

Clinical Study of the Efficiency of Poetam in the Treatment of the Anemic Syndrome in Pubertal Uterine Hemorrhages

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Clinical study of the efficiency of Poetam (affinity-purified antibodies to recombinant human erythropoietin) in the treatment of anemia in patients with pubertal uterine hemorrhages proved that combined therapy with Poetam and iron preparation normalized erythron parameters, structural and metabolic status of erythrocytes, and ferrokinetic parameters of the peripheral blood sooner than monotherapy with Poetam or sorbifer.

Key Words: *pubertal uterine hemorrhages; posthemorrhagic iron deficiency anemia; erythron; Poetam*

Pubertal uterine hemorrhages (PUH) are a pressing problem of pediatric gynecology. Uterine hemorrhage is the most prevalent gynecological disease (10-37%) and most frequent cause of gynecological consultations for girls during sexual maturation. Disorders in the menstrual cycle persist later in 85% of patients with a history of PUH, 82% of these patients develop primary sterility, 8% have miscarriages and are in general at a high risk of hyperplastic processes in the endometrium and breast cancer [1,4].

Protracted and relapsing course of the disease and complications in uterine hemorrhages are responsible for severe clinical status of children requiring long-term treatment. The main complication of PUH in adolescents is the development of chronic posthemorrhagic iron deficiency anemia (IDA) causing dysadaptation and decrease in working capacity. Anemia in PUH augments disorders in hemo-

stasis system, hormone homeostasis, induces immunodeficiency.

Therapy with iron preparations aimed at normalization of peripheral blood parameters and compensation for tissue iron reserves is the main method for the treatment of IDA. Ferrotherapy should be sufficiently long for complete correction of not only anemia, but also tissue iron deficiency. Iron preparations for parenteral treatment are contraindicated for children. Hemotransfusions during pubertal period are undesirable because of possible immediate and remote immune complications. This necessitates the search and development of new highly effective methods for correction of disorders developing in blood system in uterine hemorrhages, which is one of the tasks of protection of reproductive health in adolescent girls [2,6].

The therapeutic use of antibodies is a perspective actively developing trend in pharmacology. Antibodies are used mainly as inhibitors (blockers) of functions of respective molecules. A series of experimental and clinical studies carried out in Russia showed that antibodies can be used for the

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regulation of activity of the respective molecule. An obligatory condition for this is special technology of antibody treatment, due to which they exhibit activity upon oral treatment in superlow doses [5]. Poetam preparation represents affinity-purified antibodies to recombinant human erythropoietin. According to experimental findings, one of the main mechanisms of erythropoiesis activation under the effect of Poetam is the increase of endogenous production of erythropoietin [5]. The drug is allowed for medical use and is referred to pharmacotherapeutic group of hemopoiesis stimulators.

We evaluated the clinical efficiency of Poetam in the treatment of anemic syndrome in PUH.

MATERIALS AND METHODS

Controlled comparative randomized clinical study of the efficiency and safety of Poetam in the treatment of anemic syndrome in girls suffering from uterine hemorrhages was carried out at Institute of Pharmacology, Gynecological Clinic of Department of Obstetrics and Gynecology of Siberian State Medical University, and Municipal Center for Family Planning.

The study was carried out in 90 patients aged 13-18 years with confirmed diagnosis of PUH complicated by the development of severe and medium-severe IDA.

The patients were distributed into the main group (Poetam), reference group (Poetam and sorbifer), and sorbifer group. Poetam for clinical studies was offered by Materia Medica Holding. Each group consisted of 30 patients; the groups were similar by the severity of anemia. Placebo group was also formed, but inefficiency of treatment and deterioration of the general status in IDA patients receiving only placebo precluded continuation of this variant of therapy in pediatric patients. For this reason we formed a sorbifer group in our study: the patients received placebo and an iron preparation (sorbifer).

The study was carried out for 5 weeks. Each patient visited the doctor 5 times: before the study, at the beginning of treatment, and after 1, 2, and 3 weeks of treatment. Poetam and placebo were taken at the same intervals: 8 tablets during week 1, 6 during week 2, and 4 during week 3; sorbifer was taken 1 tablet twice a day.

