EPO	43	0.09	0.426
Visual (1)			
EPO	37	0.00	0.000
NO EPO	43	0.33	0.747
Facial palsy (1)			
EPO	37	1.16	0.958
NO EPO	43	1.16	0.814
Motor arm (1)			
EPO	37	2.43	1.144
NO EPO	43	2.44	1.053
Motor leg (1)			
EPO	37	2.32	1.292
NO EPO	43	2.16	1.233
Limb ataxia (1)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000
Sensory (1)			
EPO	37	0.24	0.435
NO EPO	43	0.37	0.757
Best language (1)			
EPO	37	0.70	0.968
NO EPO	43	0.63	1.024
Dysarthria (1)			
EPO	37	0.95	0.780
NO EPO	43	0.70	0.558
Extinction and inattention (1)			
EPO	37	0.05	0.229
NO EPO	43	0.00	0.000
Level of consciousness (2)			
EPO	37	0.03	0.164
NO EPO	43	0.21	0.412
LOC questions (2)			
EPO	37	0.05	0.329
NO EPO	43	0.33	0.680

Table 3: continue...

Group	*N*	Mean	Standard deviation
LOC commands (2)			
EPO	37	0.03	0.164
NO EPO	43	0.33	0.680
Best gaze (2)			
EPO	37	0.00	0.000
NO EPO	43	0.05	0.213
Visual (2)			
EPO	37	0.00	0.000
NO EPO	43	0.33	0.747
Facial Palsy (2)			
EPO	37	0.59	0.599
NO EPO	43	1.09	0.781
Motor arm (2)			
EPO	37	1.03	0.763
NO EPO	43	2.23	1.109
Motor leg (2)			
EPO	37	1.00	0.782
NO EPO	43	2.05	1.194
Limb ataxia (2)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000
Sensory (2)			
EPO	37	0.00	0.000
NO EPO	43	0.33	0.747
Best language (2)			
EPO	37	0.19	0.397
NO EPO	43	0.53	1.032
Dysarthria (2)			
EPO	37	0.43	0.502
NO EPO	43	0.49	0.592
Extinction and inattention (2)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000
Level of consciousness (3)			
EPO	37	0.03	0.164
NO EPO	43	0.00	0.000
LOC questions (3)			
EPO	37	0.03	0.164
NO EPO	43	0.19	0.546
LOC commands (3)			
EPO	37	0.00	0.000
NO EPO	43	0.12	0.324
Best gaze (3)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000
Visual (3)			
EPO	37	0.00	0.000
NO EPO	43	0.33	0.747

Table 3: continue...

Group	*N*	Mean	Standard deviation
Facial palsy (3)			
EPO	37	0.38	0.492
NO EPO	43	0.84	0.814
Motor arm (3)			
EPO	37	0.57	0.502
NO EPO	43	1.88	1.219
Motor leg (3)			
EPO	37	0.65	0.588
NO EPO	43	1.74	1.236
Limb ataxia (3)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000
Sensory (3)			
EPO	37	0.00	0.000
NO EPO	43	0.28	0666
Best language (3)			
EPO	37	0.08	0.277
NO EPO	43	0.37	0.757
Dysarthria (3)			
EPO	37	0.38	0.492
NO EPO	43	0.30	0.588
Extinction and inattention (3)			
EPO	37	0.00	0.000
NO EPO	43	0.00	0.000

LOC=Level of consciousness, EPO=Erythropoitin

After 4 weeks, it was 0.38 ± 0.492 in erythropoietin group and 0.84 ± 0.814 in control group, which had significant difference ($P = 0.003$).

Upper limbs movement score was 2.43 ± 1.144 in erythropoietin and 2.44 ± 1.053 in control group as the first assessment. After 2 weeks, they decreased to 1.03 ± 0.763 and 2.23 ± 1.109 respectively ($P = 0.0001$). After 4 weeks, they reached to 0.57 ± 0.502 in erythropoietin and 1.88 ± 1.219 in control groups, which had significant difference ($P = 0.0001$).

Lower limbs movement score was 2.32 ± 1.292 in erythropoietin and 2.16 ± 1.233 in control group as the first assessment. After 2 weeks, they decreased to 1.00 ± 0.782 and 2.05 ± 1.194 respectively ($P = 0.0001$). After 4 weeks, they reached to 0.65 ± 0.588 in erythropoietin and 1.74 ± 1.236 in control groups, which had significant difference ($P = 0.0001$).

Initially, sensory score in erythropoietin group was 0.24 ± 0.435 and in control group was 0.37 ± 0.757. After 2 week, they decreased to 0.00 ± 0.000 and

0.33 ± 0.747 in two groups respectively (P = 0.007). After 4 weeks, it was 0.00 ± 0.000 in erythropoietin group and 0.28 ± 0.666 in control group, which had significant difference (P = 0.009).

And finally, best language score was 0.70 ± 0.968 in erythropoietin and 0.63 ± 1.024 in control group as the first assessment. After 2 weeks, they decreased to 0.19 ± 0.397 and 0.53 ± 1.032 respectively (P = 0.047). After 4 weeks, they reached to 0.08 ± 0.277 in erythropoietin and 0.37 ± 0.757 in control groups, which had significant difference (P = 0.023) [Table 4].

