Neuroprotective Effects of Erythropoietin in Acute Ischemic Stroke

Bahador Asadi, Gholam Reza Askari¹, Fariborz Khorvash², Ali Bagherpur², Farzad Mehrabi, Mohammad Karimi², Majid Ghasemi³, Abolfazl Najjaran²

ABSTRACT

Background: Ischemic brain strokes consist two-thirds of strokes and 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’s randomized 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 days 14 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 leading cause of disability in the United States.$^{[1-5]}$ Annually, 750,000 new cases are recorded with 150,000-200,000 deaths.$^{[2-4]}$ 80% of all strokes are ischemic and the reminders are hemorrhagic including subarcoide 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.\(^8\)\(^-\)\(^\text{13}\)

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 creatine (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. 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 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** |
| EPO | Male | Female |  |
| Count | 21 | 16 | 37 |
| % within group | 56.8 | 43.2 | 100 |
| NO EPO | Male | Female |  |
| Count | 27 | 16 | 43 |
| % within group | 62.8 | 37.2 | 100 |
| Total | 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 \( (P = 0.002) \).

**Table 2:** 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 |   | 9.03 | 4.833              |
| EPO         | 37 | 9.70 | 5.821              |
| NO EPO      | 43 |      |                    |
| Second total score |   | 3.35 | 2.176              |
| EPO         | 37 | 7.95 | 5.652              |
| NO EPO      | 43 |      |                    |
| Third total score |   | 2.11 | 1.612              |
| EPO         | 37 | 6.05 | 4.874              |
| NO EPO      | 43 |      |                    |

**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                    |

**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              |

EPO=Erythropoietin
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 | 0.666              |
| 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=Erythropoietin

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.

**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.\(^{[21-29]}\)

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

| Week   | \(P\) value | Mean difference | Standard error difference |
|--------|-------------|-----------------|--------------------------|
| 1st week |            |                 |                          |
| 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 |            |                 |                          |
| 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 |            |                 |                          |
| 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

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.\textsuperscript{30} In addition, Ehrenreich \textit{et al.} reported uselessness of concomitant treatment of erythropoietin and t-PA\textsuperscript{31} although, his study in 2002 showed high-dose erythropoietin in acute stroke is safe and effective.\textsuperscript{32}

In this study, erythropoietin group had better outcome in comparison to control group. Total NIHSS was significantly lower in erythropoietin group. This effect was 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 and hence 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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