Objective criteria for evaluating the clinical efficiency of Poetam as a drug for the treatment of anemia in PUH were as follows: peripheral blood values (erythrocytes, reticulocytes, hemoglobin, color index, hematocrit, mean erythrocyte volume, mean concentration of hemoglobin in an erythrocyte, mean content of hemoglobin in an erythro-

cyte, mean corpuscular concentration of hemoglobin in an erythrocyte — analyzed in an Abacus hematological analyzer, Diatron), erythrocyte concentrations of lipoprotein complex and SH groups (evaluated by routine methods), iron metabolism parameters (serum iron, total serum iron-binding capacity, transferrin, and ferritin; evaluated using Cormay and Lahema standard diagnostic kits).

The safety of Poetam treatment was evaluated by subjective (complaints, common well-being) and objective (examination, blood and urine tests, biochemical blood tests, ECG, ultrasonic examination of abdominal organs) status of the patients, and status of the underlying disease (gynecological examination, ultrasonic examination of pelvic organs). Presence and type of side effects during active therapy, relationship between side effects and drug intake, and time of their manifestations were taken into consideration.

The data were processed statistically using methods of variation statistics.

RESULTS

By pharmacological effect Poetam is a hemopoiesis stimulator. Its efficiency as an antianemic agent was evaluated by the effect on the erythron morphology and function and ferrokinetics in comparison with traditional therapy with iron preparation.

The maximum blood content of reticulocytes (5-6-fold increased vs. the initial level, mean content 64‰) was recorded on day 14 of therapy in patients treated with Poetam. Later a trend to a reduction of this parameter was observed, but the count of reticulocytes on day 21 3-fold surpassed the initial level ($p < 0.003$). In the sorbifer group the content of reticulocytes only reached the upper threshold normal value (14-16‰; Table 1).

The count of erythrocytes in the peripheral blood increased 1.5 times during Poetam therapy (from $3.36-3.48 \times 10^{12}/\text{liter}$ to $4.84-4.89 \times 10^{12}/\text{liter}$; $p < 0.005$), while in the sorbifer group just a trend to an increase in erythrocyte level was observed (from $3.13 \times 10^{12}/\text{liter}$ to $3.82 \times 10^{12}/\text{liter}$). By the end of the study erythrocyte count in Poetam group was 20-25% higher ($p = 0.0012$) than in sorbifer group (Table 1).

Hemoglobin level did not increase in patients receiving Poetam monotherapy and even exhibited a trend to decrease, while treatment with iron preparation (Poetam+sorbifer or sorbifer+placebo) resulted in a significant increase in hemoglobin level. The best final value ($136.40 \pm 0.04 \text{ g/liter}$) was observed in the group treated by Poetam and iron preparation (Table 1).

TABLE 1. Morphology and Function of the Erythron in IDA Patients with PUH during Treatment by Different Methods ($X \pm m$)

