

Prediction of Thrombotic Complications in Children with Acute Kidney Injury

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Annotation:

Hypercoagulability syndrome occupies one of the leading places in the development of acute kidney injury in children. Methods of intensive therapy with glucocorticosteroids and cytostatics has an effect on haemostasis, but it is insufficiently studied evaluation of the effect of pulse therapy on platelet-vascular haemostasis. Such an evaluation will allow the detection and prevention of possible thrombotic or thrombohemorrhagic disorders that are induced or exacerbated by pulse therapy.

Key words: glucocorticosteroids, hypercoagulability, platelet-vascular haemostasis, pulse therapy programmes

Introduction. 20 patients with nephrotic syndrome were studied. They were divided into 2 groups. In the first group, pulse therapy with methylprednisolone was performed, and in the second group cyclophosphan was added to it. Platelet aggregation function was investigated in all patients. Pulse therapy and combined pulse therapy had a pronounced anti-inflammatory and immunosuppressive effect and led to a decrease in the increased indices of platelet-vascular haemostasis. The study showed that intensive therapy with megadoses of glucocorticosteroids and cyclophosphan, in addition to a positive effect on platelet-vascular haemostasis, can have its own activating effect on it, which is a risk factor for the development of thrombotic complications in the nearest terms after the end of pulse therapy.

Hypercoagulability syndrome is one of the leading factors in the development of nephrotic syndrome (NS) and can be the initial manifestation of it in children, as well as the cause of death [3, 6]. Platelet activation by antiplatelet antibodies, immune complexes, biologically active substances with the subsequent development of the platelet reaction cascade also plays an important role in the development of microcirculatory disorders, microthrombosis, ischaemia and tissue damage [1,4]. Current therapy of nephrotic syndrome in children, including intensive therapy with glucocorticosteroids (GCS) and cytostatics - cyclophosphane (CP), along with pronounced anti-

inflammatory and immunosuppressive effects, allowing to achieve a significant improvement in the condition of patients and improve their life prognosis, can also affect haemostasis [7], but the nature of this effect is ambiguous. There are data that the use of GCS leads to increased consumption and activation of a number of coagulation factors, decreased synthesis of prostacyclin by the vascular wall, increased adhesion-aggregation function of platelets [9], and the use of cytostatics causes a decrease in plasma fibrinolytic activity, activity of anti-thycoagulants, inhibition of thrombocytopoiesis, endothelial damage [1, 8]. At the same time, GCS have membrane-stabilising effect, inhibit the synthesis and secretion of mediators and inflammatory inducers with prothrombotic effect [5]. В ряде работ отмечена нормализация коагуляционных тестов при лечении ГКС [2]. Циклофосфан также действует на клетки-медиаторы сосудистого повреждения, а его протромботическое действие подтверждено не всеми исследователями [2, 4, 9].

Thus, the widespread use of GCS and CHF, particularly intensive care methods, in the treatment of nephrotic syndrome in children has an impact on the blood coagulation system. However, to date, the evaluation of the effect of pulse therapy on platelet-vascular haemostasis has not been sufficiently studied. Such an evaluation will allow to detect and prevent possible thrombotic or thrombohemorrhagic disorders that are induced or aggravated by pulse therapy, and thus improve the effectiveness of treatment of patients with nephrotic syndrome.

Purpose of the study. To reveal the peculiarities of changes in the parameters of thrombocyte-vascular haemostasis in patients with nephrotic syndrome, to evaluate the dynamics of their changes against the background of different programmes of pulse therapy with megadoses of GCS and CF.

Objectives: To evaluate the parameters of thrombocyte-vascular haemostasis in patients with NS before and after pulse therapy with megadoses of GCS and CF. To conduct a comparative analysis of the effect of different pulse therapy programmes on the parameters of thrombocyte-vascular haemostasis in patients with NS. To evaluate the risk of adverse events from the side of primary haemostasis system in patients with NS depending on the scheme of the conducted intensive therapy.

