Influence of Poetam Preparation on the State of Autonomic Nervous System in Patients with Severe Anemia Caused by Dysfunctional Uterine Bleedings

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The use of poetam in the treatment of anemia in patients with dysfunctional uterine bleedings promotes recovery of the major parameters of the tone and reactivity of the autonomic nervous system.

Key Words: *pubertal uterine bleeding; posthemorrhagic iron-deficient anemia; erythron; autonomic nervous system; poetam*

Pubertal dysfunctional uterine bleedings (UB) rank first in the structure of gynecological pathology in adolescents [3-5]. An important role in the etiology of UB is played by autonomic nervous system (ANS) disturbances [1,6]. The main complication of UB is the development of chronic posthemorrhagic anemia, which determines poor general state of the adolescent. Taking into account the regulatory effect of ANS on the erythropoiesis processes and immune status, the relationship between ANS and the blood system in pubertal dysfunctional UB seems to be a very interesting problem.

Here we evaluated the effect of preparation containing ultralow doses of antibodies to erythropoietin administered to patients with severe iron-deficient anemia caused by pubertal UB on the state of ANS.

MATERIALS AND METHODS

We examined 90 adolescent girls. The main group included 60 patients with UB complicated by severe anemia, the control group consisted of 30 age-matched healthy girls without menstrual cycle disturbances. Inclusion criteria for the main group were: age 13-18 years, severe iron-deficient anemia (hemoglobin <70 g/liter), compensated state, no need in urgent hemotransfusion, the absence of active UB, treatment with sex steroids for prophylactics of bleeding relapse. The patients were divided into 2 groups, each group included 30 girls. Group 1 patients received iron preparations only; group 2 patients received iron preparation in combination with poetam, a preparation containing ultralow doses of antibodies. Sorbifer (Egis, one tablet contains 320 mg iron sulfate) was used as the iron preparation. Sorbifer was administered in a dose of 1 tablets 2 times a day. Poetam (Materia Medica Holding) was administered in a dose of 1 tablet 3 times a day with equal time interval irrespective of meals.

The duration of treatment was 6 weeks. The patients were examined before, at the start, and then weekly during the treatment. The state of ANS was evaluated before and after antianemic therapy.

Scheme of examination for detection of symptoms of autonomic disturbances [1] was used for detection of symptoms of autonomic disturbances in patients with pubertal UB and in controls. In healthy individuals, the score did not exceed 25. Higher scores attest to the presence of autonomic dystonia syndrome (ADS). Kerdo autonomic index was calculated for evaluation of the tone of the autonomic nervous system. The state of ANS (sympathetic and parasympathetic influ-

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ences) was evaluated by cardiointervalography using an Ankar-131 cardioanalyzer. Using the cardiointervalogram, we evaluated the state of the sympathetic nervous system (by mode amplitude), parasympathetic nervous system (dispersion value or variation range), strain and centralization of regulatory mechanisms of ANS (by strain index), reactivity of ANS, and effect of humoral factors on the state of ANS.

The significance of differences between the compared parameters was evaluated using Student's *t* test (in case of normal distribution of data) and Mann—Whitney *U* test (in cases when the data did not fit to normal distribution).

RESULTS

Screening diagnostics and ADS scoring showed that the severity of autonomic disturbances was high in patients with severe anemia caused by UB (mean score was 46 *vs*. 18 in the control group). Estimation of Kerno index in patients with UB revealed increased sympathetic tone in 66%, increased parasympathetic tone in 28%, and normotonia in 16% patients. In the control group, 74% girls were normotonics and 10 and 6% girls were hyperparasympathetics and hypersympathetics, respectively.