Parameter, group	Before therapy	Day of therapy		
		7	14	21
Erythrocytes, $\times 10^{12}/\text{liter}$				
Poetam	3.36 \pm 0.40	3.54 \pm 0.02	4.42 \pm 0.06 ⁺	4.84 \pm 0.02 ⁺
Poetam+sorbifer	3.48 \pm 0.20	3.94 \pm 0.30	4.62 \pm 0.40 ⁺	4.89 \pm 0.30 ⁺
sorbifer+placebo	3.13 \pm 0.04	3.46 \pm 0.04	3.74 \pm 0.02	3.82 \pm 0.06
Reticulocytes, ‰				
Poetam	10.00 \pm 0.45	30.00 \pm 0.26	64.00 \pm 0.18 ⁺⁺	34.00 \pm 0.24 ⁺⁺
Poetam+sorbifer	11.00 \pm 0.25	34.00 \pm 0.15 ⁺	58.00 \pm 0.21 ⁺	38.00 \pm 0.16 ⁺
sorbifer+placebo	10.00 \pm 0.6	16.00 \pm 0.15	14.00 \pm 0.24	12.00 \pm 0.08
Hemoglobin, g/liter				
Poetam	97.40 \pm 1.22	100.40 \pm 0.01	96.60 \pm 0.04 ⁺⁺	94.30 \pm 0.02 ⁺⁺
Poetam+sorbifer	96.30 \pm 0.18	106.60 \pm 0.02	124.10 \pm 0.01 ⁺	136.40 \pm 0.04 ⁺
sorbifer+placebo	98.20 \pm 1.14	104.20 \pm 0.02	116.00 \pm 0.01	120.60 \pm 0.04
Hematocrit, %				
Poetam	28.3 \pm 0.1	30.8 \pm 0.2	31.1 \pm 0.5	32.00 \pm 0.03
Poetam+sorbifer	29.10 \pm 0.01	31.40 \pm 0.02	31.20 \pm 0.02	32.10 \pm 0.01
sorbifer+placebo	28.80 \pm 0.02	30.60 \pm 0.06	31.40 \pm 0.02	32.40 \pm 0.04
Color index				
Poetam	0.800 \pm 0.004	0.780 \pm 0.015 ⁺⁺	0.700 \pm 0.006 ⁺⁺	0.680 \pm 0.002 ⁺⁺
Poetam+sorbifer	0.820 \pm 0.002	0.860 \pm 0.004	0.960 \pm 0.001	1.000 \pm 0.006
sorbifer+placebo	0.820 \pm 0.006	0.900 \pm 0.002	0.980 \pm 0.003	0.980 \pm 0.006
Mean erythrocyte volume, fl				
Poetam	62.0 \pm 0.1	72.0 \pm 0.3	74.0 \pm 0.1	84.0 \pm 0.2
Poetam+sorbifer	58.0 \pm 0.3	72.0 \pm 0.4	78.0 \pm 0.1 ⁺	88.0 \pm 0.6 ⁺
sorbifer+placebo	64.0 \pm 0.3	68.0 \pm 0.5	70.0 \pm 0.1	72.0 \pm 0.2
MCH, pg				
Poetam	23.3 \pm 0.2	24.3 \pm 0.1	24.7 \pm 0.2 [*]	24.4 \pm 0.3 ⁺⁺
Poetam+sorbifer	24.3 \pm 0.1	26.4 \pm 0.2	28.4 \pm 0.3 ⁺	30.6 \pm 0.3 ⁺
sorbifer+placebo	23.6 \pm 0.4	25.7 \pm 0.1	24.7 \pm 0.4	26.4 \pm 0.1
MCHC, g/dl				
Poetam	358 \pm 4	369 \pm 6	370 \pm 5	358 \pm 4 [*]
Poetam+sorbifer	362 \pm 3	368 \pm 2 ⁺	374 \pm 8	385 \pm 2 ⁺
sorbifer+placebo	356 \pm 5	360 \pm 3	368 \pm 2	360 \pm 7

Note. $p < 0.05$ compared to *Poetam+sorbifer group, +sorbifer+placebo group. MCH: mean content of hemoglobin in erythrocyte; MCHC: mean corpuscular hemoglobin concentration.

Poetam only stimulates erythropoiesis processes, because it consists of affinity purified antibodies to recombinant erythropoietin and contains no iron essential for hemoglobin synthesis. The study was carried out in patients with IDA, and therefore a significant increment in the count of red blood cells and decreased level of hemoglobin were observed after Poetam monotherapy. The production of these erythrocytes was confirmed by evaluation of the color index: Poetam monotherapy led to a significant increase in hypochromatism (from 0.800 \pm 0.004 to 0.68 \pm 0.02; Table 1).

The best therapeutic effect was attained in the group of patients receiving Poetam and sorbifer: by the end of observation these patients presented with the highest counts of reticulocytes and erythrocytes, their color index being 1.000 \pm 0.006. Normal hemoglobin level was attained in these patients as soon as after 2 weeks of therapy (Table 1).