Material and Methods: 98 patients with NS undergoing inpatient treatment and dispensary observation in the Department of Paediatric Nephrology of Tashkent Nephrology Hospital in the period of 2009-2012 were included in the study. A group of patients with ineffectiveness of standard therapy, high activity of the process was selected for the use of pulse therapy with the use of GCS and cytostatic immunosuppressants. Criteria for inclusion in the study groups for pulse therapy: Presence of high proteinuria, polyserositis, hypoalbuminemia. High fibrinolytic activity. Ineffectiveness of standard therapy. The above criteria were met by 60 NS patients, the control group consisted of 20 healthy children. All patients included in the study groups, at the moment of admission to the clinic (before intensive care) received prednisolone at a dose of 2 mg/kg/day, as well as maintenance doses of antiaggregants (curantil 5 mg/kg/day). Доза антиагрегантов не изменялась в ходе пульс-терапии и в течение 10 дней после нее, в дальнейшем больным с повышенными показателями тромбоцитарно-сосудистого гемостаза антиагреганты назначались внутривенно.

Methods of research: 1. Platelet aggregation function was studied in vitro using a two-channel laser platelet aggregation analyser BIOLA-230LA according to the method of Born G.V.R. modified by Gabbasov et al. (1989), based on registration of changes in light transmission of platelet-rich plasma. The analysis of changes in the parameters was performed automatically using the attached commercial programme AGGR version 2.20 on IBM-486 under MS-Windows-95. The study of spontaneous platelet aggregation was carried out according to the light transmission curve, as well as the study of platelet aggregation with inducers of aggregation. The conducted study shows significant initial violations of a number of indicators of thrombocyte-vascular haemostasis in patients with NS compared to the control group. First of all, it should be noted the initial increase in spontaneous

platelet aggregation, platelet aggregation with ristocetin. The increase in spontaneous platelet aggregation serves as an unconditional sign of primary haemostasis activation. In NS patients included in the study, such an increase was found in 48 (80%) cases. Markers of hypercoagulability in children with NS are an increase in agonist-induced platelet aggregation [6]. One of such agonists is ristocetin, which indirectly may also reflect the degree of endothelial activation, as it depends on the concentration of von Willebrand factor and its activity in plasma. The introduction of intensive therapy with massive doses of glucocorticoids and shock doses of cyclophosphan into nephrological practice has improved the prognosis of patients with such previously non-curable NS conditions. There is no doubt that in addition to a pronounced effect on inflammation and immune reactions of the organism, therapy with GCS and cytostatics affects the state of the blood coagulation system. In the present study of the influence of intensive therapy on platelet-vascular haemostasis in patients with SLE, the peculiarities of changes in the studied parameters depending on the schemes of the conducted pulse therapy were revealed. Assessment of the state of thrombocytic-vascular haemostasis. On the background of the conducted therapy there appeared reliable differences in the index of platelet aggregation with ristocetin on the 1st and 10th day after pulse therapy ($72,18 \pm 3,96\%$ and $59,96 \pm 2,68\%$ on the 1st day after pulse therapy with 6-MP and combined therapy with 6-MP+CP respectively; $64,54 \pm 2,68\%$ and $55,7\% \pm 2,57\%$ in 10 days after these two schemes respectively). These differences can be explained by the dependence of platelet aggregation with ristocetin on the state of endothelium, in particular, on the amount and activity of von Willebrand factor synthesised by it. Taking this into account, it can be assumed that more significant effect of therapy in the second group of patients (greater reduction of aggregation with ristocetin in comparison with the reduction of the index in the first group) is associated with a pronounced suppression of immune aggression against vascular endothelium by cyclophosphan.

The absence of reliable differences in 2 groups of patients on other indicators of thrombocyte-vascular haemostasis on the background of intensive therapy suggest a similar effect of pulse therapy programmes on primary haemostasis.

However, in addition to assessing the reliability of differences between the indicators in two groups of patients, it is equally important to assess the reliability of changes in each indicator under the effect of treatment separately in each group, which will allow to clarify the nature of the effect of different schemes of pulse therapy on the components of primary haemostasis.