Other parts of NIHSS showed no significant difference between two groups after 4 weeks. Results are shown in appendix.

Table 4: Mean and standard deviation of outcome variables in EPO and no EPO groups

1st week	*P* value	Mean difference	Standard error difference
Level of consciousness (1)	0.143	−0.25	0.166
LOC questions (1)	0.086	−0.30	0.173
LOC commands (1)	0.361	−0.16	0.174
Best gaze (1)	0.620	−0.04	0.078
Visual (1)	0.007	−0.33	0.114
Facial palsy (1)	0.997	0.00	0.198
Motor arm (1)	0.969	−0.01	0.246
Motor leg (1)	0.569	0.16	0.283
Sensory (1)	0.364	−0.13	0.141
Best language (1)	0.739	0.07	0.224
Dysarthria (1)	0.102	0.25	0.150
Extinction (1)	0.160	0.05	0.038
2nd week	***P* value**	**Mean difference**	**Standard error difference**
Level of consciousness (2)	0.010	−0.18	0.068
LOC questions (2)	0.024	−0.27	0.117
LOC commands (2)	0.008	−0.30	0.107
Best gaze (2)	0.160	−0.05	0.032
Visual (2)	0.007	−0.33	0.114
Facial palsy (2)	0.002	−0.50	0.158
Motor arm (2)	0.0001	−1.21	0.211
Motor leg (2)	0.0001	−1.05	0.223
Sensory (2)	0.007	−0.33	0.114
Best language (2)	0.047	−0.35	0.170
Dysarthria (2)	0.653	−0.06	0.124
3rd week	***P* value**	**Mean difference**	**Standard error difference**
Level of consciousness (3)	0.324	0.03	0.027
LOC questions (3)	0.075	−0.16	0.088
LOC commands (3)	0.024	−0.12	0.049
Visual (3)	0.007	−0.33	0.114
Facial palsy (3)	0.003	−0.46	0.148
Motor arm (3)	0.0001	−1.32	0.203
Motor leg (3)	0.0001	−1.10	0.212
Sensory (3)	0.009	−0.28	0.102
Best language (3)	0.023	−0.29	0.124
Dysarthria (3)	0.523	0.08	0.118

LOC=Level of consciousness

CONCLUSIONS

As noted stroke is the third leading cause of death and stroke prevention by modifying related risk-factors, such as alcohol consumption, smoking, oral contraceptives, hypertension, and hyperlipidemia is very important. However, an important question is what can we do in acute phase of stroke? Nearly two-third of strokes is ischemic and various treatments are introduced for acute ischemic strokes, which are diagnosed by prompt neuroimaging. Antiplatelet drugs such as aspirin and anticoagulants including, heparin and warfarin are the most current treatments. Some other treatments such as vitamin E, vitamin C, Citicoline, minocycline, and folic acid are suggested with lesser importance. Some controlled clinical data but not all of them are in favor of recombinant tissue plasminogen activator (rt-PA). Treatment with *t*-PA within 3 h after onset of symptoms lowers mortality and morbidity. The most important side-effect of *t*-PA is intracranial hemorrhage therefore, some limitations are defined to use *t*-PA in acute stroke.[17-20]

Treatments to increase brain cell tolerance to ischemic and hypoxic insults can improve survival and rehabilitation course. New studies show some receptors for erythropoietin are detectable not only in brain but also in peripheral nervous system, cerebrospinal fluid and retina. Erythropoietin seems to be a cytokine with neuroprotective and neurotrophic effects on central and peripheral nervous systems. Some studies show effectiveness of erythropoietin in regeneration of peripheral nerves.[21-29]

New studies show simultaneous administration of erythropoietin and *t*-PA is harmful and leads to increase mortality. Zecharia *et al*. reported cellular DNA fracture in-patients who received *t*-PA after

treatment by erythropoietin in an animal model.[30] In addition, Ehrenreich *et al*. reported uselessness of concomitant treatment of erythropoietin and *t*-PA[31] although, his study in 2002 showed high-dose erythropoietin in acute stroke is safe and effective.[32]

In this study, erythropoietin group had better outcome in comparison to control group. Total NIHSS was significantly lower in erythropoietin group. This effectwas of value in LOC Commands (P= 0.024), facial palsy (P= 0.003), motor arm (P= 0.0001), motor leg (P= 0.0001), sensory (P= 0.009), and best language (P= 0.023).

A major limitation in this study was high number of patients, which excluded even after complete administration of erythropoietin because some unwanted conditions such as infections. In addition, patients with high NIHSS rate had poorer condition and more risk for infection and bedsore andhence these patients were more prone to be excluded. Therefore, majority of our cases were gathered in patients with low NIHSS rate.

In Iran, we frequently encountered patients with acute ischemic stroke, which arrive in emergency room after 3 h. So erythropoietin could be helpful to treat patients with acute ischemic stroke in this condition. We believe complementary studies are needed to establish the best dose and the most effective interval between stroke and drug administration.

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