RESEARCH ARTICLE

The Role of Piracetam in Treatment of Sickle Cell Anemia

Hayam Mostafa[1], Saadia Tayel[2], Mohamed Abdelrahim[3], Ahmed Khamees[4], Mohamed El Maraghy[5], Mohamed Meabed[5]

[1] Teaching Hospital of Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[2] Pharmaceutics and Industrial Pharmacy Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt

[3] Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

[4] Pharmaceutics and Industrial Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

[5] Pediatric Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

Correspondence to:
Mohamed Abdelrahim (mohamedemam9@yahoo.com)

Received: 23.07.2011

Accepted: 28.09.2011

ABSTRACT

Aims & Objectives: Sickle cell anemia is a chronic hemolytic disease presented by special clinical course attributed to ischemic changes resulting from vascular occlusion by masses of sickle cells. In-vitro studies with piracetam indicate that it has potential for inhibition and reversal of the process of sickling of erythrocytes so it has been reported to be an effective drug for the treatment of patients with SCA. The aim of this prospective study was to evaluate and compare the effect of different doses of Piracetam on clinical status and laboratory investigations of sickle cell anemia patients.

Materials and methods: The study was carried out on 30 sickle cell anemia patients (14 females), aged ranged from 5 to 16 years old and their weights ranged from 18kg to 33kg; from hematology clinic at Beni Suef University Hospital. Patients were divided into three equal groups. Group A received 80mg/kg/day piracetam, group B received 160mg/kg/day piracetam and group C represents the control group which did not receive Piracetam. Patients were treated and followed for 6 month. They were represented to full history taking, clinical examination, laboratory investigations and determination of frequency of packed red cells transfusion, crises and hospitalization on admission and every month for six months.

Results: There was an improvement in general health of children after therapy and pallor, decrease in the elevated serum ferritin level, decrease in frequency of crises and hospitalization, decrease in the frequency of transfusion, increase in packed red cells transfusion intervals and increase in hemoglobin level. The increase in Reticulocyte count% was in all groups, more in control group, but still with no significant difference between the three groups.

Conclusion: Dose of 160mg/kg/day of Piracetam showed more improvement than dose 80mg/kg/day in pallor and laboratory findings except Reticulocyte count% and more effective in reduction of frequency of transfusion, crises and hospitalisation.

KEY WORDS: Sickle Cell Anemia; Painful Sickle Cell Crises; Hemoglobin Level; Serum Ferritin; Piracetam

INTRODUCTION

The term sickle cell disease is used to describe a group of genetic life-long blood disorder characterized by the production of the abnormal hemoglobin S (Hb S).[1] The production of the abnormal hemoglobin S (HbS) results in red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications (damage to organs and tissues and results in painful episodes known as sickle cell "crises").[2]

Piracetam, (2-oxo-1-pyrrolidine acetamide), a cyclic derivative of gamma-amino butyrate, is an antisickling agent which has been used for the treatment of psycho senescent syndromes with no known side effects. It was considered as a possible therapeutic agent for sickle cell disease. It is a peripheral vasodilator and it has been shown to reverse and inhibit sickling. It acts to suppress platelet activity and prevent red cells dehydration.[3] The piracetam has significant amelioration effect on the clinical presentation of sickle cell disease as the numbers of crises, extent of hospitalization and blood requirement per year have been decreased. It was observed that the patient continued to feel better for several months even after discontinuation of piracetam.[4-5]

Piracetam has been reported to be an effective drug for the treatment of patients with sickle cell anemia during crises and as maintenance therapy.[6-7]

MATERIALS AND METHODS

The study was an intention-to-treat, open label, on controlled and non-randomized study. A local hospital research ethics committee approval was obtained for the patients study.

30 Paediatric patients of either sex were included in the study; their ages ranged from 5 to 16 years old and their weights ranged from 18 kg to 33 kg, they were collected from hematology clinic at Beni Suef University Hospital with sickle cell anemia. The study was conducted during the period of March to November/ 2009. An informed consent was obtained from parents or legal guardians.

Inclusion criteria

- Patients diagnosed as sickle cell anemia

Exclusion criteria

- Regular blood transfusion, whatever the indication
- Use of hydroxyurea
- Cognitive dysfunction that would hinder the reporting pain

Precautions

- In case of convulsions, severe kidney diseases and any allergies to piracetam

Patients in the study were evaluated by:

1. Detailed history and thorough clinical examination which include name, age, sex and present history, with concentration on pallor, jaundice, dark urine, family history (As positive consanguinity and similar condition in the family), frequency of packed red cells transfusion, painful crises, hospitalisation, medications, weight, splenomegaly and hepatomegaly.
2. Laboratory investigations in the form of CBC (Smear Air Dried 2 -Blood on EDTA kept at room temperature), Retics count % (Blood on EDTA at room temperature), serum ferritin level (ELISA method).