Patients treated with Poetam developed a significant ($p < 0.005$) increase in the mean volume of erythrocytes during therapy. Histograms of incidence of erythrocytes of different volume show a decrease ($p = 0.0022$) in anisocytosis degree. The mean volume of erythrocytes showed

TABLE 2. Ferrokinetic and Cytochemical Parameters in IDA Patients with PUH during Treatment by Different Methods ($X \pm m$)

Parameter, group	Before therapy	Day of therapy		
		7	14	21
Serum iron, mmol/liter				
Poetam	10.40±0.02	10.00±0.04*	9.20±0.01**	9.00±0.03**
Poetam+sorbifer	10.20±0.01	13.80±0.03+	16.80±0.01	17.60±0.08
sorbifer+placebo	10.10±0.04	11.40±0.01	16.20±0.05	16.60±0.04
TICS, μ mol/liter				
Poetam	56.0±0.2	63.0±0.5**	63.5±0.1	63.4±0.2**
Poetam+sorbifer	54.0±0.1	60.0±0.3	62.4±0.6	66.8±0.3
sorbifer+placebo	53.0±0.1	60.0±0.3	62.5±0.1	65.6±0.3
SICS, μ mol/liter				
Poetam	33.7±1.3	34.5±1.2	32.5±0.8	34.5±0.2
Poetam+sorbifer	32.8±0.6	33.4±1.3	35.8±1.2	36.8±1.5
sorbifer+placebo	33.3±1.0	33.8±0.6	34.6±1.4	35.2±1.6
Ferritin, μ g/liter				
Poetam	45.1±0.6	45.5±0.4	46.0±0.5	46.0±0.6
Poetam+sorbifer	44.6±0.3	45.8±0.8	46.1±0.2	47.8±0.1
sorbifer+placebo	44.8±0.2	45.4±0.6	45.8±0.5	46.2±0.4
Sulfhydryl groups, arb. units				
Poetam	0.263±0.140	0.278±0.130	0.318±0.060	0.352±0.240
Poetam+sorbifer	0.264±0.120	0.284±0.040	0.324±0.120	0.364±0.160
sorbifer+placebo	0.265±0.080	0.272±0.100	0.312±0.060	0.318±0.140
Lipoproteins, arb. units				
Poetam	0.620±0.012	0.632±0.015	0.696±0.014	0.726±0.014
Poetam+sorbifer	0.620±0.024	0.634±0.024	0.699±0.018	0.732±0.018
sorbifer+placebo	0.618±0.014	0.626±0.012	0.684±0.015	0.688±0.016

Note. SICS: saturating iron-binding capacity of the serum; TICS: total iron-binding capacity of the serum. $p < 0.05$ compared to: *Poetam+sorbifer group, +sorbifer+placebo group.

just a trend to an increase in patients treated with sorbifer, with retained abnormal cell populations (microcytes).

The mean content of hemoglobin per erythrocyte increased significantly in patients treated with sorbifer. The best result was observed in patients receiving a combination of Poetam and sorbifer. The mean corpuscular concentration of hemoglobin reflects the true saturation of erythrocyte with hemoglobin, because hemoglobin content in an erythrocyte depends on cell volume, while corpuscular concentration of hemoglobin does not depend on this parameter. A significant increase in this characteristic was observed in patients receiving combined treatment with Poetam and sorbifer (Table 1).

Parameters of iron metabolism (serum iron, total iron-binding capacity of the serum, transferrin, and ferritin) were evaluated in patients receiving different antianemic treatments. The best ferrokinetic

values were observed in the group treated with a combination of Poetam and sorbifer (Table 2).

Qualitative characteristics of the erythron morphology and function were no less interesting than its quantitative characteristics; it could be evaluated by the concentrations of sulfhydryl groups and lipoproteins in erythrocytes [3]. Analysis of these characteristics revealed a positive effect of Poetam, which normalized erythrocyte membranes, due to which cell resistance to negative effects of hypoxia increased and their gas-transporting function improved (Table 2).

In order to obtain statistically significant results of treatment efficiency evaluation, all red blood values in anemias of different severity were analyzed. Poetam effect on the erythron morphology and function and iron metabolism were observed in IDA of any severity. The efficiency of Poetam therapy was significantly higher in patients with more severe anemia (Fig. 1).