In the group of patients receiving 'classical' three-day therapy with methylprednisolone, there was a significant decrease in the initially increased spontaneous platelet aggregation ($1.48 \pm 0.13\%$) both on day 1 after therapy ($1.15 \pm 0.10\%$, $p < 0.05$) and by day 10 after it ($0.99 \pm 0.08\%$, $p < 0.05$), but normal values of this parameter were not achieved. In the group of patients who received combined therapy with MF and CF, the dynamics of the indicators of thrombopigorous-vascular haemostasis had a slightly different character. The platelet aggregation with ristocetin gradually significantly improved ($59.96 \pm 3.27\%$ on day 1 after therapy and $55.7 \pm 2.57\%$ by day 10 after it, $p < 0.05$). As noted above, this positive effect may be realised through the powerful anti-inflammatory effect of TF on vascular endothelium. However, in contrast to group 1 of NS patients, spontaneous platelet aggregation increased (up to $1.21 \pm 0.16\%$, $p > 0.05$) after combined pulse therapy on day 1 after it.

Thus, both programmes of pulse therapy by the 10th day after its termination led to similar changes in the parameters of thrombocyte-vascular haemostasis (improvement, though without reaching the norm by the majority of them), which is explained first of all by suppression of the activity of the immuno-inflammatory process, which plays the main role in activation of the haemocoagulation system in NS.

At the same time, the absence of normalisation of platelet-vascular haemostasis parameters after both pulse-therapy schemes suggests that in addition to suppressive effect on NS activity, both 'classical' three-day pulse-therapy with methylprednisolone and combined pulse-therapy with methylprednisolone and cyclophosphan have some own activating effect on platelet-vascular haemostasis. This effect is less pronounced compared with the positive effect on NS activity, but may still play a role in increasing the risk of thrombotic complications, which may occur delayed, increasing ischaemia of target tissues and organs.

Conclusions:

1. Three-day pulse therapy and combined pulse therapy in NS patients were characterised by a pronounced anti-inflammatory and immunosuppressive effect and lead to a decrease in the increased indices of thrombocyte-vascular haemostasis.
2. Intensive therapy of NS with megadoses of glucocorticosteroids and cyclophosphan during the period of its implementation, in addition to the positive effect of platelet-vascular haemostasis, is able to exert its own activating effect on this system, as evidenced by a significant decrease in platelet aggregation with collagen on day 1 after both schemes of pulse therapy, as well as a tendency to increase spontaneous platelet aggregation after combined pulse therapy on day 1 after its completion.

References:

1. Abdelraheem M.B., Ali E1-T.M., Mohamed R.M. et al. Pattern of glomerular diseases in Sudanese children: a clinico- pathological study // Saudi J. Kidney Dis. Transpl.- 2010. - Vol.21.- N4. - P.778-783.
2. Bagga A., Naga A. Management of Steroid Resistant Nephrotic Syndrome // Indian Pediatrics. - 2009.-V. 46.-№ 35. - P. 35-47.
3. Daskalakis K, Winn M. Focal and segmental glomerulosclerosis: varying biologic mechanisms underline a final histopathologic end point // Semin. Nephrol. 2006.-N26. - P. 89-94.
4. Fomina S., Pavlenko T., Englund E., Bagdasarova I. Clinical Patterns and Renal Survival of Nephrotic Syndrome in Childhood: A Single-Center Study (1980-2006) // The Open Urology and Nephrology J.- 2010.-N 3.-P. 8-15.
5. Hetal R.S. Comparison of two biopsy devices in pediatric nephrotic syndrome. // Pediatr. Nephrol.-2004.-N19.-P. 142.
6. Moghazi S. Correlation of renal histopathology with sonographic findings// Kidney International.- 2005.-Vol.67.-P. 1515-1520.
7. Noer M. S. Long Versus Standard Initial Steroid Therapy For Children With Idiopathic Nephrotic Syndrome. // Folia Medica Indonesiana.- 2005. -Vol. 41.-No.3.-P.205- 211.
8. Thomas D.B., Franceschini N., Hogan S.L. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants.// Kidney Int,- 2006.-N69.-P. 920-926.
9. Wilmer A.W., Rovin H. B., Hebert J. C., Rao V. S., Kumor K., Hebert A. L. Management of Glomerular Proteinuria: A Commentary. // J. Am. Soc. Nephrol.- 2003.-N4,-P.3217-3232.