Patients were divided into three equal groups A, B and C. Each group consisted of (10) patients.
Group A: Represented patients who received 80 mg/kg/day Piracetam.
Group B: Represented patients who received 160 mg/kg/day Piracetam.
Group C: Represented (control group) patients who did not receive Piracetam.

All these patients were subjected to:

1. Thorough clinical examination every month for six months, which includes:

- General examination: Pallor, weight, dark urine and jaundice.
- Local examination (abdominal examination) for detection of improvement in organomegally (splenomegaly or hepatomegaly).

2. Laboratory investigations in the form of CBC, Retics count %, serum ferritin level every month for six months. Samples were taken early in the morning in the same day of every month for six months.
3. Reporting the frequency of their crises, hospitalization and packed red cells transfusion every month for six months.

Statistical Analysis

A two-way analysis of variance (ANOVA) test was used to compare the effect of different doses of piracetam on clinical data and laboratory investigations using SPSS V15.0 (SPSS Inc., Chicago, IL).

Data was summarized as mean and standard deviation (SD). p-value was calculated to compare between the groups, it is considered significant if < 0.05.

RESULTS

The study was conducted on 30 SCA patients, collected from Hematology Clinic at Beni Suif University Hospital. Out of 30 randomly selected cases, 16 cases (53.3%) were males, and 14 (47.6%) were females. Their ages ranged from 5 to16 years old. Their weights ranged from 18 to 33 kg. Group A mean (SD) age and weight are 9.6±2.3 years and 25.6±3.6 kg respectively. Group B mean (SD) age and weight are 8.5±2.8 years and 25.1±4.7 kg respectively. Group C mean (SD) age and weight are 10.9±3.5 years and 25.5±4.1 kg respectively. All enrolled patients (10 patients in each group) continued throughout the study with no dropouts.

In terms of age, weight and sex all groups were statistically homogenous. Also data analysis of all three groups before the beginning of study showed no significant differences concerning total hemoglobin concentration, reticulocytic count percentage, serum ferritin level, the frequency of previous crises, packed red cells transfusions and hospitalization.

Clinical data of all patients before inclusion in the study are shown in Table 1. Means and SD of the collected data after therapy of the three groups are shown in Table 2.

Table-1: Number of patients in each group presented with different clinical problems before inclusion in the study, n=10 in each group

	GROUP A (no.)	GROUP B (no.)	GROUP C (no.)
Splenomegaly	2	3	2
Hepatomegaly	5	5	4
Consanguinity (positive)	4	6	4
HCV infection	0	1	0
Pallor	5	7	6
Dark urine	0	0	0
Jaundice	2	1	1

The study showed that the effect of the high dose in group B has a better effect than that in group A which has better effect than the control group C on total hemoglobin concentration, reticulocytic count percentage, serum ferritin level, number of packed red cells transfusion, the number of previous crises and number of hospitalization.

In serum ferritin level, there was an insignificant increase after the Piracetam treatment in group B (p=0.379) and there was significant increase in group A (p=0.048) and C (p=0.039).

In reticulocytic count percentage, there was no significant increase after the Piracetam treatment in group A (p=0.853), B (p=0.610) and in C (p=0.477).

In total hemoglobin concentration, there was a significant increase after the Piracetam treatment in group B (p=0.001) and there was no significant increase in group A (p=0.168) and C (p=0.620).

In number of crises there was a significant decrease after the Piracetam treatment in group B (p<0.026) however there was insignificant decrease in A (p=0.818) and there was insignificant difference in C (p= 0.507).

Table-2: Means and SD of the collected data before and average of after 6 months therapy of the three groups after therapy, n=10 in each group

	Group A			Group B			Group C		
	Before	After	p-value	Before	After	p-value	Before	After	p-value
Number of crises/ 6 months	3.4±1.9	3.2±2.0	0.818	3.5±1.8	1.8±1.2	0.026*	2.6±1.9	3.1±1.4	0.507
Number of hospitalisation/ 6 months	2.1±1.2	1.5±1.1	0.255	1.7±1.1	0.8±0.8	0.045*	1.8±1.1	1.6±0.8	0.66
Number of packed red cells/ 6 months	1.7±1.1	1.1±0.9	0.184	1.6±1.1	0.7±0.8	0.049*	1.8±1.9	1.8±1.5	1.00
Hb (g/dl)	7.7±1.0	8.3±0.6	0.168	7.4±0.6	8.7±0.7	0.001***	7.8±1.2	7.6±0.7	0.620
Retics %	7.4±3.5	7.7±3.4	0.853	7.6±3.0	8.3±2.6	0.610	7.8±3.0	8.7±2.8	0.477
Ferritin (ng/ml)	396.2± 217.3	662.7± 332.7	0.048*	364.7± 201.8	455.0± 243.6	0.379	445.4± 246.4	759.9± 371.2	0.039*

* p < 0.05 ** p <0.01 *** p <0.001

In number of hospitalization there was a significant decrease after the Piracetam treatment in group B (p<0.045) however there was insignificant decrease in A (p=0.255) and there was insignificant difference in C (p=0.66).