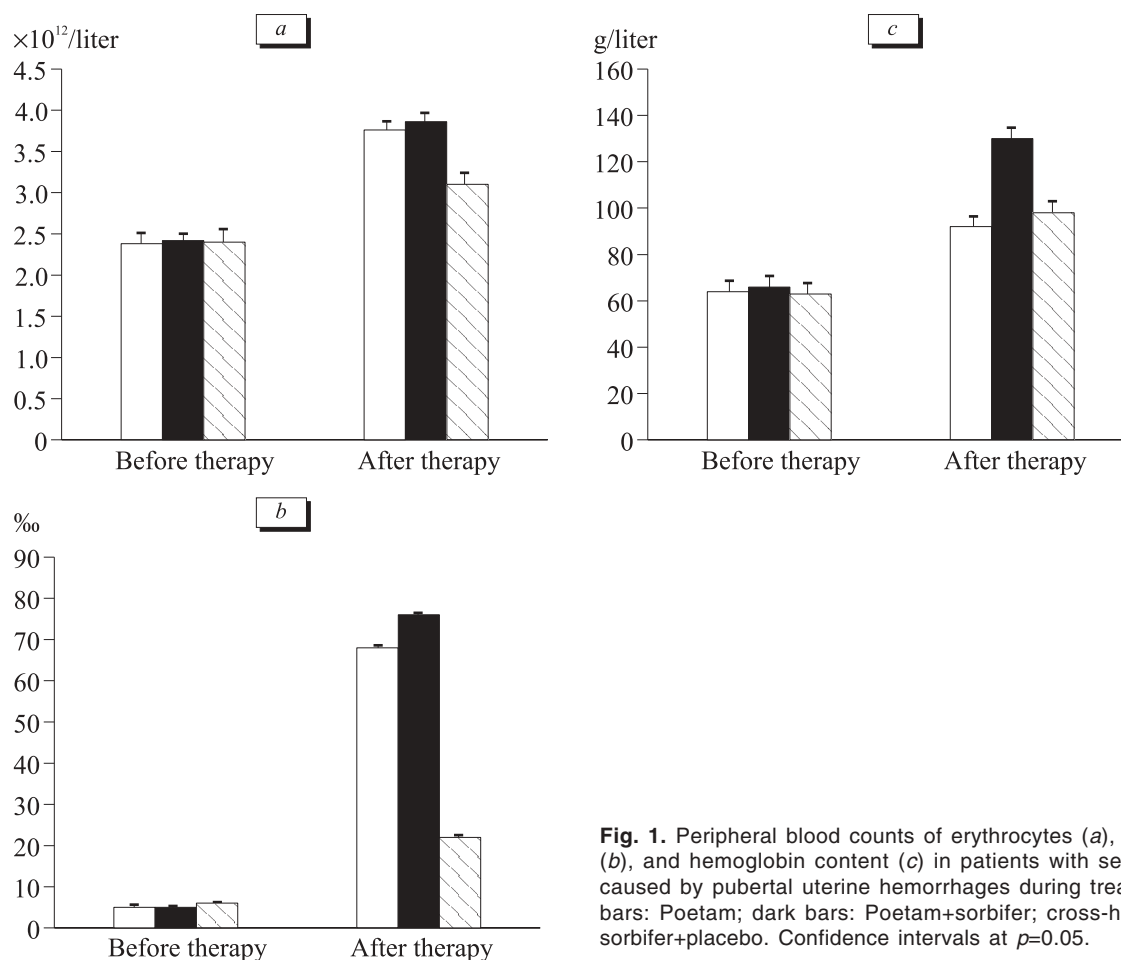


Fig. 1. Peripheral blood counts of erythrocytes (a), reticulocytes (b), and hemoglobin content (c) in patients with severe anemia caused by pubertal uterine hemorrhages during treatment. Light bars: Poetam; dark bars: Poetam+sorbifer; cross-hatched bars: sorbifer+placebo. Confidence intervals at $p=0.05$.

In none of the patients side effects were observed. No deviations in the somatic status were detected during 3-week study and subsequent 6-week observation. This was indirectly confirmed by the absence of manifest changes, evaluated by biochemical tests, common analyses of the urine and peripheral blood. Hence, variants of therapy including Poetam proved to be safe for the patients.

The findings indicate that Poetam improved significantly the efficiency of treatment in patients with anemic syndrome resultant from uterine hemorrhages.

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