Parameters of cardiointervalogram in the control group primarily corresponded to normotonic type of *RR* interval distribution curve. The strain index reflected a balanced state of the central and autonomic mechanisms of heart rhythm regulation, while the values of autonomic rhythm index and autonomic regulation index attested to relative balance between activity of the sympathetic and parasympathetic systems. Parameters of rhythmograms in patients with anemia caused by UB considerably differed from the control. Heart rhythm parameters in patients with severe anemia attested to enhanced sympathetic and attenuated vagus influences: the spectrum of *RR* intervals was shifted towards lower values, variation range was reduced, while mode amplitude, index of autonomic regulation and autonomic rhythm index were increased.

Only the data of patients completing the treatment were used for the analysis of clinical efficiency of the two variants of antianemic therapy. In group 2, normalization of the erythron parameters and pharmacokinetic parameters of the peripheral blood and improvement of qualitative cytochemical and morphological characteristics of erythrocytes were observed earlier ($p<0.05$). In group 1, these parameters attained the normal values only by the end of the study.

Screening diagnostics and ADS scoring showed that the severity of autonomic disturbances after completion of antianemic therapy remained high in group 1 patients: mean score was 32 *vs*. 21 in group 2 and 18 in the control group. Thus, ADS persisted in group 1 patients and became less pronounced in group 2 patients.

Evaluation of the autonomic Kerdo index in group 1 showed that increased sympathetic tone was observed in 58% patients, increased parasympathetic tone in 24%, and normotony in only 18% patients. In group 2, normotony was observed in 68% patients, increased parasympathetic tone in 18% and increased sympathetic tone in 14% patients.

The variation range of *RR* intervals (marker of reduced tone of the parasympathetic nervous system) was significantly reduced ($p<0.05$), while the mode amplitude (marker of increased tone of the sympathetic nervous system) was significantly elevated ($p<0.05$) in patients with dysfunctional pubertal UB complicated by severe iron-deficient anemia before the start of treatment compared to the control. Index of strain of regulatory systems (reflects the interrelations between the sympathetic and parasympathetic systems) was also increased in this group compared to girls without menstrual cycle disturbances. Analysis of cardiointervalogram parameters after completion of the study showed that the variation range in group 1 patients remained low compared to the control, while the mode amplitude was high, which suggests that sympathetic influences still predominated in these patients. In group 2, the distribution of *RR* intervals by the end of treatment approached the normotonic curve. The

TABLE 1. Dynamics of Heart Rhythm Variability in Patients with Pubertal UB Receiving Different Variants of Antianemic Therapy ($M\pm m$)

Parameter	Before treatment	After treatment	
		group 1	group 2
Variation range, sec	0.19±0.02	0.24±0.03	0.48±0.06*
Mode amplitude, %	72.6±14.1	76.2±12.6	42.4±9.5*
Index of strain of regulatory systems	804.3±22.7	796.2±18.0	324.8±12.6*

Note. *$p<0.05$ compared to values before treatment.

values of the strain index, autonomic rhythm index, and index of autonomic regulation indicated recovery of the balance between activities of the sympathetic and parasympathetic systems. The dynamics of heart rhythm parameters in group 2 patients attested to attenuation of the sympathetic tone and strengthening of the vagus influences: shift in the spectrum of *RR* intervals towards higher values, widening of the variation range, decrease in mode amplitude and index of strain of the regulatory systems (Table 1).

It is now proven that ANS directly and indirectly regulates the processes of proliferation and differentiation of hemopoietic precursor cells [2]. In light of this, the results of studies of different variants of antianemic therapy in patients with dysfunctional UB can be of scientific and practical importance for better understanding of the relationships between ANS and blood system. The persistent hypersympaticotonia and reduced reactivity of ANS in monotherapy with IP probably determined longer course of treatment compared to that in combined treatment with IP and preparations containing ultralow doses of antibodies to erythropoietin.

Thus, the use of poetam, a preparation containing ultralow doses of antibodies to erythropoietin, in the therapy of severe anemia caused by pubertal dysfunctional UB improves patient's quality of life, among other things due to proven indirect modulation of the tone and reactivity of ANS.

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