In number of packed red cells transfusion, there was significant decrease after the Piracetam treatment in group B (p<0.049) however there was insignificant decrease in A (p=0.184) and there was insignificant difference in C (p= 1.00).

Table-3: p values of the comparison of Group A vs. Group C and Group B vs. Group C, n=10 in each group

	GROUP A vs. GROUP C	GROUP B vs. GROUP C
Ferritin	0.545	0.0430*
Retics count %	0.480	0.696
HB (g/dl)	0.028*	0.003**
Number of crises/6 months	0.895	0.038*
Number of hospitalisation/ 6 months	0.820	0.042*
Number of packed red cells transfusions /6 month	0.213	0.044*

* p < 0.05 ** p <0.01 *** p <0.001

After treatment, there was a significant difference between B and C groups regarding ferritin, hemoglobin, number of crises, number of hospitalisation and number of packed red cells transfusion with p-value 0.043, 0.003, 0.038, 0.042 and 0.044 respectively.

Also, after treatment, there was a significant difference between A and C groups regarding hemoglobin with p-value 0.028.

However, there was no significant difference between A and C groups and B and C groups, after the six months therapy regarding reticulocytic count % with p-value 0.480 and 0.696 respectively.

There were no reports of toxicity, sickness or adverse effects with piracetam treatment through the study except one patient in group B who experienced headache which was transient.

DISCUSSION

The aim of the study was to evaluate the effect of Piracetam on the clinical features and the hematological parameters of patients of sickle cell anemia and to estimate the dose of choice for better effect, 80mg/kg/day or 160mg/kg/day.

Descriptive clinical statistics of patients in all six months of the study showed that there were significant decrease number of crises, number of hospitalization and number of packed red cells transfusion in group B compared to control group. On the other hand there were insignificant decreases in group A compared to control group according to the same parameters.

These results are in consistence with an earlier study which tested micro-sieving diluted suspensions of oxygenated sickle cell anemia (HbSS) cells on polycarbonate filters shows that piracetam improves the red cell deformability in-vitro. Also that study detected that in-vivo an oral intake of 160 mg/kg/day divided in four doses enhances the HbSS cell deformability as actively as it did in-vitro experiments, the drug was also able partially to restore the impaired deformability of physiologically deoxygenated HbSS cells so these findings are consistent with the results of clinical trials, which show that continuous treatment with piracetam reduces the incidence of vaso-occlusive crises in patients with sickle cell anemia.[8]

These results also are similar to an earlier study which reported that piracetam was considered as a possible therapeutic agent for sickle cell disease as it was shown that it had an antisickling effect, both in-vivo and in-vitro.[4] This study reported the effect of piracetam in two groups of children suffering from sickle cell disease ranging in age from 3-6 to 6-12 years and the follow-up was for a period of up to 1 year in 13 centers in 10 different regions of Saudi Arabia. Data analysis showed that the clinical severity of the disease, the number of crises, the extent of hospitalization and the blood transfusion requirements significantly decreased during piracetam treatment with ($p < 0.001$), though no statistically significant changes occurred in the placebo group.[4]

Another Study found that piracetam significantly reduced the incidence of sickle cell crisis compared with placebo (average number of crises per month per patient: 0.89 with piracetam vs. 1.85 with placebo; p value<0.05), which by that results confirms the results of the study represented here.[9]

On the other hand the results of the study presented in this study oppose a study which evaluated the drug in a double-blind crossed placebo-controlled clinical trial in 73 children and adolescents suffering from moderate to severe painful crises for 13 months then reported that the pain score in the second semester of the study - both in the experimental and in the control groups - was significantly smaller than that in the first semester, so they concluded that piracetam was found to be ineffective in the prevention of painful crises; a powerful placebo effect due to adequate patient care was demonstrated.[10]

Having a short life span of irreversible sickled cells (ISC), the severity of hemolytic process is directly related to the number of ISC in the circulation.[11]

Most of the in-vitro studies with piracetam have shown that it interferes with HbS polymerisation, causes a reduction in blood viscosity, an increase in erythrocyte elasticity, inhibits platelet aggregation[8, 12] and has the potential for inhibition and a reversal of the process of sickling of erythrocytes and so reduces the RBCs destruction.[6]

These previous concepts agree with the results in this study which showed *a* significant increase in the hemoglobin level in groups A and B compared to control group. These indicate an improvement in group A and B patients with a better effect in Group B.

Also this study results agreed with a study that was conducted on twenty-two sickle cell anemia children between 5 and 18 years old using piracetam in a dose of 80 mg/kg/day (I.V), reported that the variation in hemoglobin though not statistically significant, suggest a moderate involution in the hemolytic process.[7]

In contrary another study reported that, in the levels of the hematological parameters, no significant changes were documented in the two groups treated with piracetam comparing with the control group.[4]

Ferritin concentrations increase drastically in the presence of an infection or cancer; this is necessary to counter the infective agent's attempt to bind iron from the host's tissue[13]

The concentration of ferritin has been shown to increase in response to stresses such as anoxia[14] and this implies that it is an acute phase protein.[15]

As transfusion therapy has become more widely used in the treatment of patients with sickle cell disease (SCD), iron overload has become increasingly more common.[16]

Serum ferritin, serum iron binding capacity, and iron stores are normal or moderately elevated during childhood unless repeated transfusions have been given. Elevation of serum ferritin during vaso-occlusive crises has been reported.[17] In this study no direct information from clinical trials about the effect of piracetam on serum ferritin level in patients of sickle cell anemia was found.

However the previous concepts agreed with the clinical statistics of patients in all six months of the study which showed that groups A and B did not increase the serum ferritin level like the control group with a superior effect by group B (which showed significant decrease in number of packed red cells transfusion after treatment). These results showed that serum ferritin level in group A and B increased after therapy but in lower rate than control group and this is an indication to improvement in group A and B than control group. There was an insignificant increase after the Piracetam treatment in group B but there was significant increase in group A and C, so these indicate a better and effective effect in Group B.

Also, Comparison between before and after therapy according to serum ferritin for group A and group B, showed that there was significant increase in group A and no significant increase in group B.

Piracetam (400 mg/kg) has also been reported to have beneficial effects on the maturation of blood cells in rats. Increased iron incorporation into newly formed red blood cells, increased reticulocytes (a red cell precursor), and increased maturation of erythroblasts (a red cell progenitor cell line located in bone marrow) were all indications of piracetam-induced erythropoiesis (the generation of new red blood cells).[18] In contrary our study reported that there was no significant difference between groups before and after therapy regarding reticulocytic percentage also there was no significant difference between the three groups after the treatment, this may be due to that the administered dose here is much lower than that therapeutic dose, 400 mg/kg, which was used in that study.

The insignificant differences observed in the study presented in our study regarding reticulocytic percentage are in agreement with a study reported that, in the levels of the hematological parameters no significant changes were documented in the two groups treated with piracetam comparing with the control group.[4]

Piracetam has been found to have very few side effects, and those it has are typically "few, mild, and transient".[19] A large-scale, 12-week trial of high-dose piracetam found no adverse effects occurred in the group taking piracetam as compared to the placebo group.[20] Many other studies have likewise found piracetam to be well-tolerated.[19, 21-24]

These trials results agreed with our study which showed that there were no reports of toxicity or adverse effects with piracetam other than one patient in group B who experienced headache which was transient.

The study reported that there was an improvement in the quality of life (e.g. absence from school, general activity and satisfaction), the pallor and general health of treated patients. This is in agreement with reports of several studies which have been done using piracetam in the treatment of sickle cell anemia patients.[25]

Finally the present work shows that prescribing Piracetam has a very good effect on the sickle cell anemia and 160 mg/kg/day dose of Piracetam is better and more effective than 80 mg/kg/day dose in all laboratory parameters and in

reduction of packed red cells transfusion frequency, number of crises and hospitalisation.

CONCLUSION

The sickle cell anemia patients in groups A and B who received dose 80 mg\kg\day of Piracetam and dose 160mg\kg\day respectively showed more improvement than control group (in hemoglobin level, serum ferritin, pallor, frequency of packed red cells transfusion, number of crises and hospitalization).

The dose 160 mg/kg/day of Piracetam was more effective than dose 80 mg/kg/day and Piracetam has a significant role in improving general health of patients. Hence, we concluded that to obtain the desired effect of Piracetam, it is recommended to be taken as a maintenance dose in a relatively high concentration (160 mg/kg/day). Further wider studies are needed to confirm the results of the presented study.

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Source of Support: Nil
Conflict of interest: None declared